37

NOSOCOMIAL INFECTIONS IN INTENSIVE CARE

Janet Margaret Justine Hammond

To my parents, Herbert and Justine Hammond,

and Peter

Acknowledgements

I should like to acknowledge, with much gratitude, the invaluable assistance and support so generously provided by the following people, in the preparation of this thesis:

Professor Peter Potgieter, who as mentor has spent many hours advising, helping and encouraging during each stage of my research, and who has so ably taught me about Critical Care Medicine, and infection, as well as providing insight into computer management.

Professor S.R. Benatar who enabled me to complete my research while in the Department of Medicine by assisting with financial support.

Professor A.A. Forder for his guidance and for the participation of the Department of Medical Microbiology, without whom this work could not have been performed, and who assisted in the publication of certain aspects.

Dr Lance Saunders, who while a registrar in the Department of Medical Microbiology, meticulously performed the microbiological surveillance and assisted with the microbiological data.

Mrs Helen Plumb, Department of Medical Microbiology, who provided technical assistance in the processing of specimens, and assisted with the research into resistance patterns.

Ms Julie Steere who worked as Research Sister in the Respiratory ICU for the duration of the study, and assisted with the collection of samples and the day-to-day running of the trial.

The nursing and medical staff in the Respiratory ICU, for the dedicated care given to the patients during the study.

Dr Carl Lombard from the MRC, Department of Biostatistics who assisted with statistical analysis.

Roussel Laboratories, who provided the financial support, and all the drugs, which made the study possible.

TABLE OF CONTENTS

PART ONE: REVIEW OF THE LITERATURE

CHAPTER 1. INTRODUCTION

The Italian scholar, Girolamo Fracastoro, in his book De Contagione published in 1546, distinguished three methods of the spread of infection [1]: by direct touching of a patient's body, by contact with fomites and at a distance through the air. He described infection as being due to the transmission of invisible "seeds" or "germs"; different kinds were the specific causes of different diseases; their ability to multiply in successive hosts was a necessary attribute for their continued spread. Much of his thinking was lost for centuries: another Italian, Agostino Bassi in 1835 showed clearly for the first time that micro-organsisms played a pathogenic role, but the germ theory of disease was not firmly established until Robert Koch reported his observations with Anthrax in 1876 and Koch's postulates were established.

Preventive measures in infection control owe their origins to the Austrian Ignaz Semmelweis who, in 1846, was able to demonstrate that puerperal fever was caused by a putrefactive agent transmitted on the hands of doctors when attending patients or performing necropsies, and thence to the birth canal when assisting at deliveries. Without knowing the nature of the agent responsible, he was able to reduce the maternal mortality from 8.3 to 2.3% by instituting a policy of handwashing.

Within the hospital itself, the development of the techniques of antiseptic and aseptic surgery for the prevention of wound sepsis were developed by Joseph Lister in 1867. He covered surgical wounds with dressings soaked in carbolic acid to kill any bacteria present in them, and to prevent the entry of further bacteria. He also was responsible for introducing the disinfection of hands and surgical instruments, and was able to reduce the incidence of sepsis significantly in his patients.

Despite the advent of antibiotics, nosocomial infections have remained a significant challenge, and the emergence of antimicrobial resistance has further complicated the problem. Until the 1970s there were no new developments which seemed capable of producing any dramatic improvements in the incidence of nosocomial infection; techniques of sterilisation and disinfection had advanced considerably, but although the incidence of puerperal sepsis and postoperative infection had been reduced to very low levels in most hospitals with hygienic control methods, the emerging problem of hospital-acquired infection or "nosocomial infection" remained a difficult and seemingly insoluble issue.

With the increasing complexity and invasiveness of medical and surgical procedures and, in particular the development of powerful immunosuppressive and antineoplastic chemotherapy, the phenomenon of nosocomial infection began to assume still greater importance as a cause of morbidity and mortality.[2,3]

It was in patients who were profoundly granulocytopaenic, either due to their disease or as part of a conditioning regimen in preparation for bone marrow transplantation, that it was first recognised that the gut, the upper respiratory and lower genito-urinary tracts formed important reservoirs of potential pathogens which caused nosocomial infections, often resulting in major morbidity and mortality.

During the 1970s, the importance of Gram-negative bacillary carriage as a result of impaired colonisation resistance, was demonstrated to be the initial step in the pathogenesis of endogenous infection; this carriage is followed by colonisation with the potential for progression to infection of other major organ systems.

W.G.Johanson in 1969 [4,5] was able to show that the very fact of being ill predisposed to the oropharyngeal carriage of Gram-negative bacilli. Schimpff in 1972 [6] demonstrated that the route of infection is practically always endogenous in seriously ill patients (the patient infects himself after first carrying the identical microorganisms in

the throat/stomach or gut.) Le Frock in 1979 [7] reported that illness was associated with intestinal carriage of Gram-negative bacilli other than the individual's own *Escherichia coli*; healthy people do not normally carry Gram-negative bacilli, other than their own *E.coli*, in their throat or gut, because they are able to resist colonisation by these organisms.

Intensive Care Units (ICUs) represent the single largest identifiable source of infection within the hospital [8]; among the most frequently observed infections are nosocomial pneumonias, post-operative wound infections, urinary tract infections and septicaemias. It is estimated that 30 to 50% of all such nosocomial infections are endogenous in origin [9]. Within the ICU, nosocomial infection causes a threefold increase in mortality and considerable additional morbidity, significantly increasing the costs of hospitalisation [10]. Daschner [11] estimated from data in the U.S.A. that the average nosocomial infection cost $1 800, while a life threatening nosocomial pneumonia could cost $42 000.

The technique of selective decontamination of the gastrointestinal tract, or SDD, owes its origins to attempts to reduce the incidence of secondary infection in patients with haematological malignancy [12]. The theory in broad outline being that the use of broad spectrum antibiotics promotes the overgrowth of aerobic Gram negative bacilli and yeasts, which are the major pathogens encountered in secondary infection; by preserving the normal, predominantly anaerobic flora of the gastrointestinal tract, and maintaining normal colonisation resistance, such overgrowth seems to be prevented and, with it, the incidence of secondary infection reduced.

Guiot et al [13] described the successful use of topical and enterally administered antibiotics to leukopaenic patients with an almost 50% reduction in the incidence of major secondary infection. Other trials confirmed the benefit of this technique, which became standard practice in one form or another in most centres treating such patients.

If a technique for preserving the normal intestinal flora and eliminating colonisation by potential pathogens seemed to work to prevent secondary infection in immunocompromised patients, the logical next step was for it to be applied in further selected population groups at high risk of nosocomial infection; thus the technique of selective decontamination was launched into ICU practice by Stoutenbeek et al [14] in the early 1980s, but its efficacy still remains controversial.

The objectives of this thesis are :

1) To provide a review of the literature on the significance, pathogenesis, diagnosis and management of secondary infections in the Intensive Care Unit.

2) To present the findings of a study of the technique of selective parenteral and enteral antisepsis regimen (SPEAR) in the patient population of the Respiratory ICU at Groote Schuur Hospital, aimed at reducing the incidence of secondary infection and, further to evaluate the study in terms of the effect of SPEAR on the incidence of secondary infection and its influence on the mortality due to secondary infection.

3) To present the findings of the effect of SPEAR on patient bacterial colonisation in the ICU, and to evaluate its longterm influence on the microbial flora of the ICU.

CHAPTER 2. DEFINITIONS

The terminology in this field has evolved over time, and a number of terms are used loosely and often interchangeably, for this reason a number of recent publications and consensus conferences have been held attempted to achieve uniformity in the definitions [15,16].

Nosocomial infection and **"secondary infection"** have come to be synonymous with **hospital-acquired infection** and, by definition, mean the acquisition of infection at least 48 hours after admission; although some authorities use a cut- off time of 72 hours. The intention is that the infection should not have been present, or incubating, at the time of admission to hospital.

In a patient with a previously established hospital-acquired infection, a new episode of nosocomial infection should be documented as **superinfection**. This should involve new and different organisms which are cultured from the previously described site of nosocomial infection, with a coincident clinical persistence, or deterioration, in the patient's condition.

Infection acquired within hospital during the initial 48 to 72 hour period is thought to be community-acquired and already to have been developing on admission to hospital. Hospital acquired infections are further designated **"early"** or **"late"**: "early" infections are those that develop within the first 4-5 days of admission and "late" infections are those that develop subsequent to this [17]. The importance of distinguishing between early and late infections is that the aetiological agents responsible may differ in both species and antibiotic sensitivity patterns. Usual pathogens such as *S.pneumoniae*, *H.influenzae* although commonly recognised to cause early infections, may also be responsible for late infections.

With increasing duration of hospital stay, the patient's normal flora is recognised to undergo changes, both as the result of antibiotic pressure, and colonisation of the

patient by the resident hospital flora. It is well known that the healthy body carries, or is colonised by, a flora of commensal organisms, many of which are potentially pathogenic if there is a breakdown or breach of the normal defence mechanisms. These organisms provide a defence against colonisation by new flora; this resistance to colonisation by bacteria is termed **"colonisation resistance"** [18,19]. The use of antibiotics, particularly those that have a broad spectrum of activity, eliminates many of the normal commensal flora, thereby creating a more favourable environment for the proliferation of organisms. Such organisms may be merely opportunistically pathogenic, or intrinsically more pathogenic than the original host organisms. These organisms may multiply in an uncontrolled fashion in the altered host environment and thus cause infection at the site they have newly colonised, or, by invasion, may cause disease elsewhere.

There are a series of processes that ultimately result in infection: the attachment of potentially pathogenic microorganisms to epithelial cells (eg in the oropharynx), proliferation at the site of attachment, invasion, with resulting tissue damage, and then possible dissemination to other sites.

There are three stages [20] in the acquisition of nococomial infection: **carriage**, **colonisation** and **infection.** The transition from colonisation to infection is not well understood, but with a breakdown in host defences, and the production of inflammatory mediators, tissue invasion may develop, resulting in **infection**.

Colonisation is the persistence of an organism at a specific site, in the absence of either a host response, or adverse effects on the host, and is determined by the culture of an identical microorganism from the same site for a minimum of two consecutive samples. There is, however, still some controversy as to whether it should be regarded as an entirely pathological process, or whether it is a phenomenon not always associated with disease. It is regarded by some as the prolonged presence of an organism at a site which it does not normally occupy , and against which the host does not mount a

serious immune response, but it is recognised that an antibody response to commensals is made and so this definition is not absolute.

van Saene [15] defined colonisation in a paper which he presented to the First European Consensus Meeting on Selective Decontamination, Paris 1991 as: the presence of a potentially pathogenic microorganism in an internal organ that is normally sterile eg the lower airways or the bladder. The diagnostic sample should yield fewer than 100 000 colony forming units per ml. The question still remains as to when the carriage of an organism should be regarded as colonisation. van Saene chooses to regard colonisation as the state where the same strain of a potentially pathogenic micro-organism is isolated from at least two consecutive surveillance samples (saliva, gastric fluid, faeces, throat and rectal swab) in any concentration over a period of at least a week. It is evident from the above that there is no clear distinction between colonisation and carriage.

For the purposes of this thesis, **carriage** means the identification on at least two occasions of the same micro-organism. **Colonisation** means the acquisition of a potentially pathogenic micro-organism which can be carried by the host in both normally colonised and sterile sites.

Infection is also a difficult concept to define [21], as it involves both clinical and microbiological diagnoses. It is the presence of microorganisms at sites that are not normally colonised eg the blood, or the presence of microorganisms that are not components of the normal flora eg *Mycobacterium* species, but requires, in addition, the evidence of a host response to the organism eg pyrexia, leukocytosis, inflammation. In the realm of the highly immunocompromised, where such clinical responses may be altogether absent, the diagnosis is still more difficult, requiring a high index of suspicion, and the early treatment of organisms found at abnormal sites, without any clinical features, regardless of the potential pathogenicity of the organism. An organism which proliferates excessively, or is present in large numbers, may be also be regarded as evidence of infection.

The development of infection may arise from either **exogenous** or **endogenous** sources.

Exogenous infections are transmitted from other infected patients, either directly, or by means of healthy carriers, or from inanimate or animate sources from the environment; infection may occur without the preceding stages of carriage and colonisation. Exogenous infection should be almost entirely preventable with the use of strict hygienic measures, including handwashing, disinfection and decontamination of equipment.

Endogenous infections are due to organisms carried by the host, which opportunistically invade tissues in the presence of compromised or breached host defences. These organisms may be community-acquired or hospital acquired and of varying degrees of pathogenicity and invasiveness. The main reservoirs for endogenous infection are the skin and the gut including the naso and oropharynx and the organisms responsible for this type of infection include *Staphylococcus aureus*, *Staphylococcus epidermidis* and the *Enterobacteriaceae*, enterococci, yeasts and anaerobes. The flora present on admission is involved in primary endogenous infections, while microorganisms acquired during hospitalisation are designated "secondary endogenous"; such organisms are acquired exogenously from the hospital environment, but are called endogenous because oral and gastrointestinal carriage form an essential stage in the development of infection.

Thus the source and type of organisms causing exogenous and endogenous infections differ considerably : the epidemic type of diseases eg cholera, typhoid, bubonic plague and leptospirosis are all classic types of predominantly community-acquired exogenous infection caused by pathogenic organisms, but in the hospital environment *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Acinetobacter spp* and other potentially pathogenic organisms which are found on hands and fomites, or in fluids or feeds administered to patients also become important sources of exogenous infection, given the right circumstances.

With antibiotic use and prolonged hospital stay, aerobic Gram-negative bacilli (AGNB) become important colonisers of the gastrointestinal tract and methicillin-resistant staphylococci of the skin and oropharynx, thereby assuming importance as potential nosocomial endogenous sources of infection. Antibiotic resistance is common, possibly as a result of microbial exposure to small quantities of parenteral antibiotics, which reach the gut in saliva, bile and mucus.

The spectrum of organisms encountered in the hospital may differ significantly from that in the community depending on the local and hospital antibiotic usage patterns. The patient's normal commensal flora begins to resemble that of the hospital within 48 to 72 hours of admission [7]. Even without the use of antibiotics, the patient gradually becomes colonised by flora which show a wider spectrum of antibiotic resistance, and may also differ in species eg *Acinetobacter spp*.

Bone [16] in an editorial on sepsis, and the septic syndrome makes a plea for greater precision in the use of terminology in defining infective states. He proposes that the term "septicaemia" should be abandoned, because it has been used interchangeably to mean both the presence of a blood-borne infection, and a systemic disease caused by the spread of microorganisms and their toxins in the circulating blood, and has thus lost clarity of meaning. He suggests instead that "**bacteraemia**" should be used to define the presence of viable bacteria in the circulating blood, a syndrome which has a positive blood culture as a diagnostic criterion. "**Sepsis**" should be defined as clinical evidence of infection, in the presence of tachypnoea, tachycardia and hypo or hyperthermia.

Such standardisation of, and precision in definitions would be enormously helpful in enabling meaningful and easier comparisons between studies, but is unfortunately not a reality as yet.

CHAPTER 3. THE PATHOGENESIS OF NOSOCOMIAL INFECTION

3.1 The Host

The healthy individual is able to protect himself from potentially harmful microorganisms in the environment by a number of very effective mechanisms which are present from birth, and which do not depend upon his having had previous experience of the particular organism. Such innate defence mechanisms are non-specific and are determined genetically, varying widely among different races (eg the increased susceptibility seen in some racial groups to infection with *Mycobacterium tuberculosis*) and to a lesser extent, with the individual. Age, sex, nutritional factors and hormonal balance all contribute to this protective mechanism. The acquired immune response however, is specific to the organism inducing the disease.

Mechanical factors such as an intact skin and mucosae act as important physical barriers, providing effective protection against non-pathogenic bacteria, and a high degree of protection against pathogens.

Such characteristics as the relatively dry conditions on the skin and the high concentration of salt in sweat, are inhibitory or lethal to microorganisms. The sebaceous secretions and sweat also contain bactericidal and fungicidal fatty acids, which constitute an effective protective mechanism against many potentially pathogenic microorganisms. The protective ability of these secretions varies at both extremes of life. The nasal secretions and saliva also contain mucopolysaccharides capable of inactivating some viruses, and the tears and the mucous secretions of the respiratory, alimentary and genitourinary tracts contain lysosyme which is especially active against Gram positive bacteria . Fibronectin may facilitate the adherence of certain types of organisms, particularly Gram positive microorganisms to the buccal mucosa, and thus prevent the adherence of Gram negative organisms [22-24]. The acidity of gastric juices, vaginal secretions and sweat help to maintain the normal flora of the upper

gastrointestinal tract, lower genitourinary tract, and skin. Secreted immunoglobulins (eg IgA in the intestinal secretions) have antimicrobial properties. There are a variety of other basic polypeptides eg lactoferrin that are derived from the tissue and blood cells and which act non-specifically on bacteria, by depriving them of nutritional co-factors, or in other inhibitory ways [25].

The mucous secretions covering the mucous membranes of the respiratory tract act as a trapping mechanism; under normal circumstances, the mucociliary escalator serves to sweep the secretions containing particulate matter towards the oropharynx, where they can be swallowed and destroyed by the powerful acid and enzymes, which are a normal constituent of the intestinal juices. The mucus trapping and expulsion by the ciliated epithelium, together with the constant desquamation of epithelialised surfaces with adherent organisms, facilitate mechanical decontamination [25]. There is also a system of surface phagocytosis which operates via the alveolar macrophages in the lungs and the epithelial cells in the bladder. The ongoing peristalsis in the gastrointestinal tract helps to move organisms and secretions, thereby preventing adherence and overgrowth from occurring.

Thus the endogenous flora of the healthy individual is the normal flora which is dependent for its maintenance on the physicochemical milieu, bacterial interference, and epithelial cell adherence. If these mechanisms are intact, colonisation resistance, which is determined by the above, will determine whether a patient is colonised by potentially pathogenic organisms on admission to the ICU, and the subsequent potential for infection.

Various individual host factors render susceptibility to the development of infection. Susceptibility is greatest in the very young and the very old; malnutrition, drug and alcohol abuse favour both a greater incidence and severity of infection, and are associated with a higher mortality [23]. Metabolic diseases such as diabetes, renal disease, collagen vascular diseases, immunological deficiencies, neoplasia, especially

haematological, and the hormonal and immunological derangements caused by high dose steroid or other immunosuppressant therapy, may all reduce host resistance to infection. Infections in such instances may occur with organisms not usually regarded as being of high pathogenicity eg pneumococci, *Candida spp* and *Klebsiella spp*, all of which are well-capsulated organisms; there may be a silent invasion due to poor host response to pathogens that ordinarily are not highly invasive against healthy tissues.

Antecedent disease of particular tissues and systems lowers resistance to infection Eg chronic skin diseases such as psoriasis and eczema, chronic bronchitis and bronchiectasis, rheumatic heart disease and neurological disease.

It is well recognised that such host factors as age, obesity, the size of the wound, wound drainage, duration of operation and the length of stay before and after the operation are important factors in the development of wound sepsis. Tissue trauma and anaesthesia associated with surgery also alter the host's immunological response and resistance to the development of infection [26-28].

Foreign bodies such as respiratory devices, sutures, indwelling urinary catheters, intravenous cannulae, all of which are commonplace in the hospital, may considerably add to the risk of infection [29] particularly in the intensive care unit where all of the above invasive, monitoring and therapeutic devices are frequently used. The normal host defences are breached by the passing of endotracheal tubes, which bypass the normal laryngeal, cough and mucociliary escalator defences against aspiration; or similarly tracheostomy tubes, which may also facilitate the direct transmission of organisms to the lower respiratory tract [29]; these devices are the most significant factors predisposing to the development of nosocomial respiratory tract infection. Central venous catheters breach the skin and may remain in the main venous system of the right side of the heart for days at a time; pulmonary artery catheters further are in contact with the pulmonary circulation and the right heart valves. Lines placed for haemodialysis or peritoneal dialysis are yet a further potential site for organisms to

penetrate the normally sterile internal environment. Nasogastric tubes may facilitate the migration of organisms from the stomach to the oropharynx and thence to the lungs. Both endotracheal and nasogastric tubes may block the normal drainage from the sinuses thus setting up a site for infection [30]. The patients often have underlying diseases and may often be receiving aggressive treatment with immune response modulating therapy which may further increase their susceptibility to infection.

3.2 The Organisms

Pathogenicity, or the ability to initiate disease, requires that the organism possess the attributes of transmissibility, infectivity to breach the host's defences and virulence to cause harm to the host.

There are no specific factors which can be used to measure clinically the ability of a microorganism to cause infection. The virulence of a bacterium depends on the susceptibility of the host, the interaction of host and bacterium and intrinsic properties of the organism such as the presence of fimbriae or a capsule; the site of host/bacterial encounter is also important and the size of the bacterial inoculum is a further determinant of virulence.[31]

Truly pathogenic bacteria possess properties that enable them to overcome the host's defences and infect the tissues of a normal healthy individual. The intrinsic pathogenic index (IPI) is the number of infected patients per number of patient carriers and is close to one for the high level pathogens including *Salmonella* species. Such types of infection are of more importance in the community.

Many commensal or non-pathogenic organisms are transmissible from person to person, or are derived from the environment and are present on the skin, in the upper respiratory tract, the gastrointestinal tract and the lower genitourinary tract, thereby constituting the normal bacterial flora of the body. Under normal circumstances, their infectivity is low and they do not cause disease, as they are unable to overcome the

body's normal defences; however the balance is a delicate one and many of these organisms are able to initiate disease if they are transferred to another site eg aerobic Gram negative bacilli are commensals in the gastrointestinal tract but cause infection in the urinary tract. Such organisms are designated "potentially pathogenic", having an intrinsic pathogenicity index which lies between 0.1 and 0.3. Potentially pathogenic microorganisms may cause infection in a subject with impaired defence mechanisms.

Potentially pathogenic microorganisms most commonly causing community acquired sepsis include *S.pneumoniae*, *H.influenzae*, *M.catarrhalis*, *E.coli*, *S.aureus* and *Candida species*. Potential pathogens in the hospital include *Klebsiella* , *Proteus*, *Morganella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Acinetobacter* and *Pseudomonas species*.

In general, the microorganisms considered as potential pathogens in the community, cause infection in a previously healthy individual with intact defences, whereas the hospital Gram negative bacilli cause infection in patients with impaired defences due to underlying disease.

The indigenous throat, gut and skin flora including viridans streptococci do not easily fit into the definition of potential pathogens, because of their low intrinsic pathogenicity.

The pathogenicity of organisms is determined by their intrinsic properties of virulence, adherence, invasiveness and the production of toxins. Bacterial-host cell secretion interaction plays a role in the adherence of bacteria to cell receptors, and is important in the development of colonisation. The earliest stage of bacterial colonisation is bacterial adherence to the epithelium, which is promoted by severe illness, malnutrition, intubation, tracheostomy, uraemia, cigarette smoking and ciliary dysfunction [22,23].

Adhesion is a colonisation factor both for pathogens and for organisms of the normal flora, but in pathogens may allow the expression of other virulence factors eg both commensal avirulent *E.coli* and toxigenic virulent *E.coli* can adhere, but the difference in outcome of colonisation is toxin production. Todd et al [24] demonstrated that the bacterial adhesion index for *Pseudomonas aeruginosa* paralleled the clinical condition of the patient, but showed no correlation with intubation or its duration.

The host's indigenous flora prevents colonisation by more pathogenic strains - a phenomenon called "colonisation resistance" which is achieved by a variety of mechanisms including secretion of bacteriocines, and the competition with the indigenous flora for nutrients at adherence sites [18]. In the abnormal environment of the intensive care unit, organisms which are normally regarded as commensals , or new colonisers from the environment, are translocated to new sites where circumstances may be favourable for their proliferation, which is often uninhibited and excessive.

Certain properties of bacteria such as their ability to react with certain components of the surface membrane of cells can kill the host cells and result in the haemolysis, cytolysis and leukocidal activity which are characteristic of pathogenic staphylococci, streptococci and clostridia. The lysis of tissue cells makes extra nutrients available to the bacteria, and killing of phagocytes protects the organisms from destruction. The specific antigenic character of Gram negative bacteria is determined by the pattern of hexoses that compose the lipopolysaccharide molecule. This has an affinity for, and tends to become incorporated in, the lipoprotein membrane of tissue cells where it may exert its toxic effects by disturbing the function of these membranes. The presence of a capsule may confer virulence on bacteria, by enabling them to resist phagocytosis or lytic attack and protect them from bactericidal substances in the body fluids. *Pseudomonas aeruginosa* in natural aquatic systems has been observed to colonise available surfaces and proliferate to form adherent biofilms, within which the sessile cells grow in a hydrated matrix partially composed of their own uronic acid containing

alginate hexopolysaccyharides [32]. In the catheterised patient, a thick adherent biofilm of similar composition from rapidly on the surface of the urinary catheter and confers a considerable degree of protection to the organism, protecting the viable organisms within this matrix from antibiotics.

Other protective or aggressive factors that are not toxins, but may contribute to the ability of capsulate and non-capsulate pathogens to invade and multiply in the host's tissues include: hyaluronidase which permits organisms such as *Streptococcus pyogenes* to penetrate the tissues; coagulase which is a thrombin-like enzyme produced by all pathogenic staphylococci which may protect the pathogen by forming fibrin-like barriers around the staphylococci and inactivating a bactericidal substance present in the serum; fibrinolysins, which by breaking down fibrin barriers may again promote the spread of streptococcal infection. There is a host of other depolymerising enzymes such as mucinases, proteases etc which may or may not contribute to virulence.

The route of introduction of the organism to the host is also important eg haemolytic streptococci may produce dangerous infection if they are introduced through the skin or into the bloodstream, but are likely to be harmless if swallowed.

Further properties of the bacteria such as the poorly understood adherence mechanisms may also contribute to pathogenicity at a specific site.[33] An organism may not be observed to have colonised and invaded by the usual means, but on introduction to such a site, rapidly sets up infection.

The use of antiseptics, chemotherapy and aseptic techniques all apply strong selective pressure on the hospital flora so that only those that are resistant survive. This may lead to the local multiplication of opportunist bacteria in disinfectant solutions or water eg *Pseudomonas spp* , thence contaminating and infecting patients. The widespread use of antibiotics produces similar selective pressures so that antibiotic-resistant variants of the common bacteria predominate in patients, staff and the environment [34].

The consumption of food contaminated with drug-resistant organisms can give rise to colonisation of the gut which under the right circumstance may lead to infection.

After admission to the ICU, acquisition and colonisation by the ICU flora of the oropharynx, trachea and digestive tracts occurs rapidly. Kerver et al [35] in a prospective study of 39 patients admitted to a surgical ICU, using microbiological surveillance cultures, showed that after 5 days in the ICU, the oropharyngeal cavity and the lower respiratory tract of 60% of the patients were colonised by ICU acquired organisms. After 10 days this figure had increased to 85% and the colonisation of the remainder of digestive tract showed a similar pattern. The predominant pathogens were *Enterobacteriaceae*, *Pseudomonaceae* and yeasts and were regarded as endogenous sources of infection, because of the pattern of acquisition followed by colonisation of the gastrointestinal tract. The authors found that the use of systemic antibiotics favoured colonisation with these organisms. Patients who became colonised by these organisms were found to be highly susceptible to the development of subsequent infection. In this study, 75.6% of patients who were colonised by a potential pathogen, went on to develop nosocomial infection due to the same organism. Organisms such as *Acinetobacter baumanii* and *Pseudomonas aeruginosa*, were regarded as exogenous causes of lower respiratory tract infection, because such organisms were frequently isolated as colonisers and causes of lower respiratory tract infection, without having previously colonised the oropharynx. The source of the *Acinetobacter* was subsequently identified by antibiograms as being the ventilator. *Pseudomonas aeruginosa* was identified as coming from disinfected glass thorax drainage systems. In contrast to other studies [9], they could not show that similar colonisation of the urinary tract occurred.

Johanson et al [5] prospectively studied the frequency of colonisation of the respiratory tract with Gram negative bacilli, and the relationship of this colonisation to infection, in patients admitted to their medical ICU. They demonstrated that 45% of all admissions became colonised, 22% on the first hospital day, which contrasts with only

2% of normal subjects who are colonised by Gram negative bacilli. Nosocomial respiratory infection developed in 23% of colonised patients, but in only 3.3% of those who were not colonised. The frequency of colonisation of the respiratory tract with Gram negative bacilli was 76% in patients with primary respiratory diagnoses, which was significantly higher than for patients with other diseases; suggesting that conditions that impair lung clearance may also promote colonisation. They were, however, unable to relate the use of inhalational therapy to either colonisation or infection.

Patients with cardiovascular diagnoses were at significantly less risk of developing nosocomial respiratory infections than patients with respiratory diagnoses, 5% versus 24%, drug overdoses (26%) and other diagnoses (20%); the common denominator being the presence of an endotracheal tube or coma, the prevalence of colonisation increasing as the severity of illness increased. They identified the factors already mentioned as risk factors for colonisation, but in addition, the presence of leukocytosis or leukopaenia, and sputum expectoration were related to colonisation. While noting that patients who were colonised tended to have more protracted stays in the ICU, they showed that 22% of these same patients tended to be colonised on the first day of admission, suggesting that colonisation was not only dependent on the duration of stay. 76% of patients, who were persistently colonised, were colonised on their first day in the ICU, but there appeared to be a susceptible subgroup admitted to the ICU, among whom colonisation increased for the initial four days following admission, and thereafter plateaued. Importantly, they were unable to identify any potential environmental reservoirs for Gram negative organisms, except for the isolation of some species in the immediate vicinity of the patient, but were unable to determine whether this represented contamination from colonised patients, or whether the patients had been colonised at source. The previous use of antimicrobial drugs was significantly associated with colonisation by Gram negative bacilli: in a subgroup, they showed colonisation in 55% before antibiotic therapy, which rose to 79% during or after therapy.

Antibiotics increase the risk of infection by interfering with the normal flora of the upper and lower airway, and eliminating the Gram positive organisms and anaerobes; thus allowing Gram negative organisms to occupy the bacterial binding sites usually filled by the normal flora. There are, in addition properties specific to certain bacteria which enhance their ability to bind to epithelial cells, including the presence of a capsule, the type of surface appendages, and the nature of exoproducts released by the bacteria [1].

Prior treatment with antibiotics may hasten the advent of such "hospital type" pathogens [36]. Meduri [37] reports several studies that demonstrated convincing evidence of an increase in the number of potential bacterial pathogens following antibiotic therapy. Graybill [38] reported superinfection in 16% of patients with hospital-acquired pneumonia, and this represented 45% of all Gram negative bacillary pneumonias. The mortality with primary Gram negative pneumonia was 44%, but this increased to 60% with Gram negative bacillary superinfection. The colonisation of the respiratory tract is of considerable significance in determining both morbidity and mortality. Schwartz et al [39] reported that patients who were colonised by Gram negative bacteria one week after intubation were four times more likely to develop pneumonia and three times more likely to die, than those who were not colonised.

3.3 The environment

The spread of infection can occur by a variety of mechanisms. Exogenous infection is important, because its spread is potentially preventable by hygienic precautions, based on a knowledge of its source and modes of spread. The concentration of patients in the ICU, both with and without infection, ensures dissemination of large numbers of microorganisms, so that most individuals become rapidly colonised with the institutional flora.

Those mechanisms operative in the transmission of infection in the hospital environment include: the airborne dissemination of infected secretion droplets, which occurs either by droplet spray or dried dust containing viable organisms. Droplet spread of infection is a danger mainly within the room of its origin, and spread to other rooms within the same building is usually slight. The use of moist dressings which prevent the wide aerial dissemination of bacteria, which can often be demonstrated to be present several hours after the change of dressings, may be helpful [1].

Air-conditioning plants with contaminated filters can act as major reservoirs in the dissemination of viruses, *Legionella spp.* and other organisms, resulting in the development of respiratory tract infections which may assume epidemic proportions. Special air conditioning systems and the use of laminar flow, have been designed to prevent exogenous infection from airborne infected dust and droplet infection in vulnerable sites or especially vulnerable patients.

Modern hospital design should provide the facility for the isolation of patients who are either at risk of developing, or who are a potential source of infection. Barrier nursing, the segregation of all articles in contact with the patient and hand washing are all important in the management of such problems. The incidence of nosocomial infection has been shown to be reduced when there is sufficient space between the beds and adequate numbers of hand basins are provided [40].

Most studies confirm that, even with aggressive educational programmes [41], hand-washing is still not adequately performed [42] and, compliance with regular hand washing in staff of more than 48% is difficult to achieve. The conversion of an open plan ICU to single isolation units was shown to reduce the number of staff-patient interactions, but failed to improve hand-washing techniques, in spite of conveniently located hand basins; the rate of nosocomial infection, although slightly lower, did not even approach statistical significance [43]. An improvement in the rate of handwashing from 30% to only 48% following patient staff encounters, was shown to reduce the

incidence of nosocomial infection considerably in a study with an educational programme and motivated staff, reported as recently as 1992 [42]. In spite of extensive education and understanding of the importance of this simple method in preventing the spread of infection, handwashing continues to be neglected.

Fomites may become contaminated with secretions and sedimentation of airborne infected dust, and thus act as an important reservoir of infection which may cause infection either by direct contact eg touching of bodies as in contact of clothes, hands or indirect contact involving an inanimate vehicle of infection such as eating utensils , door handles, towels and other fomites. Respiratory tract infections, skin, wound and burn infections may all arise in this way. Considerable environmental contamination has been shown to result from routine tracheal suctioning using a conventional catheter [44].

The faecal-oral route of the spread of intestinal pathogens may be important where techniques of food preparation are inadequate, both in the hospital kitchen and where enteral or parenteral feeds are produced, but may also come into play where water filtration mechanisms break down and when water or other fluids become contaminated through inadequate hand-washing and hygienic control methods.

Important sources of iatrogenic infection are intravenous fluids and medications (either for topical or intravenous use) which can easily become contaminated both during manufacture and, unless used before their expiry, while awaiting or during use. Careful control of each stage in the use of these fluids and agents has helped reduce the incidence of infection introduced in this way, but the constant potential for life-threatening infection to be caused by this means, requires continued surveillance and scrutiny of each stage, to guarantee the safety of products designed for use in this way.

Breakdowns in the sterility of invasive devices eg central venous catheters, intravenous cannulae, etc can occur at the time of production : during sterilisation, storage,

or at the time of utilisation; when the device is actually in situ and, even subsequently while in situ, if the portal of entry is not adequately cared for, and also at removal; thus allowing all the above mechanisms to introduce infection directly into the tissues or bloodstream. A system of careful checks at each stage is an ongoing necessity to prevent breakdown at any stage.

The migration of organisms in the opposite direction to proposed drainage eg with urinary catheters has led to sophisticated valves and "no touch" techniques in an attempt to prevent the iatrogenic introduction of infection.

Central to almost all of the above methods for preventing the spread of infection, are the simple techniques of hand-washing, thorough cleaning of the skin before embarking on invasive procedures, and the careful handling, storage and maintenance of the sterility of fluids, feeds and equipment. Such procedures are facilitated if the design of the hospital, ward or theatre permits easy and logical distinction between "clean" and "dirty" areas, and if there is a sequential flow in movement from the one to the other; something which is always made easier if there is adequate space.

However, these in turn are all dependent upon high standards of staff training and motivation, which is, yet again, contingent upon there being an adequate complement of personnel to devote the necessary time to such procedures. This may often appear to be tedious and over-ambitious if the staff is over-extended. The bacteriological monitoring of staff may be indicated in certain high risk areas, or during outbreaks of infection. Alternative duties, or sick-leave, should be prescribed if staff members have skin or upper-respiratory tract infections, which can further jeopardise the health of those for whom they care.

Highly topical at present is the spread of diseases such as Hepatitis B and HIV which are spread by the contamination or spillage of body secretions and blood products on to broken skin, or mucosae, or may be introduced by needle-stick injuries. Both clinical

and laboratory staff and patients are at risk from this iatrogenically introduced form of infection. The further discussion of techniques of prevention and the handling of needles and specimens is beyond the scope of this text.

All of the above methods of spread and techniques of prevention - which are by no means a comprehensive list of the techniques being used in the prevention of exogenous infection - have had no impact at all on endogenous infection which, with the generally effective control of exogenous infection, is now recognised still to be a major cause of morbidity and mortality, and a problem which has been largely ignored.

The problem of endogenous nosocomial infection is of particular relevance in the intensive care unit. As described above, the patient in the ICU provides very fertile "soil" for infection to develop, owing to the severity of the underlying disease, the effect of broad spectrum antibiotics both on the flora of the patient and the ICU. The use of invasive therapeutic and monitoring devices provide easy and obvious portals of entry; however, in spite of meticulous attention to sterile techniques and improved staff to patient ratios, infection has continued to occur, and the methods of infection control have now shifted to the prevention of endogenous or autoinfection, by means of selective decontamination of the digestive tract.

The organisms causing endogenous infection are typically the organism shown to be colonising the patient, and thus usually his environment. Mechanisms leading to infection are dependent on the properties of the organisms and the breaching of the normal host defences described previously.

3.4 Colonisation

Colonisation is the persistence of an organism at a specific site, in the absence of either a host response, or adverse effects on the host, and is determined by the culture of an identical microorganism from the same site for a minimum of two consecutive samples. The problem in defining colonisation lies in when and whether it should be considered

to be pathological, particularly as abnormal colonisation probably precedes infection. As soon as there is host damage or inflammation, colonisation has clearly progressed to infection, similarly there are sites where colonisation is abnormal eg the bladder or the lower respiratory tract ; however, the colonisation of sites by organisms not normally found in those sites eg the presence of hospital-acquired potential pathogens in the upper airway is a more difficult "grey area", especially in the immuno-compromised patient.

The normal flora contains only certain organisms owing to a variety of host, bacterial and environmental factors which have already been alluded to. Although the flora in an individual may change from time to time, and with age, the tendency is for it to remain fairly stable, and the relative proportions of organisms found in any individual are characteristic of that individual. There are also specific anatomical sites for specific organisms, so that cultures of the buccal mucosa will reveal a different spectrum of organisms to that in the nasopharynx, even though the areas are contiguous. The characteristics of the normal flora include the concept that there may be sterile areas contiguous to areas that are massively colonised Eg the upper and lower airways, the oropharynx and the stomach.

Bacterial interference was first described by Louis Pasteur, who noted that if urine was contaminated with *Anthrax* bacilli, the bacilli not only failed to multiply but were actually killed. This is an important mechanism for maintaining the normal flora and probably results from the production of bacteriocines by the normal bacterial flora, which have an inhibitory, or bactericidal effect, on other bacteria. Substrate utilisation in a preferential fashion by one species over another, and alterations in the physico-chemical environment, may be further mechanisms which may produce unfavourable conditions for other species to survive. Bacterial adherence is also important in determining which type of organisms comprise the normal flora of a particular site; it

can be demonstrated that the resident flora adhere readily to the intact surfaces of the area in which they are usually encountered.

The flora in the hospital differs from that in the community and the colonising bacterial flora therefore changes gradually following admission to hospital. These changes are more pronounced when the admission is to the Intensive Care Unit rather than to the general ward, because of a variety of host factors, antibiotic pressure and other factors which affect the organisms and the environment. The transference of organisms on the hands of staff, leads rapidly to the colonisation of patients by the resident flora. Further, the patient's own gastrointestinal flora may become translocated from one site where there is normal colonisation, to other sites.

Gram negative bacilli (AGNB) are found in the oropharyngeal flora of 2-10% of normal, healthy individuals and the prevalence of such organisms is no greater in healthy hospital personnel than in those who have no hospital contact[4]. The prevalence of these organisms also does not increase in those who are hospitalised for non-medical reasons. However, in those who are ill, stressed or aged, the prevalence of colonisation by AGNB increases with the severity of their illness[45],[46] and may occur rapidly. The colonisation of the trachea and oropharynx of critically ill patients by AGNB is related to the underlying disease eg those with cardiac arrhythmias admitted for observations show a much lower incidence than those admitted in cardiogenic shock [5] which may be due to a variety of host factors or bacterial host interactions. Studies have shown the presence of AGNB colonisation of the respiratory tract in over 80% of patients who were not colonised pre-operatively.[47] Such colonisation appears to be related to the duration of the procedure, and the presence of underlying disease rather than the simple introduction of these organisms by the passing of an endotracheal tube.[48]

Alteration in, or loss of, the cell-surface fibronectin layer on the buccal surfaces, due to an increase in the proteolytic activity of the oral secretions [49], may predispose to the adherence of Gram negative bacilli, by exposing receptors for bacterial binding -

although the exact mechanism for the increased proteolytic activity is uncertain. There is a reciprocal relationship between the cellular binding of Gram positive cocci and the AGNB. Thus colonisation of an area is dependant on the host environment specifically related to the site, host interactions with the colonising microorganism, the interaction with the colonising microorganisms and the flora already present, and certain intrinsic properties of the microorganism which favour its colonisation under certain circumstances, such as the presence of pili or other adherence mechanisms.

The micro-environment in which bacteria meet the epithelial cells is also a determinant of adherence. Both the protease and mucin components of the respiratory secretions can influence whether or not bacteria bind to the epithelial surfaces. Mucins can serve as receptors for bacterial binding, and thus have the capacity to competitively inhibit binding if they bind to bacteria, rather than to the cells. However, if the mucins attach directly to the cellular surface, they may then act as a receptor "bridge" for the bacteria, and further increase the capacity of the epithelium to bind bacteria [33].

Todd et al [24] studied the correlation between bacterial adherence to tracheal epithelial cells, and the effect of intubation and its duration, on the acquisition of pneumonia in the ICU. They were unable to show any correlation between intubation or its duration and the bacterial adhesion index, although an increased adhesion index alone did correlate with an increased risk of pneumonia. Using adherence of *Pseudomonas aeruginosa* to the trachea as a model, they showed that the maximal number of bacterial receptor sites per tracheal epithelial cell was higher in noninfected subjects; which would suggest that an increased adhesion index in patients is not due to the creation of a larger number of receptor sites, but rather to a change in the tracheal epithelial surface, which alters bacterial binding. They suggested that this change in the cell surface which resulted in elevated or augmented bacterial adherence and the development of pneumonia, was possibly due to the nutritional status of the patient causing alterations in the levels of elastase, secretory IgA, or an altered pH in the

airway. They reviewed a number of other factors which also might have been expected to alter bacterial adherence, such as smoking, age, sex, whether the patients were fed, the method of feeding, the administration of antibiotics, and the presence of renal failure, but were unable to demonstrate that any of these factors had an effect on bacterial adherence.

Niederman has shown that tracheal cells are able to bind Gram negative bacteria and that *Pseudomonas aeruginosa* exhibits greater affinity to tracheal than to buccal cells[22]. Further he was able to show that there are host factors which determine this increased tracheal adherence to bacteria such as malnutrition, possibly by directly altering the ability of the tracheal cells to bind to bacteria [23]. There are also bacterial factors which help to determine the site of binding. *Pseudomonas aeruginosa* preferentially colonises the lower respiratory tract[50], but other Gram negative bacilli show the opposite phenomenon: *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis* and *Enterobacter cloacae* all were shown to preferentially colonise the oropharynx when serial paired samples of oropharyngeal and tracheobronchial cultures were taken from patients with endotracheal tubes requiring mechanical ventilation for chronic cardiac or respiratory disease[51].

3.4.1 Relationship between Colonisation and Infection

The contents of the normal stomach are sterile, or have only low counts of oral microorganisms, owing to the bactericidal activity of the normally very low pH of gastric juice. Other defence mechanisms, as outlined previously, include the protective effect of the normal enteric flora, the presence of specific intestinal immune mechanisms viz. phagocytic, humoral and cell mediated. However, microbial overgrowth has been demonstrated to occur in the stomach of critically ill patients and to be a source of bacteria colonising the trachea and respiratory tract .[52]. The organisms are most commonly AGNB, which can be demonstrated to colonise the stomach before they are isolated from the tracheal aspirate.

It is well known that aspiration of pharyngeal secretions occurs in up to 70% of normal individuals during sleep and seemingly without ill effect, yet the lower respiratory tract remains sterile. The explanation for this must lie with the size of the inoculum, bacterial virulence and the intact host defences.[53]

du Moulin et al [54] were able to demonstrate similar organisms when culture of the oropharyngeal secretions and gastric aspirates were performed, in patients being treated with antacids; they were also able to show a clear sequence of transmission from the stomach to the airway in a high proportion of subjects, with the subsequent development of pneumonia caused by AGNB, whereas in those whose flora differed at the two sites, pneumonia did not occur.

There have been a number of studies which have demonstrated that colonisation of the stomach is promoted by antacids and H-2 antagonists or an increase in pH [30,54-59]. There is also a qualitative change in the organisms, with the presence of higher numbers of anaerobes and AGNB being isolated.[57] At a pH of greater than 4, rapid colonisation of the gastric aspirate occurs, predominantly with coliforms and yeasts, whereas below 4, significant bacterial growth is rare.

It is uncertain how the organisms which colonise the stomach in critically ill patients initially arrive there. The assumed mechanism is that gastric colonisation follows colonisation of the oropharynx; the stomach then acts as a reservoir of bacteria for further colonisation. The increased bacterial load eventually overwhelms the lung's defences against infection and pneumonia results. The fact that AGNB may first be isolated from the stomach, suggests that the organisms may reach the stomach from the lower gastrointestinal tract, either because of ileus, or by reverse peristalsis. Alternatively the stomach, oropharynx and trachea may all be colonised separately in sick patients with diminished host defences, rather than requiring a stepwise transmission of organisms from one site to another.

Colonisation of the lower airways and pneumonia are more likely after oropharyngeal and gastric colonisation, because aspiration of secretions is more likely to involve potentially pathogenic microorganisms which have already shown themselves to be suited to the abnormal environment of the critically ill patient.[5] Part of the rationale for the technique of selective decontamination hinges on this, because if oropharyngeal and gastric colonisation are necessary antecedents for the colonisation of the lower airway, this and the subsequent development of pneumonia should be preventable by elimination of the colonising organisms from these sites. However, it would seem that colonisation of the lower airway can occur independently of colonisation of the upper airway or either the oropharynx and stomach, in the mechanically ventilated patient [39].

The aerobiology of inhaled micro-organisms appears to be a major factor in bacteria-host interaction, and in determining the development of disease. Experiments on mice have shown that the response to inhaled *Streptococcus pneumoniae* depends on whether they are delivered as an aerosol of monodispersed organisms, or as a cloud of aggregated bacteria. When bacteria are inhaled in the aggregated form, a smaller inoculum has been observed to cause saturation of the pulmonary macrophage system and induction of a neutrophil response, than when they are administered in an aerosolised form [60]. Similar findings were reported by Berendt [31] who demonstrated that the virulence of *Klebsiella pneumoniae* was significantly less when administered to mice and squirrel monkeys by aerosol, than when it was instilled either into the nose or trachea. It seems that aggregated bacteria are more resistant to phagocytosis than are monodispersed organisms.

3.4.2 Factors Influencing Colonisation

The risk factors for bacterial colonisation appear to be the severity of illness, a prolonged duration of hospitalisation, prior or concomitant use of antibiotics, an elevated gastric pH, azotaemia, the presence of underlying disease of the organ system

which becomes infected, and most important of all, particularly in the ICU, the presence of invasive devices.

1) Gastric pH

The controversy over the role of H-2 blockers/antacids in causing pneumonia in critically ill patients has now raged for over 10 years; while increased bacterial colonisation of the stomach can clearly be demonstrated in patients receiving such therapy [61], patients at risk of stress ulcers in the ICU setting are already extremely ill and thus already at risk of abnormal bacterial colonisation. With altered gastrointestinal motility, there is a further predisposition to the development of upper gastrointestinal colonisation by AGNB, yeasts or flora more typically found lower down the gastrointestinal tract, but it is more difficult to show cause and effect than merely to demonstrate an association.

Craven et al [30] analysed the risk factors for pneumonia and mortality in patients receiving mechanical ventilation and showed that pneumonia occurred in 21% of ventilated patients. They identified a number of factors which were individually predictive, by univariate analysis, of the risk of developing pneumonia: the presence of an intracranial pressure monitoring device, hospitalisation during the winter months, the change of the ventilator circuitry every 24 hours rather than every 48 hours and the use of cimetidine therapy. This indirect evidence was reported without data on gastric colonisation but interpreted to implicate H-2 antagonists as a distinct risk factor for pneumonia, which was further associated with a high mortality in the study.

Tryba [55] reported a prospective randomised double blind trial for the prophylaxis of stress bleeding, comparing the efficacy of sucralfate and antacids and showed that nosocomial pneumonia developed in significantly fewer patients who received sucralfate. Driks et al [62] found an incidence of nosocomial pneumonia among ventilated patients receiving antacids combined with H-2 antagonists of 49%, compared

with only 23% in those receiving sucralfate, but surprisingly, in those receiving an H-2 antagonist alone the incidence of pneumonia was still lower at only 6%. Although their results fell short of statistical significance, they did show that there was less gastric colonisation in the sucralfate group. These studies failed to prove that either antacids, or H-2 blockers alone, increase the incidence of pneumonia; perhaps because a single agent applied in conventional doses does not invariably achieve alkalinisation, whereas a combination may be more effective in achieving this, and thus increase the incidence of pneumonia. Cook et al [63] performed a meta-analysis of the evaluable studies and showed that the incidence of pneumonia was lower in critically ill patients receiving antacids and/or H-2 blockers than no stress ulcer prophylaxis at all. With the current data, it would seem that the use of sucralfate is associated with a lower incidence of nosocomial pneumonia than with agents which raise the gastric pH, but this is an area in which further study is still needed [63,64]. The gastric luminal pH is elevated in many patients in the ICU who are not receiving any form of stress ulcer prophylaxis. This is thought to be due to splanchnic hypoperfusion [62], and the inhibitory effect of hypoxia on the energy requiring process for acid generation, and further complicates the interpretation of results on drugs designed to alter the gastric pH.

The incidences of pneumonia reported by both Tryba and Driks (33% and 16%) are similar to those normally encountered and the incidence in both studies in the patients receiving sucralfate was unusually low (10 and 7%) - suggesting that sucralfate may have some other beneficial effect independent of gastric pH. Tryba and Mantey-Stiers investigated the antibacterial activity of sucralfate in gastric juice, compared with antacids and control, and confirmed that inhibition of the growth of *Pseudomonas aeruginosa* by sucralfate did indeed occur.[59] Other mechanisms are still being investigated and include the influence of sucralfate on the production of prostaglandin E_2, mucus secretion, and mucosal blood flow, which may all serve to maintain the integrity of the whole gut mucosa. There is also experimental evidence that sucralfate

can reduce bacterial translocation across the intact gut wall, which may also play a role in the pathogenesis of nosocomial pneumonia [65].

2) The Endotracheal Tube

Mechanical ventilation itself has been viewed as the major risk factor for the development of nosocomial pneumonia in the intensive care unit, the risk seems to increase with the duration of ventilation and appears to be maximal within the first 10 days of intubation [66]. The endotracheal tube serves to connect the patient to the tubing of the ventilator. It is thus able to increase the risk and susceptibility of the patient to infection through a variety of mechanisms.

The endotracheal tube by-passes the natural defences of the pharynx, namely the epiglottis, the false and true vocal cords, the mucociliary escalator, the non-specific and the specific immune mechanisms located in the mucosal walls of the pharynx and trachea, and the cough reflex; thus serving to allow the direct introduction of potentially contaminated secretions, or condensation from the humidifier or whatever foreign matter or biofilm is in its lumen, to the lungs [67,68].

The endotracheal tube also acts as a foreign body and, however soft the manufactured substance may be, a certain amount of trauma to the pharyngeal mucosa, the larynx and the tracheal epithelium is inevitable. By traumatising the epithelium, its properties change and the ability of bacteria to adhere to the altered surface, predisposes to colonisation by potential pathogens and thus to infection both at the local site and more distally in the lungs.

By breaching the larynx, the cough reflex is abolished and, although this is often so poor that it has been one of the indications for intubation, the placement of the tube imposes a need for careful suctioning of retained secretions. The secretions from the lower airway are often infected and are well recognised to be an important cause of the further dissemination of existing infection by the so-called bronchogenic route. Even if

the secretions are not primarily infected they serve as an ideal culture medium for bacteria to proliferate and need aggressive management by nursing staff and respiratory therapists.

It has been suggested that tracheal suction dislodges biofilm from the tracheal tube and carries it into the lungs. Biofilm is a matrix of bacteria and glycocalyx that has been shown to build up on the surface of tracheal tubes used for prolonged periods [68]. Such a mechanism would explain the dissemination of bacteria to the larger airways distal to the carina, further dissemination to the smallest airways is thought to be the result of this biofilm being broken up and scattered as small contaminated particles by the process of mechanical ventilation. The accumulation of biofilm seems to be a time related phenomenon - the longer the tube is in situ, the greater the accumulation. However there are a number of other factors which influence its formation including the quantity of respiratory secretions produced, the frequency of tracheal suction and the type of humidification system used. The bacterial colonisation of the inner lumen of the tube, seems to be via an endogenous route, because it has been demonstrated to occur even with the presence of microbial filters in the ventilator circuit.[69]

There is impairment of the normal swallowing mechanism while an endotracheal tube is in place, purely on a mechanical basis, but also depending on the underlying disease for which the tube is in place. Swallowing normally plays an important part in the mechanical clearing of bacteria and secretions from the naso and oropharynx. It also protects against the aspiration of secretions from the pharynx and gastrointestinal tract. When swallowing is impaired, there is an increased risk of the pooling of secretions in the oropharynx, and of aspiration past the endotracheal tube and into the lungs, particularly if the secretions are copious and thus not easily dealt with. Furthermore, the flora of the mouth changes with the presence of a foreign body such as an endotracheal tube, so that AGNB, yeasts and faecal flora may predominate, increasing the infectivity of the secretions.

Although the endotracheal tube is designed both to facilitate mechanical ventilation and to protect the airway, its ability to protect the airway is not entirely foolproof. If the catheter used for suctioning is not sterile, or the technique of usage is inadequate, the contaminated upper airway secretions can actually be carried and introduced lower down. One of the ways in which secretions may bypass the tube is via the cuff. Part of the tracheal toilet performed as routine care in the ICU is regular suctioning down the endotracheal tube; however, it is not possible to clean or suction down the sides of the tube. The epithelium on the sides of the pharynx and trachea continues to produce secretions, and secretions from above may pass down the sides of the tube and thus accumulate above the cuff. In order to prevent erosion and pressure necrosis of the trachea, it is part of routine nursing care to adjust the pressure on the cuff which may involve letting it down somewhat; alternatively, the cuff has a constant slow leak which may be increased by coughing or other changes in intrathoracic pressure which alter the intra-tracheal diameter. In either event, the net result is that secretions which have accumulated around the cuff are allowed to pass directly into the lower airway, thus easily introducing a potential source of infection. The application of positive end expiratory pressure, which limits the degree of negative intrathoracic pressure, helps to prevent aspiration around the cuff.

The nasotracheal tube is advocated by many because of its stability and the improved comfort that it affords the patient. Owing to its natural stability, the patient does not require as deep sedation to maintain a secure airway as with an oral tube, and is therefore able to be mobilised considerably more actively. It is thought that this active, early mobilisation may also be beneficial in preventing the development of pneumonias, as well, of course, as deep venous thrombosis, pressure sores etc[70,71]. The nasotracheal tube tends to ride up and down less than its oral equivalent and thus may prevent laryngeal and mucosal injury through constant chafing which can lead to local ulceration and infection , with the obvious risk of seeding farther down the airway.

However, its opponents claim that the above are far outweighed by the increased risk of sinusitis caused by the obstruction of the sinus orifices in the nose.

Sinusitis certainly is a well recognised site of, often occult, nosocomial infection, and computerised axial tomography (C.T.) scanning of the sinuses in patients with nasotracheal tubes does show the presence of mucosal thickening in a high proportion of cases [72]. This however should not be regarded as proof that there is infection in this area, and X-rays showing air-fluid levels may actually be of more value. In any event, if there is concern, the tube can be withdrawn and replaced. Often if there is obstruction, the very act of removing the tube is reported to allow the free drainage of accumulated pus, thus resolving the problem. One last advantage of the nasotracheal tube over its oral counterpart, is that oral toilet is greatly facilitated which is important in preventing excessive oral colonisation from developing, and spilling down the pharynx.

In spite of all the above, emotions run high in individual units all over the world as to which placement of endotracheal tube is to be preferred. Part of the problem is probably due to there being very little careful analysis in the literature of the relative merits of either technique.

Outbreaks of pharyngeal colonisation with microbes which may lead to infection have also been reported from the use of contaminated ventilatory equipment, such as anaesthetic equipment, ventilators, and nebulisers for the administration of medication and not only due to the endotracheal tube. The ventilator tubing can lead to infection if there are breakdowns in the disinfection process eg *Pseudomonas aeruginosa* [73] was found to contaminate respiratory tubing which did not dry adequately during the disinfection process. Initially it was recommended that the tubing should be changed every 24 hours to prevent infection, however new evidence suggests that this may actually serve to increase the incidence of infection by allowing the spillage of heavily contaminated condensate into the tracheobronchial tree during manipulation, and the

recommendation at present is that the ventilator tubing should be changed every 48 hours [30].

One of the main sources of contamination in this setting is the large volume nebuliser, such as the Venturi nebuliser, as the aerosolised droplets emitted can deliver large numbers of Gram negative bacilli directly to the terminal bronchioles and lead to pneumonia. Cascade humidifiers reduce the problem somewhat by allowing the gas to bubble through water maintained at a pasteurising temperature prior to delivery, and thus preventing the generation of the microdroplets; however, contamination of the cascade humidifier can still occur during the cleaning process, or when replenishing the water, or if the temperature is inadequate. Modern paper-wick humidifiers (eg Fisher - Paykel) that humidify at a higher temperature are less likely to become contaminated and are now the humidifiers of choice [29,74]. The organisms commonly encountered in these circumstances include: *Pseudomonas aeruginosa* or *cepacia*, *Serratia marcescens*, *Acinetobacter baumanii* and *Flavobacterium menigosepticum*.

Ventilation may also be carried out via a tracheostomy tube. Although this circumvents the problems associated with sinusitis and poor oral hygiene, the problems pertaining to the cuff still remain, as the pooling of secretions above it may still occur, and cause erosion into the sides of the trachea. There may also be associated wound infection with the problem of introduction of organisms from the wound directly into the airway.

Unfortunately there are again no adequate studies evaluating the place of the tracheostomy compared with the endotracheal in the ICU setting specifically. High rates of complications and infection rates are published [29], but these report the incidence in the general hospital, and thus probably relate to the larger otorhinolaryngeal patient population, who have primary laryngeal problems with longterm tracheostomies, and are receiving lower grade care in the general ward for a different type of disease process.

In spite of all the above, it is the severe impairment of airway and pulmonary defence mechanisms following the onset of a critical illness that seems to be the most important factor in the pathogenesis of pneumonia.

3) The nasogastric tube

The presence of a nasogastric tube has been shown to be associated with a higher incidence of nosocomial pneumonia [30], which may be due to the adherence of bacteria to the foreign material, facilitating their migration from the stomach to the oropharynx, and thence to the trachea; the breaching of the oesophageal sphincter may also play a role [62], as larger quantities of both gastric and oropharyngeal secretions are aspirated with a nasogastric tube in situ.

By performing cultures of the oropharynx, trachea and stomach before and daily for 5 days after feeding was begun, Pingleton et al [58] were able to show clearly that 16 of 18 patients developed tracheal colonisation; of whom 6 had no evidence of preceding colonisation at another site. In the other 10 there was evidence of the organisms on gastric culture prior to tracheal culture in 5, and of oropharyngeal to tracheal transmission in 3. In some, more than one mode of transmission was apparent. Nosocomial respiratory infections occurred in 11 of the 18 patients. One of these infections was associated with transmission of a gastric organism. They suggested that colonisation of the trachea by gastric flora may be associated with enteral nutrition, thus resulting in nosocomial respiratory infections.

The nasogastric tube is placed in the ventilated patient to prevent gaseous distension of the stomach, to avoid the problem of aspiration, which is a particular risk in the critically ill patient where gastrointestinal motility is often uncertain, and to facilitate enteral feeding in patients who are unable to swallow. However, the nasogastric tube itself may increase the risk of aspiration. It also acts as a foreign body which may increase the risk of oropharyngeal colonisation [75]; by impairing swallowing, it may encourage the pooling and accumulation of secretions in the mouth; by breaching the lower oesophageal sphincter, it may promote gastric reflux, and also acts as a conduit up which bacteria may migrate to the oropharynx. The size of the nasogastric tube may play a role in determining the likelihood of aspiration and infection. While large bore

tubes clearly may cause greater impairment of deglutition and the oesophageal sphincter and thereby allow greater quantities of secretions to pass into the lungs, the fine bore tubes, which cause less mechanical effect, may themselves migrate into the lungs.

4) The urinary catheter

Almost all nosocomial urinary tract infections occur in patients who have undergone some form of instrumentation; the commonest form of instrumentation being catheterisation, which accounts for about 80% of hospital-acquired urinary tract infections [76]. The remainder are not associated with urological manipulation and presumably arise from haematogenous dissemination, although the exact mechanism is uncertain.

Until the 1950s the urethral catheter system involved drainage into an open container with the almost inevitable development of early infectious complications. The indwelling urinary catheters in use in the modern hospital and ICU have a closed drainage system so that the system remains connected for the duration of catheterisation in an attempt to reduce the incidence of colonisation and infection and, although there are no studies comparing the two techniques, it would appear that the incidence of urinary tract infection has almost certainly been reduced by this[77], with a prolongation of the time from insertion to the average time of onset of infection.

The same mechanisms predisposing to colonisation hold for urinary tract infections, the organisms being predominantly the patient's own colonic flora, their source being the perineum, vagina with the close proximity of this area to the faecal and lower intestinal flora. The majority of infections arise from colonisation of the catheter by the introduction, or migration, of organisms from the perineum, which gain access to the bladder along the external surface or lumen of the catheter. The tube offers a niche on its surfaces for bacteria to develop a microenvironment within a biofilm layer[32]. This glycocalyx covers and secures the bacteria against the mucosal or catheter surface and

has been demonstrated to be present on drainage bags, catheters, and the uroepithelium; it seems to offer protection from antibiotics, host defence mechanisms and even the mechanical flow of urine. The biofilm may permit the development of a microenvironment in which the organisms may move into the urine, where they are measured and detected as bacteriuria. The uroepithelium may allow more easy bacterial adherence in catheterised patients which may precede the onset of bacteriuria [78], in addition the bacteria maintain themselves within the urinary tract by interaction with the surfaces to which they can adhere by means of specific adhesins, including fimbria and pili.

Further pathogenic mechanisms may include the inflammation of the bladder and urethra from mechanical and chemical irritation, which may also blunt the antibacterial function of the polymorphonuclear leukocytes. The organisms may also promote the formation of struvite and apatite crystals which can lead to catheter obstruction, increased intravesical pressure , transmucosal migration or vesicoureteral reflux of bacteria [78].

Even with meticulous attention to catheter care, the opportunity exists for bacterial entry at the external meatus between the catheter and the urethral mucosa. The colonisation of this area within 24 hours with hospital type pathogens has been demonstrated and once such organisms exceed a certain density, bacteriuria results. Even after catheter removal, patients may develop bacteriuria which may be related to the presence of pathogens already present in the urinary tract during catheterisation. The indwelling catheter system may be opened at two sites once in place: the junction between the catheter and the collection tube may be disconnected for irrigation or urine collection and bacteriuria may result from this. Alternatively, the drainage tube of the collection bag has to be opened periodically and if the lumen of the drainage tube is contaminated with bacteria from an unwashed, contaminated jug previously used to collect urine from an already infected patient, organisms may enter the drainage bag

and multiply to high concentrations, persist in the bag and ascend the surface to the tubing or be passed into the patient by refluxing urine.

Unless the organisms are adequately dealt with as they colonise the bladder, they may migrate further up the urinary tract to involve the kidneys, where a similar microenvironment may be set up with the invasion of the interstitium and the development of pyelonephritis.

The organisms responsible for urinary tract infections in the community are predominantly the *Enterobacteriaceae*; under normal conditions 80% of community acquired urinary tract infections are due to *Escherichia coli*, however in the hospital *Proteus*, *Klebsiella* and *Pseudomonas* species as well as *Candida* and other yeasts assume importance with the use of broad spectrum antibiotics, the presence of foreign bodies, the possible introduction of the hospital organisms on the hands of staff, as well as the common occurrence of stress-induced glycosuria altering the environment. The same factors as previously highlighted affecting the colonisation of the hospitalised patient operate in this site, so that hospital-type organisms are again encountered.

5) Percutaneous Intravascular Devices

Included in this broad heading are peripheral and central venous catheters, arterial lines, pulmonary artery catheters, arterial lines and central lines for total parenteral nutrition. Brief mention only will be made of the catheters placed for longterm central venous access such as the Hickman catheter, which is not used in our respiratory ICU, although the haematologists make extensive use of it for the administration of drugs in their patients where access becomes a difficult problem.

It is estimated that 25% of all admissions to hospital in the United States receive intravenous infusions and that the mortality of patients with primary nosocomial bacteraemia is 14 times higher in those patients who develop this complication compared with those who have the same primary diagnosis without bacteraemia [79]. The types of infection that may result include wound infections, tunnel infections, bacteraemia (which may often occur without any local signs), septic thrombophlebitis, and infective endocarditis etc.; these infections may then disseminate to other sites with the development of metastatic abscesses.

Bacteria may gain access to an intravascular device at several sites [79,80]: the skin remains the most important site for potential contamination, however contamination may also occur at the junctions of catheter and administration sets, where the spike of the administration set is inserted into the fluid container; such contamination may occur when the container is initially set up, or whenever the container is changed. The container itself may of course be defective and its contents thus contaminated, or the sterilisation process may have been inadequate for a number of reasons so that the contamination of the infusate has already occurred. The air filter of the container too may malfunction and thus allow contamination. The relative importance of these other sites has not been assessed.

Further portals of entry for contamination include pressure measuring devices and transducers, heparinised flush solutions, stopcocks, piggyback IV lines, Y-junctions, CVP manometers. Again, handwashing as a preventative measure when handling such devices cannot be over-emphasized.

The contamination of the infusate has been well shown to be a potential source of infection, as the recently much publicised local court cases involving several paediatric deaths related to the infusion of intravenous solutions contaminated during admixture procedures, have reminded us all of this risk. Different types of solutions support the growth of different types of bacteria[80], but even distilled water can harbour *Pseudomonas cepacia*. *Klebsiella* and *Enterobacter species* as well as *Citrobacter freundii* and *Serratia marcescens* are frequently associated with contaminated infusions. The routine use of bacterial filters to prevent this extrinsic source of infection is not recommended [79] as the incidence of infection has not been shown to be affected and the bacteria retained in the filter are still able to produce endotoxin which enters the patient along with the infusate.

The high nutritional value of parenteral nutrition solutions predisposes to their contamination by bacterial flora and they may be contaminated both at the industrial site of manufacture and also in the pharmacy when then they are reconstituted. They form excellent substrates for the growth in particular of *Candida albicans*, and the other *Candida species* [81]; *Malassezia furfur* is another yeast which is lipid dependant and fungaemia has been associated with its growth in lipid emulsions.

Blood and related products are well-recognised sources of infection from viral and other causes but will not be dealt with further, except to mention that platelet infusions carry with them a higher risk of catheter related sepsis than other products.

Contamination at the catheter insertion site is thought to be an important means of entry for microorganisms. The hub of the catheter is the portal of entry in over 50% of cases

and the insertion site is the portal of entry in approximately 50% of instances. The skin flora may change owing to the use of antibiotics or the colonisation by hospital type organisms which are carried on the hands of the staff [82], or transmitted indirectly through contact with fomites. Any breaks in the skin's integrity also predipose to colonisation by other bacteria and increase the likelihood of infection. Colonisation around the catheter site may facilitate the ingress of organisms along the external surface of the catheter.

Such factors as the type of dressing may increase the bacterial load around the entry site and promote colonisation. The use of semipermeable membranes for dressing the site which can be visualised through this has not been shown to reduce the incidence of infection over plain gauze dressings although the cost may differ considerably [83]. Changing the catheter every 48 hours does not seem to alter the infection rate compared with daily changes, but a catheter left in situ for more than 72 hours is generally thought to be associated with a much greater risk of infection[80] although more recent studies would suggest that the routine changing of catheters to prevent this is unlikely to reduce the risk if strict standards of asepsis are adhered to[84,85].

The importance of handwashing to prevent the introduction of infection at these sites is well known and cannot be over-emphasized, this may be an area where epidemics are transmitted on the hands of the staff. Even the cleansing solutions or ointments applied to the catheter site to prevent infection may become contaminated and serve to transmit infection from patient to patient. The use of such ointments has not been shown to reduce the incidence of drip-site infection[86]. Similarly the removal of the catheter needs to be performed with care, including the thorough cleansing of the skin before removal, because this manipulation may also result in the showering of bacteria into the circulation.

The composition of the catheter, the presence of thrombus in association with the catheter, the nature of the pathogen, the duration of catheterisation, the duration and

intensity of bacteraemia and the host's immune status may all determine whether infection results[80].

The intensive use of the catheter for pressure monitoring and the taking of samples or other manipulation eg for repositioning is also associated with an increased likelihood that the catheter may become contaminated. The more frequently any part of the administration set is handled and the system entered, the greater the chance that line related sepsis may follow[87].

There are characteristics of the catheter which also determine its potential to cause infection[80]. Certain catheters are more prone to lead to the complication of thrombosis, by causing irritation of the intima of the vessel wall and this may initiate a nidus for bacterial colonisation and infection. Polyvinylchloride catheters are more rigid and thrombogenic than the newer, more flexible silicone elastomer and polyurethane catheters which have been shown to be associated with a lower incidence of catheter-related sepsis.[88] Polyurethane catheters are at present the catheters shown to be associated with the lowest risk of infection, followed by silastic, teflon, polyvinylchloride and silicone, in that order although doubtless there are new materials just around the corner which will be able to improve on those currently available. The composition of the catheter may also favour bacterial adherence and thus its colonisation by microorganisms eg polyvinylchloride catheters are more easily colonised than Teflon catheters. A loosely formed clot quickly forms around the intravascular segment of plastic catheters. Clot formation facilitates the colonisation of the site by trapping circulating microorganisms. The type of material that is in contact with the circulation can determine the thickness and adhesion of the thrombic layer - polyurethane causes less clot generation than polyvinylchloride [87]. Metal catheters also have a lower colonisation rate than plastic ones[85]. All catheters, however, develop a fibrin sleeve around them sooner or later, which extends into the vessel and provides a potential site for bacterial colonisation.

The size of the catheter also plays a part in increasing the risk of infection and the larger the catheter, the bigger the skin defect and the greater the potential for infection to occur. A number of studies also suggest that the use of triple lumen catheters is associated with a higher incidence of infection than single lumen catheters although this is contraversial.[80,87,89]

The site of the catheter also determines the frequency and likelihood of the development of infection; it is well known that femoral catheters become contaminated more rapidly than subclavian or internal jugular central lines because of the unavoidable proximity to the perineum; some studies have shown that internal jugular lines are more likely to become contaminated than subclavian lines possibly because this site is more difficult to keep immobile and sterile [90]; similarly central lines become contaminated less frequently than peripheral lines. However, a central venous line often remains in situ for much longer than a peripheral line and this may result in life-threatening complications such as infective endocarditis or thrombophlebitis involving the great veins.

Pulmonary artery catheters are central venous lines which not only enter the great veins, but also traverse the tricuspid and pulmonary valves of the heart to enter the pulmonary circulation; the risk of infection and the potential for serious complications, including bacterial endocarditis, thus is still greater[87].

Arterial lines used for blood pressure monitoring and for the easy taking of specimens in patients who are unstable and need repeated blood gas monitoring are frequently used in the ICU. Because of the faster flow of the circulation, such catheters are at a lower risk of colonisation than venous catheters [85], although with prolonged placement or less than perfect asepsis in insertion or maintenance, there is the risk that they too may become infected. Another source of potential contamination is the flush bag and transducer set which is reusable and thus brings with it the risk of breakdown in the sterilising procedure.

The catheters used for total parenteral nutrition often remain in place for much longer than other central lines[80], the solutions that they administer are very hypertonic and both of these factors increases the tendency to venous thrombosis [81] and infection; added to this, the patients who require prolonged parenteral nutrition are often much sicker so that their diminished host defences also render them susceptible to infection [81]. Guide-lines have been published by the Centre for Disease Control to prevent potential complications associated with TPN.[91] which include guide-lines for the sterile preparation of the solutions, sterile technique in the placement of the line, that the line should be firmly secured to prevent movement, that the system should be kept closed and where possible dedicated to TPN.

Studies using antimicrobial creams, heparin or tunnelling of the line have shown inconclusive results in preventing infection, although part of the problem is the difficulty of diagnosing sepsis related to the catheter site [81,90] - the tendency being to err on the side of suspicion that the catheter is likely to be responsible and overdiagnosis, removing it when there is clinical evidence of sepsis without an obvious alternative site . Although it is possible that many catheters are removed unnecessarily, this is a practice which should not be changed [81], because the complications related to sepsis outweigh the risks of replacing the line. Antibacterial cuffs eg with silver impregnation, applied to the tunnelled portion of a central line have been shown to reduce the incidence of sepsis (Multicenter Trial of an attachable silver-impregnated subcutaneous cuff for prevention of infection with central venous catheters: 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, Abstract, New York, October 1987).

The use of longterm indwelling catheters is mainly confined to patients undergoing chemotherapy for haematological malignancy or bone marrow transplantation. Such patients are at very high risk of infection, because of their severe immunosuppression; however, many centres specialising in the treatment of such patients report surprisingly

low infection rates[92]. The difficulties of deciding when to implicate the catheter [90] in infection are still further compounded in such a population.

A line that is placed electively is associated with a much lower rate of infection than those that are placed as emergencies. The reason most probably being that adherence to strict skin asepsis is higher in the elective setting[81,82], the severity of illness necessitating urgent placement also may be contributory by reducing the host's immune surveillance and defences. The skill of the operator [85] also is thought to play a role in determining the incidence of infection; protocols [81,82] which are carefully enforced to maintain high standards of asepsis by those responsible can have a major impact on the incidence of line related sepsis. Teams of venipuncturists[80,82] in the U.S.A. and Australia seem to be able to show lower rates of infection than more occasional operators. Percutaneously placed lines are associated with a lower incidence of sepsis than lines placed by cutdown[80,85].

Haematogenous dissemination of infection from another site [87,90] may result in the seeding of organisms on to the catheter. Patients who harbour systemic infections before the insertion of catheters are at higher risk of these being colonised by haematogenous dissemination [85]. The organisms causing this type of catheter related sepsis are the organisms responsible for the other site of sepsis and tend to be Gram negative bacilli rather than Staphylococci, which are the organisms associated most commonly with primary catheter related sepsis [79,80,87,90,93,94]. Coagulase-negative staphylococci adhere to plastic catheters more readily than other organisms giving them a selective advantage. Pseudomonas species may also cause infection from cutaneous colonisation; other organisms occur less commonly. There is a strong correlation between the organisms found on the skin and those isolated from blood cultures drawn through the catheters[90].

The same organisms and risk factors as have been described above, pertain to the catheters for haemodialysis and peritoneal dialysis, which are used for renal support

programmes, and in the ICU in patients with renal failure, and a more detailed analysis of this specific area is beyond the scope of this thesis.

3.5 Bacterial Translocation

As an alternative to aspiration, there is currently much interest in possible translocation of intestinal organisms across damaged intestinal mucosa, as a mechanism for the development of infection at distant sites, in particular in the pathogenesis of nosocomial pneumonia [95-97]. Indirect evidence in support of this mechanism in the pathogenesis of nosocomial pneumonia, has been derived from the relatively new technique of gastric tonometry, which is used to monitor gut mucosal ischaemia. The development of nosocomial pneumonia was found to occur exclusively in those ventilated patients in the ICU with gut mucosal injury as determined by gastric tonometry, guiac positive nasogastric aspiration, endoscopic evidence of mucosal injury or bleeding [95]. Gut ischaemia, haemorrhagic shock, intestinal obstruction, parenterally administered endotoxin, hyperpyrexia, thermal injury, parenteral feeding, the use of an elemental diet, cytotoxic drugs, obstructive jaundice, and antibiotics causing Gram negative bacterial overgrowth have all been cited as factors thought to promote the translocation of viable microorganisms across an anatomically intact intestinal barrier [65].

The clinical relevance of bacterial translocation still requires further eludication, as sequestration of enteric organisms in mesenteric lymph nodes is also observed in patients with inflammatory bowel disease, and to a lesser extent, in healthy people. The absence of any demonstrable association between multiple organ failure and bacterial translocation also leaves some doubt as to the validity of this postulated mechanism. Furthermore, selective decontamination (where the aerobic Gram negative bacilli are eliminated from the gastrointestinal tract), has not prevented the development of multiple organ failure. These studies also suggest that the majority of nosocomial respiratory infections are more likely to be due to colonisation of the oropharynx with aspiration, or direct tracheal inoculation, than to bacterial translocation.

The value of postoperative total parenteral nutrition in malnourished surgical patients has been controversial, but appears to be justified by the results of recent studies [98]; however, evidence is emerging of the importance to the gut mucosa of enteral feeding in supplying nutritional elements not part of TPN (such as glutamine which is too unstable for inclusion in standard solutions, and short chain fatty acids, which are produced by the gut anaerobic flora metabolising dietary fibre). While it has been shown in human studies that , even after 21 days of glutamine deficient TPN, the duodenal mucosa remains intact [99], in animal models, TPN has been demonstrated to lead to atrophy of the gut mucosa [100], and increased bacterial translocation [101].

It is thought that enteral nutrition may actually enhance splanchnic blood flow, maintain mucosal integrity and reduce bacterial translocation [102], although this too is not without adverse effects. Enteral feeding neutralises gastric acid and the number of Gram negative bacteria has been shown to increase following the institution of this form of feeding [58]. Contamination of the enteral feeding solution at the time of preparation may explain some instances, but a number of mechanisms may be invoked: the gastrointestinal motility in the critically ill is often disturbed and, although there may not be a paralytic ileus, very often gastric emptying is delayed, reverse peristalsis may occur with refluxing of more contaminated lower intestinal contents to the usually less contaminated upper gastrointestinal tract, thus predisposing to the colonisation of the stomach. The aspiration of feeds and secretions, in varying quantities, is not an uncommon occurrence even in normals [53] and occurs still more often in the critically ill, particularly in patients with endotracheal tubes or tracheostomies. It has been recommended that enteral feeding should be conducted according to more "physiological" guide-lines, and intermittently, rather than continuously, to allow periods of "natural" sterilisation when the gastric pH may return to lower levels [103].

The above supposed advantages of enteral feeding have resulted in the placement of nasoduodenal or nasojejunal tubes being currently highly favoured, as they may

facilitate the earlier institution of enteral feeding in patients with postoperative ileus, which tends to affect mainly the stomach and colon.

3.6 Wound infections

By breaching the epithelium and thus host defences, all wounds are at risk of colonisation and infection in the ways which have been outlined above. The pathogenesis of drip-site and other intravenous cannulae-associated infection has been dealt with in considerable detail, but more especially with regard to the importance that this has in the pathogenesis of bacteraemia and disseminated infection. In this section, the pathogenesis of wound infection as relates to the local wound site will be discussed, but the prevention of these infections will be dealt with under the section on prophylaxis.

In spite of improved techniques of disinfection and asepsis, wound infections have not been eliminated. The efficacy of antimicrobial prophylaxis in certain forms of high risk surgery and the importance of its timing have been well established for many years, but the optimal timing, choice of antibiotic and the dose still remain to be determined.

It seems that wound contamination by bacteria is an inevitable phenomenon, but with strict techniques of asepsis, wound infection is not a sine qua non. The host's defences against infection as previously described can often withstand heavy contamination and resist the development of infection. It is when the host's immune defences are compromised, such as with diabetes mellitus, malnutrition, obesity and age, or the bacterial load or virulence is too great, or the essential homeostatic balance of factors is too severely disrupted that infection ensues.

The presence of traumatised or devitalised tissue, foreign material or haematomas - all factors dependant on the severity of the injury and the skill of the operator, predispose to infection by providing conditions suitable for bacterial colonisation and infection. The direct inoculation of the wound with bacteria may occur from the patient's own

skin as more deeply seated bacteria lodging in sebaceous glands and hair follicles may persist even after skin disinfection, such organisms may commonly be carried into the wound by the scalpel and result in deep wound infection; from the staff Eg the nasal carriage of staphylococci is a well recognised reservoir of organisms identified as important in wound infections; contaminated surgical instruments or material should rarely be a problem, but the presence of already contaminated or infected sites for surgery are a common and important risk factor for wound sepsis, particularly when the abdomen and especially the colon is entered.

The importance of airborne infection has been demonstrated by the dramatic reduction in postoperative sepsis associated with such "clean surgery" as joint replacements under conditions of laminar flow. Even with extreme care, malfunctioning of air-conditioning equipment, or the contamination of the fomites, clothing or skin of the staff may occasionally result in contamination of the wound.

Other mechanisms for bacterial colonisation of the wound include the haematogenous seeding of organisms to the site from intravenous catheters, or other infected sites; however, this is very unusual. Following on from surgery, the drain and irrigation sites may rarely become sufficiently colonised by microorganisms to allow contamination and infection of the wound to occur.

The colonisation of the wound by resistant organisms may be enhanced by the concomitant use of antibiotics, presumably because the sensitive ones are removed which allows uninhibited proliferation - as has previously been described to occur at other sites.

CHAPTER 4. THE DIAGNOSIS OF INFECTION

4.1 Nosocomial Pneumonia

The true incidence and importance of nosocomial pneumonia in the intensive care unit are difficult to assess, as the diagnosis of nosocomial pneumonia in a patient on a ventilator in the ICU, particularly the patient who already has widespread infiltrates on the chest radiograph, is anything but simple [37,104]. The clinical parameters of pyrexia and leukocytosis may be present for a variety of other reasons, or absent through diminished host responsiveness from immunosuppression or severe illness. Purulent secretions may be the result of local inflammation caused by the endotracheal tube and, similarly, worsening hypoxaemia and a new pulmonary infiltrate on the chest radiograph, may be due to a number of other causes. Thus although the clinical features are necessary to make the diagnosis, microbiological parameters need to be taken into consideration.

The problem of diagnosis is further compounded in patients with adult respiratory distress syndrome (ARDS) from possible unknown and undiagnosed sites of sepsis, tissue trauma, fluid imbalance, myocardial depression or dysfunction, or other causes of increased capillary permeability - all of which are well known to cause changes on the chest radiograph which can be indistinguishable from pneumonia. Andrews [105] and co-workers showed that 29% of cases of ARDS were misdiagnosed as ventilator associated pneumonia and that 36% of patients who, clinically were thought only to have ARDS, had been misdiagnosed, and were shown at autopsy to have pneumonia.

The usual triad of a new radiographic infiltrate, fever, and leukocytosis which have developed in hospital serves to initiate a diagnostic sequence common to most clinicians: the patient's sputum is Gram stained and cultured, simultaneous blood cultures are taken, and pleural fluid if present, is examined as another potential culture site . A positive blood culture occurs in only 24% of nosocomial pneumonias

[37,104,106], so that although specific, it is usually unhelpful, and the frequency of pleural isolation of a pathogenic organisms is even less common [106].

The culture of the sputum or tracheal aspirate is also difficult to interpret, as it may be colonised by potentially pathogenic microorganisms - 45% of patients in the ICU and 80% of intubated patients are colonised by Gram negative bacilli after four days - which may or may not be causing infection , so that, while giving an indication of the colonising flora of the lower airway, it is more difficult to decide whether these organisms are the aetiological agent particularly in the intubated, ventilated patient.[104]

Quantitative cultures of tracheal aspirates have been shown by Johanson et al [5] to be of no value in distinguishing colonisation from pneumonia. The presence of pus cells in the tracheal aspirate, in association with microorganisms, is helpful in suggesting that infection may be present, but even this is not diagnostic [107]. Torres and co-workers [108] showed the specificity of endotracheal aspiration to be 14%.

These diagnostic dilemmas have partially been resolved by the introduction of invasive techniques attempting to eliminate the problem of contaminating organisms, particularly in the patient who is intubated.

A recent Consensus Conference on the Clinical Investigation of Ventilator-Associated Pneumonia [109,110] highlighted the recognised shortcomings in achieving an accurate diagnosis of nosocomial respiratory tract infection in the critically ill, and even deficiencies in the term "nosocomial pneumonia". While Johanson [5] had previously shown that 50% of patients required 4 days for nosocomial colonisation to have occurred, some studies have used either 48 or 72 hours only. It was proposed that nosocomial pneumonia should be divided into early-onset (<48 hours following intubation and ventilation), and late onset (>48 hours) [111]. This is certainly not what has previously been understood by the use of these terms, where infections occurring within 48 hours were regarded as being community-acquired,

while infections occurring within the first 5 days were likely to be caused by a spectrum of organisms intermediate between those causing either community or hospital-acquired infection; infections occurring after 5 days being recognised to be largely caused by hospital pathogens. Thus, this definition itself is controversial, and may not be widely adopted until the pathogenetic mechanisms are further elucidated.

The conference also highlighted the fact that risks for the development of pneumonia varied among different patient populations within the ICU, which might affect the diagnostic approach selected, and the results obtained. A further confounding factor was the use of antibiotic therapy prior to microbiological investigation, which might result in false negative results by preventing the growth of microorganisms, or false positives through enhancing colonisation of the lower airway. Chastre [112] had previously reported the adverse effects of prior administration of antibiotics on the diagnostic accuracy of specimens taken with the protected specimen brush, but there is little other documentation in the literature to support this. It was proposed that in the future, the prior use of antibiotics and its timing should be recorded and reported, so that any potential effects could be more adequately assessed.

4.1.1 **Invasive Diagnostic Procedures**

1). Trans- tracheal aspirate

The use of the trans-tracheal aspirate for obtaining tracheal secretions is a well established, although infrequently used diagnostic technique for obtaining a sputum to assist in the microbiological diagnosis of pneumonia in the non-intubated patient. Its use is thought to be indicated in cases where no sputum is being produced, where there is no clear predominance of a potential pathogen on sputum Gram stain or culture, or there has been a failure of response to antibiotic therapy selected on the basis of a Gram stain of the sputum. Although there is less contamination of the sputum by oropharyngeal organisms in the specimen obtained in this way [113], a false negative rate

for diagnosis of up to 11% and a false positive rate of up to 21% due to oropharyngeal contamination or tracheobronchial colonisation have been reported, particularly in patients with chronic obstructive airways disease [114].

While this technique is generally accepted as providing a more representative and uncontaminated sample of the flora infecting or colonising the lower airway than a conventionally obtained sputum sample, it is nevertheless not widely used, because of the significant complications that have been associated with the procedure. Well recognised complications of this procedure include: haemoptysis, subcutaneous and mediastinal emphysema, soft tissue infection, pneumothoraces, and vagal stimulation, with the resultant potentially life-threatening complications of bradycardia and cardiorespiratory arrest. In the light of the above, the trans-tracheal aspirate should be strictly reserved for carefully selected patients who are unlikely to cough violently and able to co-operate fully. It should probably not be used at all in the in the critically ill patient in the ICU, where

there is a high prevalence of coagulation abnormalities, impaired levels of consciousness, hypoxaemia and hypercapnoea, which predispose to vagal disturbances.

2) Fibreoptic Bronchoscopy

The problem of specificity in the diagnosis of nosocomial pneumonia is not resolved by the use of fibreoptic bronchoscopy. While the use of this procedure permits aspiration of secretions directly from the infected site, and might thus be expected to provide greater sensitivity and specificity, contamination of the inner channel of the bronchoscope occurs during instrumentation of the upper airway, so that isolates obtained by this method are polymicrobial and representative of the microbial flora of the oropharynx and upper airway, as shown by Bartlett et al [113].

Techniques to circumvent this problem, have involved the development of different methods of obtaining specimens with protected catheters and brushes. These include:

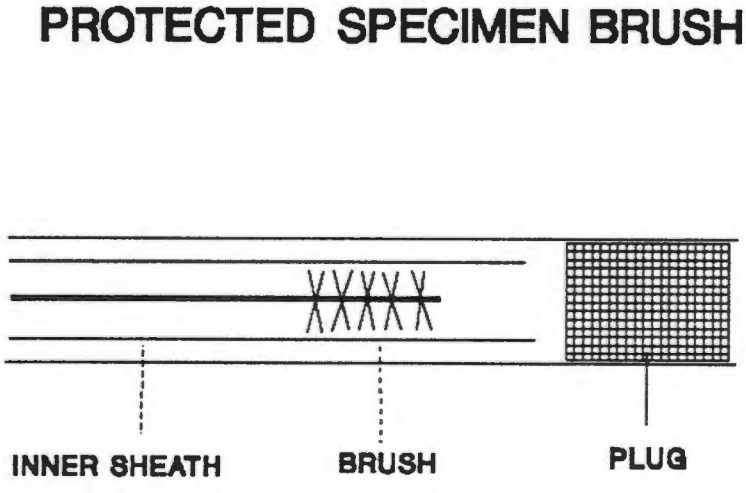
brushes within unplugged sheaths, plugged sheaths (plugged telescoping catheter) and double catheter plugged sheaths (protected specimen brush). Similar catheter designs have been used for segmental lavage. Guide-lines for the most appropriate and safest techniques for the investigation of nosocomial pneumonia, in order to standardise the way such procedures are performed and the manner in which the specimens are processed, were outlined at the recent Consensus Conference on Ventilator-Associated Pneumonia [115,116].

The most common clinical complication associated with diagnostic fibreoptic bronchoscopy in patients receiving mechanical ventilation, is a drop in their arterial oxygen saturation which may persist for as long as two hours after the procedure. This is particularly common in those in whom it is most difficult to achieve adequate oxygenation eg patients with adult respiratory distress syndrome, or in those who fight the ventilator during the procedure. The size of the endotracheal tube in relation to the size of the bronchoscope is important in limiting ventilation. Other potential complications include bleeding following use of the protected specimen brush, arrhythmias, transient worsening of pulmonary infiltrates and fever possibly related to cytokine release and more commonly associated with bronchoalveolar lavage [115].

2.1) Fibreoptic bronchoscopy with brushings

Wimberley et al [117] tested 7 types of brush catheter, in vitro, to determine the optimal catheter design for obtaining specimens for bacterial culture which are uncontaminated by oropharyngeal flora. Their findings supported the use of a plugged double catheter system (protected specimen brush) both in vitro and in nonventilated patients. The catheter has been designed with a double-walled cannula and a detachable, biodegradable plug at its tip that can be dislodged once the specimen catheter has been placed at the site of suspected infection.

Figure One: The Protected Specimen Brush



The technique for protected specimen brush sampling is as follows: the tip of the bronchoscope is positioned next to the orifice of the sampling area and the catheter advanced 3 cm out of the bronchoscope to avoid collection of pooled secretions on the catheter tip. The inner cannula is protruded to eject the distal carbon wax plug into a large airway, and the catheter is advanced into the desired subsegment. If purulent secretions are visualised, the brush is rotated in them [117]. After sampling, the brush is retracted into the inner cannula and the inner cannula into the outer cannula, and then the catheter is removed from the bronchoscope. A small quantity of brush secretions may be smeared into a sterile slide for a Gram stain, the distal portion of the outer and inner cannula are separately and sequentially wiped clean with 70% alcohol, cut with sterile scissors and discarded. The brush is advanced out and severed with a sterile wire clipper into a container with 1 ml of diluent to avoid drying and rapid loss of bacteria. The specimen is submitted for quantitative culture within 15 minutes.

The use of quantitative bacteriology, previously established in the diagnosis of infections of the urinary tract and infections related to indwelling catheter, has been applied to the interpretation of bronchoscopically obtained brush specimens in ventilated patients. Its use assumes that the bacterial density of pathogens is greater than that of contaminants. Quantitative bacteriology has a sensitivity of approximately 88% and a specificity of greater than 95% [112,118,119] in the diagnosis of pneumonia.

There is no general consensus on the cut-off that should be used in quantitative cultures to make a diagnosis of true pneumonia [118,120]. Prior administration of antibiotics can substantially reduce bacterial counts, and even using the cut-off of 1 000 cfu/ml, there are still a number of false positive results [121]. The decision as to when to treat is still thus not entirely resolved [119].

Chastre et al [112] however confirmed that quantitative cultures obtained from the protective specimen brush in ventilated patients were useful in excluding the diagnosis of pneumonia if the culture yielded < 1 000 colony forming units/ml, and that a yield of > 1 000 cfu/ml could be used "as a guide for antimicrobial therapy", by comparing the results obtained by this method with histologic and bacteriologic examinations of pulmonary specimens taken just after death while the ventilator was still working.

Further studies, using the protected specimen brush in ventilated patients suspected of having nosocomial pneumonia because of the presence of a new pulmonary infiltrate and purulent secretions, confirmed the value of the quantitative culture technique, but reaffirmed the unreliability of clinical evaluation in making this diagnosis [118,122-124]. However, using the same technique, Torzillo et al [120] experienced complications of pneumothorax in 8% of cases - a similar incidence to that reported with ultrathin needle aspiration [125], although such complications occurred at an early stage on the "learning curve".

Ha Pham and co-workers [126] compared the plugged telescoping catheter with the protected specimen brush and found the plugged telescoping catheter to be at least as accurate in the bacteriological diagnosis (sensitivity and specificity of 100 and 94.8% when excluding uncertain cases and 100 and 82.2% when all such cases as false positives were included), and substantially cheaper. The catheter that they evaluated has a single protective sealed sheath in comparison with the protected specimen brush which is double-sheathed. They suggest that the protective specimen brush has a high specificity but that it is of suboptimal sensitivity in the clinical setting (64.7% in their study). Although the technique has been used "blindly", most investigators recommend that it should be done under visual guidance, however Ha Pham et al were able to demonstrate that blinded sampling with the protected telescoping catheter was as accurate as directed sampling via bronchoscopy.

Bates et al [127] attempted to analyse the microbial aetiology of 198 patients with acute pneumonia - both community and hospital acquired, using clinical, radiological and microbiological criteria. A diagnosis was only achieved in 50% of patients, despite a whole armamentarium of special investigations. The protected specimen brush was successful in only 38% of the patients in whom it was used, a figure which they considered highly satisfactory, particularly because confirmation was obtained "in 8% of such cases" where the same organism was isolated from both the brush and blood cultures. In those who went on to post-mortem, identification of the pathogen had been made ante-mortem in 40%; an additional bacteriological diagnosis was made at autopsy in 15% (aspergillosis in one and tuberculosis in two), while the remainder were found to have non-infective pathology. Most clinicians would consider this yield unacceptably low.

In patients with bronchial structural abnormalities, who require prolonged intubation, or who are receiving antibiotics, the rates of both false positive and false negative results with the protected specimen brush may vary between 10 and 30% [126].

The above clinical studies would certainly support the use of the protected specimen brush to obtain the most reliable specimens, short of open lung biopsy, in patients who are intubated. The poor sensitivity of the techniques (38-60%) does however limit the role of this technique when deciding whether to treat a pneumonia. Fibreoptic bronchoscopy with the protected specimen brush is also an expensive and time consuming procedure. Similar results with less specificity are obtained with the single sheathed, plugged telescoping catheter.

The recent consensus conference on ventilator-associated pneumonia felt that "the literature does not provide criteria to assess the adequacy of a protected specimen brush specimen" [115]. They recommended that a value of > 1000 colony forming units/ml should be considered a significant level for bacterial nosocomial pneumonia; a positive Gram's stain is suggestive of pneumonia, but a negative microscopic analysis should not be considered definitive for the absence of pneumonia. The main factor confounding the interpretation of results was felt to be the effect of prior antibiotic therapy, and it was recommended that specimens should be taken prior to the commencement of therapy if at all possible, or after therapy had been discontinued for at least 48 hours. A patient with pneumonia might have a negative bronchoscopic yield if the investigation was performed too early in the infection for the bacterial burden to have achieved diagnostic significance; if an unaffected segment was sampled; the interval without antibiotic therapy was too short, or the processing of the specimen was incorrectly performed.

2.2) Fibreoptic Bronchoscopy with Bronchoalveolar Lavage

Bronchoalveolar lavage is another technique which has proved useful and safe for diagnosing pulmonary infections both in immunocompromised and immunocompetent patients [128]. Quantitative culture of bronchoalveolar lavage in baboons with nosocomial pneumonia was shown by Johanson to correlate better than telescoping plugged catheter specimens with lung culture, suggesting that, in this model at least, it

was a more sensitive diagnostic procedure [129]. Studies in man suggest that quantitative cultures of bronchoalveolar lavage are as reliable as quantitative cultures of telescoping plugged catheters for the diagnosis of bacterial pneumonias in mechanically ventilated patients [108] and provide a more rapid aetiological diagnosis, as Gram staining of the fluid can be performed immediately while the quantitative culture requires 24 to 48 hours to give a result [121].

Bronchoalveolar lavage is obtained by infusion and aspiration of a sterile physiologic solution through a flexible bronchoscope wedged into a bronchial subsegment. The amount of fluid injected for the assessment of infectious lung disorders has not been standardised, and amounts in various studies have ranged between 100 to 240 ml. At least 120 ml are necessary for retrieving secretions from the periphery of the lung subsegment [115]. When evaluating the results of this technique, the recent consensus was that the percentage of retrieved fluid should be recorded, excluding the first aliquot; that the presence and degree of haemorrhage should be noted, and that the location of the sampling in relation to radiographic infiltrate and presence of endobronchial pus should be noted. At least 5 ml of retrieved fluid is necessary for adequate microscopic and microbiological analysis. A level of > 10 000 colony forming units/ml is currently recommended as a significant level for bacterial ventilator-associated pneumonia [115].

The theoretical advantages of such a technique are that in comparison to the protected specimen brush, a larger and more representative area of lung can be sampled which is less dependant on the accurate placement of the brush and the quantity of secretions obtained is greater and less dilute, there is also much less risk of pneumothorax [128]. However, contamination with a properly taken protected specimen brush should be minimal and 89% of lavage specimens are contaminated in patients without pneumonia.

Both techniques have advantages and disadvantages and Chastre et al [121] found them to be complementary with the accuracy of the telescoping catheter far outweighing lavage, which nonetheless had a place by providing a rapid answer.

Further studies have been directed to improving the specificity of lavage or reducing the invasiveness of the technique to make the diagnosis. Meduri et al [130,131] performed protected bronchoalveolar lavage through a transbronchoscopic balloon-tipped catheter with a distal ejectable diaphragm for collecting distal respiratory tract secretions with a minimal degree of contamination. The sensitivity and positive predictive value of this technique was 100% and by using a quantitative culture count, it was possible to differentiate between patients with and without pneumonia more easily than with unprotected bronchoalveolar lavage; the technique was also thought to be superior in recovering organisms. In an editorial Johanson [132] welcomed the development of this technique with its seeming improved efficacy and specificity, particularly as, the broad representation of the microbial flora obtained by bronchoalveolar lavage directly from the alveolar surface with the use of this more specific technique provided refinement and rapid diagnosis. However, more experience with this technique is still required.

Pugin and co-workers [133] compared bronchoscopically obtained bronchoalveolar lavage with quantitative culture which was able to yield a sensitivity of 93% and specificity of 100%, with "blind" lavage sampling - by introducing a catheter blindly down the bronchial tree - which yielded results of lower sensitivity of 73% and specificity of 96%, but at considerably lower cost and with greater ease; this degree of diagnostic accuracy is still felt to be highly acceptable, especially if same day Gram staining provides rapid diagnosis.

2.3) Assay of Endotoxin in Bronchoalveolar lavage fluid for the rapid diagnosis of Gram negative pneumonia.

Pugin et al [134] reported recently the use of the limulus assay as a rapid diagnostic technique to quantify the endotoxin content of lavage fluid. They demonstrated a relationship between the concentration of endotoxin in the lavage fluid and the quantity of Gram negative bacteria. While 24 to 48 hours are required for the full microbiological processing of bronchoalveolar lavage and protected specimen brushings, this assay for endotoxin takes less than 2 hours and is specific and easy to perform. The authors suggest that as the causative organisms are likely to be aerobic Gram negative bacteria in more than 80% of cases of nosocomial pneumonia, there is place for such a technique which should allow the institution of earlier and more specific treatment.

While confirming that the pneumonia is Gram negative in aetiology, however, such a technique does not provide any further assistance in the specific aetiologic diagnosis of infection, nor in assisting in the choice of an antibiotic. In most instances where a nosocomial lower respiratory tract infection was diagnosed, Gram negative organisms would naturally form a large part of the differential and cognisance taken of this, when selecting a choice of antibiotic cover, while diagnostic results were awaited. The absence of endotoxin might potentially of more value in differentiating a staphylococcal or fungal pneumonia and might conceivably reduce the use of potentially harmful, or nephrotoxic antibiotics such as the aminoglycosides. Whether there is any place for the routine assay for endotoxin in the diagnosis of nosocomial pneumonia is doubtful.

3) "Blind" catheters

In centres where fibreoptic bronchoscopy is not available, Torres et al [119] were able to show that the use of the Metras catheter, used for bronchography, which has a radio-opaque tip and is introduced under radiographic screening, has specificity and

sensitivity similar to the plugged telescoping catheter or protected specimen brush, and is considerably cheaper.

4) Percutaneous needle aspiration

The technique of needle aspiration through the chest wall obviates the potential contamination from the upper airway and thus may be highly specific, however its sensitivity is dependent on the precise localisation of the involved area and the small inoculum volume obtained for microbiologic examination and thus may be much lower[125]. There is also a high risk of life-threatening pneumothorax in ventilated patients which considerably restricts its use [104,135], and although the use of ultrathin needles seems to reduce the risk of pneumothorax to a level of 8% without compromising on sensitivity in the study reported by Zavala et al [125], this incidence is still too high for the procedure to have a place as a routine diagnostic modality in ventilated patients.

5) Antibody- coated bacteria

Another technique used to distinguish between colonisation of the airway and lower respiratory tract infection in intubated patients is to measure the presence of antibody-coated bacteria. This technique was first pioneered by Winterbauer [106] who demonstrated that the detection of antibody coated bacteria in secretions obtained at bronchoscopy was 98% specific and 73% sensitive for the diagnosis of pneumonia in nonintubated patients. Wunderink et al [136] applied this technique to the tracheal aspirate in the intubated patient, where it was shown to retain a specificity of 100% and a sensitivity of 43%; importantly, patients with chronic bronchitis do not test positive by this method. The prior use of antibiotics tended to produce a negative result which they postulated to be due to the disruption of the bacterial cell wall affecting antibody binding sites. The presence of a positive test may furthermore be predictive of the development of a lower respiratory tract infection.

This technique appears to be still in its infancy and further studies using more rigourous diagnostic criteria than the largely clinical ones used by Wunderink are required before it can be established as a reliable diagnostic tool in diagnosing nosocomial pneumonia.

6) Identification of Elastin Fibres

Salata et al [137] studied intubated patients for evidence of pneumonia and found that serial examination of tracheal aspirates for elastin fibres and graded Gram's stains for neutrophils, bacteria and intracellular organisms were useful for the early diagnosis of nosocomial pneumonia. The presence of elastin fibres preceded pulmonary infiltrates by over 24 hours and had a positive predictive value of 100%, a specificity of 73%, and a sensitivity of 52% for infection.

The technique of using elastin fibres as a marker for necrotising pulmonary infection was first described by Schroeder in 1846, is simple to perform and apparently requires little expertise to interpret. The authors suggest that Gram negative pneumonias are

more likely to be necrotising and cause breakdown, which explains the low sensitivity of this technique. Certainly there is much to recommend it in being a useful, non-invasive, cheap, additional modality which seems to predict the development of pneumonia relatively early.

7) The Radiologic Diagnosis

Although much emphasis is placed on the value of daily chest radiology in the ICU to check line and tube placement, the presence of pneumothoraces, atelectasis, and the development and progression of pneumonia or ARDS, this technique is also subject to great inaccuracy in the critically ill patient, particularly in the presence of ARDS. Despite the inherent inaccuracies associated with the generally poor quality mobile anteroposterior film, the presence of a new or changing pulmonary infiltrate on the chest radiograph is required as a diagnostic criterion by virtually all studies of pneumonia.

Wunderink et al [138] confirmed that the extrapolation of roentgenographic criteria for the diagnosis of nosocomial pneumonia from those employed for the diagnosis of community-acquired pneumonia, were as unreliable as the clinical criteria used for its diagnosis. They evaluated the diagnostic accuracy of seven roentgenographic signs of pneumonia (air-bronchograms, alveolar infiltrates, silhouette sign, cavities, fissure abutment, atelectasis, and asymmetric infiltrates superimposed on diffuse bilateral infiltrates), in the portable antero-posterior film, obtained in the ventilated patient. The last film obtained antemortem in 69 ventilated patients was interpreted by three reviewers and the signs were then correlated with the findings at autopsy. Pneumonia was found to be present at 35% of autopsies, but no radiographic sign had a diagnostic efficiency of more than 68%, and the air-bronchogram was the only sign that correlated with pneumonia in the total group, and correctly predicted 64% of pneumonias. They found that in patients with ARDS only the clinical parameter of purulent sputum, but no roentgenographic feature, correlated with pneumonia. Worsening alveolar infiltrates

were found to be more commonly due to ARDS than pneumonia. Alveolar haemorrhage was detected in 38% of autopsies, associated with 29% of multiple air bronchograms and 30% of bilateral alveolar infiltrates in patients without pneumonia.

At the consensus conference on ventilator-associated pneumonia [139], guide-lines for the reading of the chest radiograph were proposed. The inherent diagnostic shortcomings of the mobile chest film were acknowledged, and it was recommended that radiographs should be assigned scores on the certainty of the diagnosis; that serial radiographs should be reviewed independently by readers and then a consensus achieved. The role of computerised tomography in ventilated patients remains unclear, through paucity of reports and limited experience, but should probably be expanded to determine the risk benefit ratio.

4.1.2 Clinical Application of Diagnostic Procedures

Nosocomial pneumonia occurs in 0.5 to 5% of all hospital admissions and is responsible for 15% of hospital deaths; however in the ICU it is still more important, as depending on the population of patients, up to 60% may develop pneumonia depending on the severity of their underlying disease [104].

Several criteria have been used to establish a clinical diagnosis of nosocomial lower respiratory tract infection. Johanson[5] et al classified pneumonia as definite when a patient had the appearance of a new or progressive infiltrate on the chest X-ray, fever, leukocytosis, and purulent tracheobronchial secretions. The diagnosis was probable if either the radiographic features or the tracheal secretions were missing. Craven [30] et al required in addition to the above, a sputum Gram stain showing more than 25 leukocytes and less than 10 squamous epithelial cells per low power field, with the recovery of a significant pathogen by stain or culture.

Such criteria in a previously healthy person free of lung disease should indicate pneumonia, but as discussed above, in the mechanically ventilated patient many other disease processes can obscure or mimic the clinical picture such as chemical aspiration, ARDS, atelectasis, pulmonary emboli, lung contusion, haemorrhage, pulmonary oedema or tumour. Pneumonia is frequently missed in patients with ARDS, but overdiagnosed in patients with respiratory failure from other causes[105,122].

Sputum analysis by Gram stain has been used in the diagnosis of pneumonia for generations, but its diagnostic value in nosocomial pneumonia is limited. Bartlett et al [140] prospectively studied patients with nosocomial pneumonia using trans-tracheal aspirates, pleural fluid and blood for microbiological specimens and showed that, even with uncontaminated samples, there was a high rate of mixed organisms obtained with more than one potential pathogen. There was an incidence of 10% false positive results for *Staphylococcus aureus* and Gram negative bacilli were recovered from 45% of

patients who did not have these organisms growing in the reliable uncontaminated specimen. In our own ICU [141], we reported a diagnostic yield of 48% from sputum or tracheal aspirate, 10% from positive blood culture, only 3% from protected specimen brush, with no microbiological diagnosis being achieved in 48% of cases. Fagon[123] and others found similar polymicrobial growth in up to 40% of cases in specimens taken with the protected specimen brush. This may, in some instances, explain the lack of response when treatment of the predominant organism is attempted. Johanson et al [129] developed the bacterial index to deal with the problem of polymicrobial growth on lung homogenates, because many specimens contained multiple organisms. The bacterial concentration was expressed as the sum of the logarithmic concentrations of the individual species; the bacterial index values of bronchoalveolar lavage were linearly related to tissue values. Such a system has been carried over into analysing bronchoalveolar lavage systems and although it has not been applied to sputum, it begs the question as to which organisms are the significant ones.

In an attempt to achieve a more accurate and reliable clinical diagnosis of lower respiratory tract infection, Pugin et al [142] recently described a "clinical pulmonary infection score". They utilised six clinical parameters:

Table One: Clinical Pulmonary Infection Score:

Parameter	**Normal**	**Slightly abnormal**	**Very abnormal**
Points	**0**	**1**	**2**
Temperature	36.5 - 38.4	38.5-38.9	> 39 or < 36
White cell count	>4 or <11	<4 or >11 bandforms0.5	
Tracheal secretions*	<14 "+"	≥14 "+" purulent	
Oxygenation PaO2/FiO2mmHg	>240 or ARDS	ARDS	<240 and no
Chest X-ray	no infiltrate	diffuse	localised
Bacteriology semiquant 0-1-2or3	<1+	pathogenic bacteria cultured >1+ >1+ same pathogen on Gram	

* The purulence and quantity of tracheal secretions were estimated by the for each endotracheal aspiration by the nurses on a score from 0 to 4 "pluses"; estimation of the total volume of secretions per day was calculated by adding together all of the pluses recorded over 24 hours.

Table One: A Clinical Pulmonary Infection Score for determining the likelihood of a Pulmonary Infection being a Pneumonia The score has a range from 0 to 12 points, and ventilator pneumonia was diagnosed when the score reached 7 and remained elevated ie ≥ 7 for 3 or more days. (Pugin et al [142]).

Unfortunately the use of such a score does not "guarantee" that the patient will unequivocally have nosocomial pneumonia; while it may serve to encourage a methodical approach to the diagnosis and alert the clinician to early changes, it would not be too difficult to score over 7 and have a site of sepsis elsewhere.

When the blood culture is positive, it can serve to provide a precise aetiologic agent, but its presence in association with a pulmonary infiltrate on the radiograph and respiratory failure is not confirmatory proof of pneumonia; Fagon showed an extrapulmonary source of the bacteraemia in 58% with an overall incidence of bacteraemia in ventilator associated pneumonia of 24% [122].

At the Consensus Conference [111] the clinical criteria for a definite diagnosis of pneumonia were defined as a new or persistent infiltrate on the chest radiograph, associated with purulent tracheal secretions and one of the following: 1. radiographic evidence (preferably CT) of pulmonary abscess and positive needle aspirate culture from the abscess. 2. pathogenic evidence of pneumonia on histologic examination of lung tissue obtained by open-lung biopsy or at a post-mortem examination immediately after death that demonstrates abscess formation or an area of consolidation that demonstrates intense polymorphonuclear leukocyte accumulation plus a positive quantitative culture of lung parenchyma ($>$ 10 000 microorganisms per gram of lung tissue). When used to confirm the diagnosis of pneumonia made by bronchoscopy, the

lung tissue for histological examination and culture should have been obtained within three days of the bronchoscopic procedure.

In the absence of any of the above, a diagnosis of "probable pneumonia" may be made if the patient meets the clinical criteria for suspicion of ventilator-associated pneumonia, by the presence of new or persistent pulmonary infiltrate, purulent tracheal secretions, and demonstrates one of the following:

1. the presence of positive quantitative culture of a sample of secretions from the lower respiratory tract obtained by a technique that minimised contamination by the upper respiratory tract flora eg protected specimen brush, bronchoalveoalar lavage or protected bronchoalveolar lavage.
2. the presence of positive blood culture unrelated to another source and obtained within 48 hours before and after respiratory sampling. The microorganism should be identical to the organisms recovered from culture of the lower respiratory tract secretions.
3. the presence of positive pleural fluid culture in the absence of previous pleural instrumentation.
4. the presence of pathologic evidence of pneumonia on histologic examination of lung tissue obtained by open-lung biopsy or at a post-mortem examination immediately after death that demonstrates abscess formation, or an area of consolidation with intense polymorphonuclear accumulation and a negative quantitative culture of lung parenchyma.

Criteria for the absence of pneumonia were equally complex [111].

The accuracy of a careful clinical assessment versus the results of protected specimen brush culture obtained with bronchoscopy was assessed by Fagon et al in a prospective study of patients receiving mechanical ventilation, who had developed purulent tracheal secretions and a new infiltrate on the chest radiograph. A team of seven physicians was asked to establish the presence, or absence of pneumonia, and to decide on a

therapeutic intervention based on clinical, radiological and laboratory data and Gram stain of the tracheal aspirate. The accuracy of the clinical predictors was 74% for patients with pneumonia, but the therapeutic plans were inappropriate in 58%, because antibiotics were not used, or the organisms responsible were insensitive to the agents that were selected[143].

The endpoints for the definition of infection are important and difficult. Much of the difference in incidence in infection quoted in the literature is as a result of this area being subjective and unstandardised. The imprecision depends on whether the definition is made by a clinician or a microbiologist, how invasively the specimens are taken, and the sophistication of the sampling procedure or imaging technique employed.

The importance of regular microbiological surveillance is not mentioned in any of the articles reviewed above, but is doubtless an important factor in deciding whether infection is developing, and what the organism is most likely to be. When the tracheal aspirate has been relatively clear and uninfected, macroscopically and microscopically, with a mixed growth only on culture of surveillance samples, in a patient with no evidence clinically of infection, it is not difficult to recognise that pneumonia is unlikely to be present. When suddenly the aspirate starts to become purulent and a predominant organism is cultured or seen on the Gram stain, in association with a clinical deterioration in the patient's condition and no other obvious source of infection; the chest is the most likely site of infection. It is reasonable to treat with agents to which the organism has been shown to be sensitive, or that the antibiotic profile of such an organism is likely to be, considering the local ICU flora. Even when there is no radiological evidence of pulmonary infiltrate - what we recognise as a "bronchial infection" - such clinical features warrant treatment in the anticipation as, unchecked, this bronchial infection will progress into a full-blown pneumonia, with all the associated risks of multiple organ dysfunction associated with severe sepsis.

A specimen obtained with the protected specimen brush at bronchoscopy, should be taken if the pneumonia fails to respond or progresses rapidly, without another cause to explain the failure of the underlying disease process to resolve. This should be performed under fluoroscopic screening, if the patient is stable enough to be moved to such a facility, to confirm accurate localisation and allow transbronchial biopsies to be taken, if indicated, with minimal risk of pneumothorax. Bronchoalveolar lavage for culture may be performed at the same time.

In the ICU, techniques such as transthoracic, transbronchial and open lung biopsies are generally reserved for immunocompromised patients and for those with suspected interstitial or vasculitic lung disease, where it is considered that the potential benefits outweigh the morbidity and mortality associated with such invasive procedures.

Pleural fluid, if present, may be sampled by fine needle aspirate and then drained formally in the ventilated patient, rather than by needle aspirate, to obviate the potential risk of a pneumothorax.

Serological screening for the "atypical pneumonias" eg *Mycoplasma pneumoniae*, *Legionella pneumophilia* and *Chlamydia pneumoniae* should also be performed where there is clinical suspicion, or failure to respond to conventional antibiotic therapy occurs.

The above is our local practice in the investigation of the critically ill patient suspected of having a nosocomial pneumonia. It is not specifically designed to be a protocol to deal with the investigation of the severely immunocompromised patient, however, this is beyond the scope of this thesis.

The potential toxicity caused by the unnecessary administration of antibiotics, together with their cost , as well as the projected costs of unnecessarily treating many patients who do not have pneumonia, have been argued to justify the routine use of invasive diagnostic techniques, which have been shown to be of high sensitivity and specificity.

The place of the protected specimen brush remains controversial however, as the estimates of cost-saving of antibiotics do not hold true until treatment has been withheld for 5 days. Missing only a few cases of pneumonia by this procedure would immediately increase costs and worsen the outcome, as delayed therapy, with the resultant prolongation of hospital stay, would then have to be added to the cost of the procedure. Thus, with the high morbidity and mortality of nosocomial pneumonia, it is preferable to err on the side of overtreatment than overbrushing.

The more discriminating invasive diagnostic tests do however have an important role in clinical studies designed to determine the incidence and aetiology of nosocomial pneumonia; they also have an invaluable role in evaluating the efficacy of new antimicrobial agents and therapeutic strategies, particularly in unblinded studies. Nevertheless there are the same drawbacks in their interpretation: the expertise of the bronchoscopist, the sophistication and standards of the laboratory, the agreed cut-off for the distinction between colonisation and infection by quantitative culture all impact on the results, and such information is seldom likely to be provided in the literature.

The diagnosis of nosocomial pneumonia is elusive, and its incidence at present depends on the resources, thoroughness and invasiveness with which the investigator/clinician wants to pursue it. The literature therefore needs to be interpreted with some caution and scepticism. While the early clinical recognition and diagnosis of infection is obviously desirable, and whether it is a bronchial or truly parenchymal infection may be unimportant, these questions assume greater significance when evaluating clinical trials. At present, the most precise way of achieving a reliable, reproducible, sensitive and specific diagnosis may hinge on the trial design - a double-blind study where selection bias and diagnostic bias are excluded may provide the best answer.

4.2 Nosocomial Urinary Tract Infection

It is only a matter of time for the catheterised patient to develop an associated bacteriuria, but it is slightly more difficult to distinguish between this colonisation and the development of true infection.

The development of bacteriuria depends on the indications for catheterisation to a certain extent: those who are catheterised for short-term management show a peak incidence at two to four days, and those who are catheterised longterm at three to six months or more. Once the catheter is in place, the incidence of bacteriuria is 3-10% per day.

To establish a diagnosis of urinary tract infection, it is generally accepted that the organism concentration should exceed 100 000 colony forming units/ml, which is thought to exclude possible contamination of the urine from the urethra, as it is virtually impossible to sterilise this area. False positives are caused by contamination or incubation of urine before processing. The level of > 100 000 colony forming units/ml applies to the *Enterobacteriaceae* only and Gram positive organisms, fungi and bacteria with fastidious growth requirements may not ever reach these titres, even when causing infection - the concentration being in the range of 10 000 to 100 000/ml.

The nature of the organism that is isolated often helps to distinguish contamination from true bacteriuria; samples with low counts often contain skin contaminants such as diphtheroids and staphylococci, which can generally be disregarded. The culture of a predominant organism or "pure growth" is more suggestive of infection. A pure growth of *Enterobacteriaceae* is uncommonly found in low-titre. A mixed culture with more than 100 000/ml may be difficult to interpret as it may either represent contamination or infection.

The presence of symptoms is often a good guide to whether infection is present. The presence of symptoms is, of course, dependant on the patient being conscious enough to be aware of these. The practice of maintaining adequate analgesia, but keeping the

patient alert and co-operative, where this is possible, is useful in assisting with the diagnosis of urinary tract infection in the ICU. The presence of local or systemic signs such as suprapubic tenderness, a change in the odour or clarity of the urine, the development of pyrexia, fever and rigors, or loin tenderness may also assist in the diagnosis. The presence of symptoms and signs are however notoriously unreliable guides to the presence of urinary tract infections, which may be present with or without them or, in the case of the "urethral syndrome", present without infection.

Samples obtained by catheter from uninfected patients should not be able to become sufficiently contaminated to demonstrate $>100\ 000$ organisms/ml and, in an asymptomatic patient, such a concentration should be considered indicative of infection; the growth of a predominant organism at concentrations between 10 000 and 100 000 is of questionable significance, but probably has a 50% chance of indicating infection. However, within several days of catheterisation - as is likely in the critically ill - most bacteria identified at low concentrations will, over succeeding days, reach the required density to qualify as significant.

Samples taken by suprapubic aspirate should be sterile and the presence of bacteria in lower concentration than obtained from a catheter specimen should still be regarded as diagnostic of infection.

The localisation of the site of infection is also problematic. In the presence of loin pain and typical symptoms of pyelonephritis, it is not difficult to diagnose that the upper urinary tract is involved, but such symptoms may be absent with significant upper tract infection. Although a number of tests involving urinary enzymes, antibodies and antibody coated bacteria have been devised in an attempt to non-invasively detect the presence of renal infection, they are unfortunately unreliable, and at present, only ureteral catheterisation can reliably predict the site of infection.

The presence of white cells in the urine may help to differentiate bacteriuria from infection and more than 10 white cells per high power field is usually indicates the presence of infection. There are a number of other conditions which can result in pyuria, particularly in the critically ill patient, but in the context of significant bacteriuria, this may be a helpful sign.

4.3 Percutaneous Intravascular Device Related Infection

Brun-Buisson et al [90] suggest that there is a continuum between contamination, colonisation and infection involving the intravascular catheter, although ideally the catheter should remain sterile. Unfortunately or fortunately, one of the modalities for proving or disproving that this is the site of sepsis, involves its removal for culture.

The clinical syndrome of intravascular device related sepsis includes the presence of systemic infection with isolation of an organism of the same species and sensitivity pattern, both from the specimen culture obtained from the catheter and from a simultaneous blood culture[87]. If the specimen culture from the catheter is positive, but the patient does not show any clinical or laboratory evidence of sepsis, or peripheral cultures are negative, or if the organism obtained from peripheral cultures differs from organisms grown from the catheter tip, the catheter should be considered to be contaminated or colonised. If the type and sensitivity of the organism cultured from the peripheral blood match that isolated from another infected site, the sepsis should be considered to originate in this other site.

The clinical detection of intravascular catheter related septicaemia, in the presence of bacteraemia occurring in a patient not otherwise at risk for this, may be difficult [90], as signs of phlebitis or local inflammation are often absent; the diagnosis can only made by the exclusion of other sources. Other pointers to the sepsis being line- related include the development of embolic phenomena, the presence of an infection which is characteristically refractory to therapy and which defervesces quite promptly

removal of the intravascular device [80]. The organisms isolated on blood culture may also give some indication of the possible source: *Staphylococcus aureus* or *epidermidis* being typically associated with line related sepsis[89].

Confirmatory evidence may often be found in the semiquantitative culture of the catheter tip yielding more than 15 colonies of bacteria. Cultures of the catheter tip have been reported to be of variable value, but using the semiquantitative culture method, the specificity is reported to vary between 76 and 96%, although there are no sensitivity values given by Maki in the report of this technique[144,145].

There have been other attempts at bacteriological diagnosis using quantitative culture in broth [90], direct Gram staining of the catheter tip, or using blood cultures, taken through the catheter, with the isolator technique [146], which allows a quantitative estimate of the microbiological burden.

There have also been reports of false positive results being obtained by pull-back samples, obtained through the catheter itself. This may depend on the type of access port used and the technique of taking the specimen [145]. Although the method is of uncertain sensitivity and specificity, repeated isolation of the same organism by this technique should not be disregarded, and is an indication for therapy, or possibly that the catheter should be removed[89]. Further adding to the problem is, that a positive result is easily obtained if the removal and processing of the catheter is not done with due care to avoid its being contaminated, by inadequate cleansing of the skin or handling after removal.

Culture of the skin site, if this is inflamed or discharging, is used by some [84], if positive, as an indication for removal, but this study controversially recommends leaving a catheter associated with erythema in situ.

The interpretation of an isolated positive culture, or sporadic positive blood cultures are problematic [94], and cognisance of the associated clinical status needs to be taken [89]. If

there is any doubt that intravascular catheter sepsis may exist, the safest policy is to provide the most effective treatment by removing it, and establishing the diagnosis by both culture of the tip and the clinical response.

CHAPTER 5 THE INCIDENCE OF NOSOCOMIAL INFECTION

The patients in the ICU are the sickest in the hospital, often also being at the extremes of life in terms of age, they are subjected to the most invasive support and monitoring equipment available; they are also nursed in what is usually one of the most crowded locations in the hospital, where they receive more antibiotic therapy during their hospitalisation than any other group of patients; the duration of their hospitalisation is also often prolonged. All these factors contribute significantly to the increased risk that these patients have for developing infection in hospital.

There are four main sites at which nosocomial infection occurs, viz the urinary tract, surgical wounds, the lower respiratory tract and the bloodstream, in that order[147]. In the mid-1970s in the U.S.A., the overall incidence was estimated to be 5.23% of all hospitalised patients: 62% had at least one urinary tract infection, 30% one or more surgical wound infections, 17% nosocomial pneumonia and 7% bacteraemia; 18% had infection at more than one site. However, when the results of those admitted to the Intensive Care Unit are analysed separately, the incidence of infection increases sharply: the risk of urinary tract and surgical wound infection is five times higher, the risk of pneumonia increases twenty-one times in the ventilated patient, and the risk of bacteraemia increases sixteen-fold. The estimated overall incidence in our respiratory ICU was reported to be 23.6% [148].

Differences in the published estimates of the incidence of infection can be explained not only by differing diagnostic criteria, but also by differences in methodological analysis: the incidence can be reported as the crude ratio of the number of patients developing an infection and the number of participating patients [30,149], or this information can be analysed to incorporate the duration of stay during which the patient was exposed to the risk of developing infection in which case the values using the Kaplan-Meier analysis may be much lower [123,150].

There are, of course, various sub-groups especially at risk of specific sites of infection, so that the incidence varies between different ICUs eg medical, surgical, coronary care, neonatal etc., and there are additional risk factors which also determine the likely outcome of such infections - nosocomial pneumonia being recognised to be associated with a particularly high morbidity and mortality [151]. This chapter provides an overview of the incidence of the most important types of nosocomial infection in the ICU.

5.1 Nosocomial Pneumonia

Nosocomial pneumonia, is the third most common hospital-acquired infection, but is associated with the highest mortality [104]. A recent analysis of its incidence over a four year period showed that it accounted for 14% of hospital acquired infections with a case fatality rate of 33% [75]. By comparing a sampled, individually matched cohort, the morbidity as measured by excess hospital stay, was shown to be significantly prolonged.

Only relatively recently have studies of nosocomial pneumonia used techniques for obtaining microbiological specimens that minimise contamination by upper airway secretions; the gold standard for the diagnosis of nosocomial pneumonia probably remains histological examination and quantitative culture of lung biopsy specimens, but techniques such as bronchoscopy with the use of the protected specimen brush, bronchoalveolar lavage, or telescoping plugged catheter specimens have gained acceptance and have been reported to have a sensitivity and specificity between 70% to 100% [119,126,133], using the number of organisms or colony forming units/ml to distinguish between colonisation and infection, with more than 10 000 cfu/ml indicating infection. It has been suggested that the use of cultures of bronchoscopy specimens reduces the estimated incidence of pneumonia in the ICU from 26% to 9% [123], but the associated mortality in excess of 70% suggests that such a technique may perhaps be too highly specific.

Graybill et al [38] , in a classic study in 1973, reported a retrospective analysis of the incidence of nosocomial pneumonia in a general hospital . The diagnostic criteria were purely clinical, or from the patients' records; using sputum or blood culture for the bacteriological diagnosis. They showed that 33% of secondary pneumonias were due to Gram negative bacilli. The study was performed at the time that gentamicin was first introduced for clinical use, and interestingly, they did not find a dramatic improvement in the outcome following this. The mortality for nosocomial pneumonia, particularly if superinfection occurred, being of the order of 50%.

Bryan et al [152] in 1984 studied episodes of bacteraemic nosocomial pneumonia in the general hospital using "standard epidemiologic criteria" for the diagnosis. The incidence was 5% and associated with a mortality of 58%, although such deaths occurred almost exclusively in patients with serious and largely irreversible underlying disease.

Mock et al [153] used an "objective numerical rating system for the assessment of the presence or absence of pneumonia on a chest X-ray film" and a positive sputum culture to assign patients to either colonisation or pneumonia. They concluded that this was a "reasonable" method for separating pneumonic infection, from patients who were merely colonised by bacteria. They added a caveat that all sputum pathogens in patients in the surgical ICU should be covered with antibiotic therapy, which then allowed them to safely conclude that, with the chest X-ray, they were able to diagnose pneumonia in over 50% of their patients, with an associated mortality of 32%.

An evaluation of the incidence of nosocomial infection in our respiratory ICU showed that the incidence of secondary infection was significantly increased in patients admitted following multiple trauma [148], and that patients who were not tracheostomised or intubated did not develop secondary infection; however the diagnostic criteria here differed from other studies, as a nosocomial infection was diagnosed if infection developed 24 hours after admission to the ICU, which may have falsely increased its

incidence. The definitions of infection were otherwise purely clinical and radiological; 86.5% of secondary infections were pulmonary with an overall incidence of 20.4% for nosocomial pneumonia, which is very different from the 50% of the previously mentioned study. Unfortunately Potgieter et al were unable to assess the effect that secondary infections had on morbidity and mortality, although they speculate that infections may have contributed to 17.5% of the deaths.

In a recently published study from Scandinavia, Nielsen et al [154] studied the incidence, aetiolgy and mortality of nosocomial pneumonia in their university hospital medico-surgical ICU. The diagnostic criteria used were clinical and radiological only. The incidence of nosocomial pneumonia in the patients who stayed in the ICU for more than 48 hours was only 10%, but they demonstrated that such patients were predominantly post-surgical, and required more prolonged intubation and ventilation, with a statistically increased duration of ICU stay, as well as a higher mortality of 43% vs 19% in those who did not develop this complication. Again the cause of death was difficult to separate from the presence of severe underlying disease in these patients. Gram negative *Enterobacteriaceae* and *Pseudomonas aeruginosa* accounted for 43% of cases. Patients treated with H-2 blockers were identified as being at greater risk, as were those who were immunosuppressed or had undergone thoracotomy.

Fagon et al [123] in their studies evaluating the protected specimen brush as the new "gold standard" in diagnosis, found an overall incidence of only 9% for nosocomial pneumonia, and showed that this was clearly related to the duration of intubation and ventilation with an actuarial risk of 6.5% at 10 days, which increased to 19% at 20 days and 28% at 30 days. The overall mortality of 71% in this study is far higher than in most reported studies.

Jimenez et al [149] reviewed the incidence and aetiology of pneumonia acquired during mechanical ventilation in their ICU in Barcelona. They also found an increasing incidence with increased duration of ventilation: 23% had developed bacterial

pneumonia after 5.6±1 days, but there were an additional 3 cases who went undiagnosed until autopsy, which increased the incidence to 27% ; the mortality in this study was 38%. The diagnosis of pneumonia in this study was made by a combination of clinical and radiographic parameters and then confirmed with cultures and pathological findings obtained by protected specimen brush or transthoracic needle aspiration. In cases where such investigations were negative, a response to antibiotic therapy was used as a diagnostic criterion of pneumonia. They were able to identify the causative pathogen in 78%: by means of the protected specimen brush in 55%, transthoracic needle aspirate in 11%, when the protected specimen brush had failed, and by means of serology, pleural aspirate and blood culture in the remainder. The incidence in this study reflects that of a population similar to our own ICU, where there are patients with primarily respiratory problems as well as a good representation from multiple trauma, post surgical and other miscellaneous categories. The diagnosis is reliably made with post-mortem follow-up and probably represents one of the most accurate analyses in the literature. In addition, it lacks the potential bias that a study designed to evaluate a new diagnostic technique may have.

An earlier multi-institutional study from Spain [150] found an incidence of nosocomial pneumonia of 31% in the general ICUs; but a bacteriological diagnosis was only made in 38% of these cases, with an associated mortality of 47%. However, no definitions of the diagnosis, nor any indication of the diagnostic techniques are provided.

Langer et al [66] reviewed 724 patients requiring ventilation and similarly confirmed a rising incidence of nosocomial pneumonia with prolonged mechanical ventilation from 5% after 24 hours, to 68.8% after 30 days; however, when analysing the same data by actuarial life tables, they were able to show that nosocomial pneumonia occurred early, with a high and constant rate of acquisition in the first 10 days of ventilation, and thereafter its development was rare. This is the only study which has analysed the patients in this way, and this data suggests that the acquisition of

not necessarily related to duration of admission. In this study, the diagnosis of pneumonia was based on clinical and radiographic criteria. The overall incidence of nosocomial pneumonia was 23.2% in those who required ventilation, 26.6% in those who were ventilated for more than 24 hours, compared to 7% in those who were not ventilated. The overall mortality was 43.6%.

Similar results are reported from yet another centre in Spain [155], where the incidence of pneumonia in 1000 consecutive patients admitted to a medical-surgical ICU is reported to be 21.9% after 7.9 days; however, here there were superinfections documented, which raised the incidence to 25.7%. The diagnosis was made on clinical and radiographic criteria and a bacteriological diagnosis was made in 69.1% by means of a variety of techniques including the telescoping plugged catheter, blood culture and necropsy. The mortality in the study was reported to be 42% for those with nosocomial pneumonia, which was not very different from the 37% in those who did not have pneumonia. They suggest that pneumonia may not actually increase the mortality in critically ill patients, which may be determined by "host factors"and underlying disease. However, nosocomial pneumonia clearly prolongs the ICU stay of those who survive - in this study the duration of stay was 26.2 days compared with 16.6 days for patients with prolonged ventilation who did not develop pneumonia.

Difficulties occur with interpretation when trying to compare the above data, where newly available diagnostic techniques have been used, with the older literature where such procedures were not available, although the data was carefully gathered. The study in 1979 by Thorp et al [156] in a respiratory ICU used clinical features alone, including the purulence of the tracheal secretions. With these criteria, they found an incidence of nosocomial respiratory infection of 31.8%, which was the most common site of infection in their unit; such an incidence would seem to be highly comparable to that from more recent studies. That nosocomial infection contributed to morbidity was well demonstrated by the fact that over 90% of those who stayed longer than a week

had developed a secondary infection. The mortality was found to be 28% overall - 45% in those with secondary infection which was significantly higher than the mortality of 19% in those without this complication.

Daschner et al [9] in a study reported in 1982, prospectively analysing the incidence of nosocomial infection in a multicentre study of nine intensive care units, reported the incidence of nosocomial pneumonia to be only 1%, with the overall incidence of nosocomial infection ranging between only 3% and 27%. Unfortunately the criteria for the diagnosis are not as clearly defined in this article, making comparison difficult.

The patient population in the ICU is not homogeneous. Although the patients are by definition critically ill, the nature of their underlying disease, the reason for their admission, their age and whether they are elective or emergency admissions, are all risk factors which may predispose to the development of nosocomial infection by interfering with host defences. Similarly, "clean" ICUs eg cardiothoracic units where the patients are elective, postoperative cases, will have different incidences of infection from those where all the patients are emergency admissions often with primary infective aetiologies such as the medical or respiratory ICU.

Craven et al [10] prospectively studied admissions to both the medical and surgical ICUs at a municipal hospital and found the incidence of secondary infection to be 31% in the surgical ICU compared with 24% in the medical ICU. The overall incidence of secondary infection was 28%. The definition of nosocomial infection was similar to that of Potgieter [148], viz. infection 24 hours after admission, and the diagnosis of pneumonia was made on clinical and radiological criteria. The incidence of nosocomial pneumonia was not significantly different in the two ICUs (being 8% in the surgical and 10% in the medical unit), but the surgical ICU patients tended to develop their infections later than the medical patients. The mortality in the two ICUs was significantly different being 18% in the medical ICU compared with 10% in the surgical unit, with an overall mortality of 31% during hospitalisation; however, the

mortality rate due to secondary infection was not significantly different - 8% in the medical and 6% in the surgical ICU.

Brown et al [8] compared the incidence of infection in the medical/surgical, paediatric, neonatal, coronary care and cardiac surgery ICUs. Their diagnostic criteria included infections which occurred 48 hours after admission; for nosocomial pneumonia the criteria were less strict than those of Craven et al, but again clinical and radiological. The total infection rates ranged from 1% in the cardiac surgery ICU to 23.5% in the medical/surgical ICU, and secondary infection rates from 0.8% in the cardiac surgery unit to 11.2% in the medical/surgical unit, with an overall incidence of secondary infection in the ICU of 5.8%. The outcome in the medical/surgical ICU was also the poorest (36.5% mortality) compared with the paediatric ICU (11.1%), neonatal (10.9%) or coronary care units (22%) for infected patients. Unfortunately, this study does not distinguish clearly between community-acquired and hospital-acquired infections, when analysing the different sites of infection.

Chandrasekar et al [157] retrospectively analysed the infection rates in the various ICUs in their hospital in Detroit. Their requirement was 48 hours of admission before the onset of infection, but again unfortunately they do not specify further the criteria they used to diagnose site specific infections. Once again the predominance of urinary tract and respiratory infections is seen, with an overall infection rate of 19.2% in the ICU compared with 9.2% in the general ward. Unit specific infection rates were 35% in the surgical ICU, 14% in the medical ICU, 30% in the burns unit and 7% in the coronary care unit. The distribution of the type or site of infection differed from unit to unit with pneumonias most common in the medical and surgical units. Importantly, they were able to show a striking significant difference in the mortality between those who developed secondary infection and those who did not, as well as increased morbidity; however, it is not clear whether those who developed secondary infection actually died with it, because of the severity of their underlying disease, or from it.

Torres et al [158] assessed the risk factors for nosocomial pneumonia in ventilated patients, using strict clinical and radiological criteria, as well as telescoping plugged catheter samples to make the diagnosis in cases where other techniques had failed. They showed a similar incidence of 24%, the male predominance encountered in the study by Chandrasekar was also demonstrated (70%). The overall mortality was 33% for those who developed nosocomial pneumonia, but admission to a non-cardiac surgery or non-surgical ICU was associated with a statistically worse prognosis. This finding was ascribed to the higher percentage of patients with ultimately fatal disease admitted to these units, in comparison with the largely electively admitted cardiac surgery patients, as well as the shorter duration of intubation and ventilation in patients following cardiac surgery.

In contrast to most of the above studies where overdiagnosis of pneumonia is likely, a population at particular risk for the underdiagnosis of nosocomial pneumonia is that with the adult respiratory distress syndrome. Andrews et al [105] showed that 36% of cases with nosocomial pneumonia in ARDS had been clinically unrecognised until autopsy.

Montgomery et al [159] analysed the factors causing and contributing to death in patients with ARDS. They were able to show a mortality of 68% compared with 34% in a control group, who were assessed as being at similar risk for the development of ARDS, but who did not go on to develop ARDS. Only 16% of the deaths in the ARDS group were from respiratory failure, which was usually in a setting of uncontrolled sepsis originating in the abdomen; however, when the development of ARDS preceded the sepsis syndrome, the lungs, rather than the abdomen, were the usual site of infection. They postulate that the necrotic lung tissue associated with ARDS may predispose to secondary pulmonary infection, but unfortunately are unable to give accurate figures on the incidence of nosocomial respiratory infection in this study.

Similar findings were shown in an animal model by Campbell et al [160], who were able to show that acquired lung infection superimposed on a model of ARDS was responsible for a rapid and marked deterioration of pulmonary function, with a high mortality. They again experienced difficulty in making an accurate diagnosis of the exact incidence of secondary pulmonary infection in this setting.

The above review of the incidence of nosocomial pneumonia reported in the literature perhaps serves best to illustrate the difficulties encountered when an attempt is made to correlate results between institutions. The diagnostic criteria used may include varying clinical and radiological techniques and the emphasis, or lack of emphasis, based on special invasive procedures to achieve an accurate diagnosis may also substantially affect the results. The differing patient populations in different regions, let alone the different units even within the same hospital, as well as interindividual variations, make the reports of questionable significance when trying to compare results.

The importance of strict and reliable diagnostic criteria cannot be over-emphasised, not only so that such comparisons can more easily be made, but also because this form of audit and ongoing evaluation is extremely important in maintaining and improving standards of care within an institution.

5.2 The Incidence of Nosocomial Urinary Tract Infections

The sheer number of patients undergoing catheterisation of the urinary tract serves to make this the most common site of nosocomial infection. The majority of patients in the ICU undergo catheterisation of the urinary tract as the catheter is almost essential in any patient where accurate fluid balance monitoring is required, where the patient is sedated, paralysed or shocked, or to facilitate nursing care of patients who are immobile due to trauma. The associated incidence of urinary tract infection might also be expected to be higher in the ICU, as, by virtue of their illness, this population is recognised to be temporarily immunosuppressed and thus susceptible to infection.

About 80% of all nosocomial urinary tract infections are associated with the use of urethral catheters, the remainder follow genitourinary manipulations (5-10%), or are of uncertain aetiology [78]. The complications resulting from catheterisation are virtually all related to infection, with the exceptions of mechanical trauma or non-bacterial urethritis. The definitions of urinary tract infection are somewhat less controversial than those for nosocomial pneumonia; usually the isolation of a single organism in cultures at a level of $>100\ 000$ organisms/ml in the presence of clinical symptoms is required. Some studies will permit the isolation of multiple organisms if the patient has an indwelling catheter, and some studies further require the presence of leukocytes. Unfortunately, many of the studies do not specify the diagnostic criteria applied in making a diagnosis of urinary tract infection.

Between 10 and 30% of all patients undergoing short-term catheterisation will develop bacteriuria in hospital, with associated fever and symptoms of infection, as compared with only 1% of non-catheterised patients. The incidence of bacteraemia from nosocomial urinary tract infection in the catheterised patient is of the order of 1-5%, representing 6-15% of the total percentage of hospital-acquired bacteraemia, with a mortality of 13% [78].

Haley et al [161] estimated the frequency of nosocomial infection in 169 526 adult patients in 338 general "mainstream" hospitals in the United States during 1975-1976 by selected patient characteristics. They estimated that 5.23% of the patients developed one or more infections in hospital and that 6.62 infections occurred per 100 admissions. Of all patients with nosocomial infection, 62% had at least one urinary tract infection and 53% of all nosocomial infections involved the urinary tract. 18% of patients had more than one nosocomial infection, of whom the percentage of those having more than one infection at the same site was 5.6% for the urinary tract, compared with 14.5% for surgical wound infection, 1.9% for pneumonia and 4.5% for bacteraemia. 24% of the patients had a urinary catheter placed at some time during their hospitalisation, 21% of

approximately 3% in the ward and 4% in the ICU. All instances of urinary tract infection were associated with urethral catheterisation. There is no comment on the contribution of urinary tract infection to bacteraemia or mortality.

Brown et al [8] similarly comparing the incidence of secondary infections in the different ICUs within the same hospital, showed an incidence of 50.8% for urinary tract infections occurring in their coronary care unit, 24.7% in the medical/surgical ICU, 20.8% in the paediatric ICU and 2.6% in the neonatal unit, with an overall incidence of 25.8%.

Craven et al [10] compared nosocomial infection in the medical and surgical ICUs and found the overall incidence of urinary tract infection to be 13% - 15% in the patients in the surgical ICU compared with 10% in the medical ICU, which was statistically significant. Of the 700 patients who had a urinary catheter in place for more than 3 days, 46% developed an associated infection. In this very carefully performed study, the authors were not able to demonstrate that infection of the urinary tract was an independent risk factor associated with mortality, although any infection was an adverse risk factor.

Daschner et al [9] in their multi-centre European study of the incidence of nosocomial infection, found the urinary tract to be the most common site of secondary infection (26.7%) and, with the exception of neonates, virtually all patients with nosocomial urinary tract infections had urinary catheters. They then went on to analyse retrospectively the risk for secondary septicaemia in patients with nosocomial infection by correlating the bacterial species, antibiotic sensitivity of organisms obtained both on blood culture and from another infected site. In this way they related 31.5% of secondary septicaemias to urinary tract infections.

Judging from the number of reports that are to be found in the literature, the incidence of urinary tract infections would appear to be of minor interest only, to the intensivist.

Its importance is difficult to evaluate accurately for this reason, but, if 31.5% of secondary bacteraemias are indeed due to infections arising at this site, it is an area which needs to be addressed urgently as deserving of more attention than it has yet received.

5.3 Nosocomial Infections due to Percutaneous Catheters and Primary and Secondary Nosocomial Bacteraemias

The incidence of device-related bacteraemia is uncertain - estimates in the literature put the figure for the United States at anything between 25 000 and 200 000 cases per year [163]. The occurrence of such cases depends on the pathogenesis of the infection, and these infections may be sporadic or occur in clusters.

Primary bacteraemias are those in which the microorganism enters the blood at a usually undetected site and subsequently goes on to produce metastatic infection; however, such infections as meningococcal septicaemia and enteric fever are generalised septicaemic states which also qualify as primary bacteraemias. Such primary bacteraemias tend to occur in clusters in the community, but form a very small proportion of nosocomial bacteraemias.

Secondary bacteraemia refers to the development of bacteraemia resulting from infection at a local site eg pneumococcal pneumonia or acute pyelonephritis, but in the hospital setting is most commonly a device related phenomenon. Such bacteraemias may occur in clusters due to the spread of the same organism on the hands of health workers, or by contaminated equipment or infusates; this type of infection may also be sporadic, resulting from the colonisation of a device, particularly if its insertion was associated with poor techniques of asepsis, or it is allowed to remain in situ for prolonged periods. Maki [80] reported that the incidence of catheter-related septicaemia increased from 2% to 8% if a catheter was left in situ for more than 48 hours.

Forgacs et al [93] identified 468 episodes of bacteraemia in the ICU at St Thomas'Hospital, London over a 15 year period, compared with 2754 epsodes in the entire hospital. The ICU was thus involved in 17% of bacteraemias in a population who occupied only 1.2% of the beds in their hospital. 25% of such bacteraemias were community acquired, 75% developing in the hospital. The mortality from bacteraemia, within the ICU, was similar, regardless of whether it was community or hospital acquired; however, the mortality of the primary disease was significantly adversely affected by the presence of bacteraemia. The overall mortality for patients in the ICU was 13.1% for those without bacteraemia, compared with 60.4% in those who were bacteraemic. Unfortunately, no severity of illness scoring system was used to compare the severity of illness in those with bacteraemia with those without, so it is difficult to draw further conclusions.

Similar alarming figures for the mortality associated with nosocomial bacteraemia are reported by Quercia et al [79], who showed a mortality 14 times higher for patients with the same primary diagnosis who developed nosocomial bacteraemia compared with those who did not.

A study looking particularly at the incidence of catheter related sepsis with triple lumen central venous catheters [89] in an ICU and on the ward, was able to show an attributable incidence of only 3.1%. 96 catheterisations in 65 patients were studied, and the catheters were removed after 5 days, or when infection was suspected. The stringent clinical criteria used for the diagnosis of sepsis in this study gives an accurate reflection of the incidence of nosocomial catheter related sepsis at this institution, but there is an absence of microbiological correlation which, however, unfortunately makes comparison with studies where no criteria are specified, or a more microbiological basis is used to distinguish between colonisation of a line, isolated unrelated bacteraemia, and true infection, difficult.

Miller et al [87] in a limited study of only 29 patients and 47 catheter placements using similar criteria to the above study by Kelly et al [89], documented an incidence of catheter related sepsis of 7%, with an incidence of contamination of 33%. Such a value correlates well with other studies [84,90], and confirms the prevalence of the problem, but unfortunately is too small to contribute further.

Brun-Buisson et al [90] designed a study to evaluate a technique of quantitative culture of catheter tips in diagnosing catheter related sepsis in the critically ill; to further improve comparability, only those catheters which were placed by the internal jugular or sublcavian vein were studied. They evaluated 331 central venous catheters obtained from 232 medical or post-operative patients, which were used in their ICU over a one year period, and removed either at death, when no longer therapeutically necessary, or after 10 days. 74% gave no growth and 25.6% grew more than 10 cfu/ml. When microbiologic and clinical data were compared, 42 catheters, or 12.7%, were able to be classified as contaminated, and 10.8% as definite catheter related sepsis, while 2% were classified as colonised from a distant septic focus. It is difficult to make accurate comparisons or to draw conclusions when comparing this very careful study with that of Kelly et al [89] where the incidence is so much lower.

Eyer et al [84] randomised 122 patients and 294 catheter placements in a study to evaluate three methods of long-term catheter maintenance in a surgical ICU. The techniques of microbiological culture were similar to those of Brun-Buisson. They reported an incidence of catheter tip colonisation of 3.3% and an associated incidence of 13% to 16% of catheter related sepsis, with the three techniques under comparison. The chance of a patient developing catheter related sepsis was 0.3% per day per catheter, confirming that the risk of infection is a function of time, they were however unable to improve this risk by frequent changing of the catheter.

There is no comment on the association of mortality with catheter related sepsis in the above two studies. This aspect was addressed by Smith et al [163] who studied the excess

mortality attributable to nosocomial bacteraemia in 34 critically ill patients in a medical ICU. The study included primary bacteraemias, occurring at least 3 days after hospitalisation. The diagnosis of primary nosocomial bacteraemia was made by a positive blood culture and the absence of clinical or laboratory evidence of another site of infection. In this study, intravenous catheters were not routinely cultured after removal, so the incidence attributable to catheter related sepsis is not clear. 384 patients without this complication in the same ICU showed an observed mortality of 38% which matched the mortality predicted by the APACHE II score. When the group was compared with a subgroup of the control, who matched their APACHE II scores, the observed mortality in those with nosocomial bacteraemia was 82.4% which significantly exceeded the predicted mortality of 54.1% for the control group. The mortality in this study is far higher than the 60% recorded by Forgacs[93], but the population includes only those with nosocomial bacteraemia which may account for the difference; however, the difference in mortality of only 28% between those who were or were not bacteraemic is much less than the 47% reported by Forgacs. The more careful matching of severity of illness in the control group in the study by Smith may account for this marked difference.

Clearly the bloodstream is one of the most important sites of nosocomial infection, which contributes to, or is the direct cause of a substantially increased mortality. The majority of studies indicate that intravenous catheters are the most common culprits in causing this, but the difficulty in achieving an accurate diagnosis is possibly as great as with nosocomial pneumonias and it is thus impossible to accurately assess the size of the problem.

The use of total parenteral nutrition is an area where infections are recognised to be a major cause of morbidity and mortality. The patients who require T.P.N. are often at greater risk for the development of secondary infection, because of prolonged ileus, severe malnutrition or other underlying reasons which have themselves necessitated the

institution of such therapy. The use of T.P.N. is often controversial, as it is often thought to cause almost as many complications as it may help resolve. There is nevertheless a substantial population of patients in the ICU who receive T.P.N.. Unfortunately, most of the studies analysing and reporting the incidence of complications related to T.P.N. have looked specifically at high risk subgroups, so it is difficult to gain an accurate impression of what the overall risk of infectious complications for the lower risk categories might be.

Detsky et al [164] reported a meta-analysis of patients receiving TPN perioperatively, but found that in 11 of the 18 studies the methodology was so poor that it was difficult to draw any conclusions. When taking the methodology into account, they were able to show that the risk of complications was such that routine use of TPN for major surgery could not be justified, except in certain high risk groups. The incidence of septicaemia and other complications varied between 0 and 25%.

The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group [98] studied 395 malnourished patients undergoing major thoracic or abdominal surgery; the patients were randomly assigned to pre and post-operative T.P.N., or to no T.P.N.. They demonstrated a statistically increased risk of infection in the T.P.N. group (14.1% vs 6.4%), although the severely malnourished patients had a lower incidence of complications - both infectious and non-infectious. They concluded that there was no role for preoperative TPN except in the severely malnourished unless there were special indications. The infections were not limited to the catheter however, as the majority were pneumonias and there is no comment on any correlation between organisms found in the lungs and on the catheter tip. The 90 day mortality did not differ significantly between those who received TPN and those who did not; unfortunately they do not specify the cause of death so it is not clear whether those who developed secondary infections died from secondary infection or their underlying disease.

5.4 The Incidence of Wound Infections

Data from the United States [27] suggest that one third of all nosocomial infections are surgical wound infections. This complication doubles the postoperative hospital stay and the cost per episode, in 1987, was estimated to range between $800 and $1 000, although the actual value might have been up to ten times higher than that, if indirect costs had also been taken into account. The incidence of wound infection depends on a number of variables such as whether the surgery is elective or emergency, and the field being entered. Host factors such as the nutrtional status of the patient, and the presence of underlying disease, also make it difficult to extrapolate results from one centre to another.

Haley et al [161] reviewed the incidence of nosocomial infection affecting the urinary tract, lower respiratory tract, bloodstream and surgical wounds in 338 hospitals across the United States. They estimated that of all patients with nosocomial infection, 30% had $\geq$ 1 surgical wound infection, and that 40% of infections among surgical patients were wound-related. The incidence of wound infection increased approximately linearly with the duration of surgery with a 21-fold increase from the lowest to the highest categories. There was a 5-fold increase in the incidence of wound infection in patients who were mechanically ventilated, which is unfortunately as close as the study comes in defining an ICU population.

The rate of infection varies according to the procedure: less than 3% for "clean" procedures, where there is no violation of aseptic technique and the alimentary, respiratory and genitourinary tracts are not entered; the rate increases to 4% for "clean-contaminated" procedures, where these systems are entered but there is no spillage, and rises still further to 9% when there is gross contamination. For specific operations the rate may increase five or more times in certain high risk groups of patients [165].

In reviewing this field, it is striking to note the change in philosophy and practice that has evolved over the past 30 years. In the 1960s, antibiotic prophylaxis to prevent wound infection was frowned upon as something which caused more complications than it solved [166] and the fear of inducing resistance amongst bacteria was cited as a reason for not even trying to prevent infection in this way; however, during the 1970s the number of procedures for which such preventative treatment was indicated, grew rapidly. The methods, choice of agents and timing of such administration have since then been undergoing repeated analysis, with innumerable reported trials, many with design flaws [28,165,167-178]. Further compounding the problem in evaluating the incidence of wound infection, is the fact that the variables which influence the incidence of wound infection are often evaluated in terms of techniques which are now regarded as obsolete, making the interpretation of any of the data difficult,if not impossible.

In none of these studies is specific reference made to the patient in the ICU, although many of the patients undergoing elective clean, major surgery will enter the ICU postoperatively. Guidelines for how long such prophylaxis should be continued and its effect on cost, morbidity and mortality are thus important. It is equally important to gain an indication of the incidence of sepsis as a cause of morbidity and mortality in the traumatised patient, who often requires ICU admission and may have a variety of wounds - both contaminated and clean. The available literature would suggest that the surgical wound is often more susceptible to becoming secondarily infected in the ICU than elsewhere, but that such infection per se seldom leads to death.

A 4 year prospective study from Barcelona [27] looking at the incidence of wound infection occurring in clean postoperative wounds, found the incidence to be 3.2%, although this rose to 5.1% for emergency surgery, and to 5.4% when drains were used. The presence of underlying, well-recognised predisposing factors such as diabetes, steroid use or carcinoma, raised the incidence still further to 7.8%, but age did not

seem to affect the infection rate adversely. There were a number of other variables which affected the rate significantly: there was up to a ten fold difference in the infection rate between different surgeons performing the same operation, the incidence of wound infection was 12% following vascular surgery as compared with 0.6% following ophthalmologic surgery.

The timing of prophylactically administered antibiotics to prevent surgical wound infection also has an impact on the incidence [178]. Classen et al demonstrated that patients who received antibiotic prophylaxis in the two hour period prior to surgery had an incidence of wound infection of 0.6% for clean or "clean-contaminated" surgery compared with those who received antibiotics in the 24 hour period prior to surgery, where the incidence increased significantly to 3.8%.

Currently there is no reliable data on the attributable mortality to secondary wound infection, but its incidence is thought to be very low[165].

Allgower et al [179] reviewed the cause of death in patients with severe polytrauma in their hospital and ICU in Basel, in 1980. Prophylactic antibiotics were not used in such cases. They showed an overall mortality of 17.6% for 300 such cases, of whom 16% died of sepsis. The overall incidence of infection in the 300 patients, using clinical definitions only, was 62.6%. 32.3% developed urinary tract infections, 18% respiratory tract infections and 12.3% wound infection. They noted a much higher incidence of wound infection in the trauma patients - 4% compared with an incidence of 1.5% for clean surgery. 8.3% of the infected patients went on to develop septicaemia of whom 65% died; 8% of the septicaemias were secondary to traumatic wound infection and these patients died. They concluded that the primary injury, the lag before therapy and the degree of shock were the determinants of outcome, and that the role of antibiotic therapy was questionable. It is interesting to note, when attempting to evaluate this study, that in 1980 this unit was not advocating the use of prophylactic antimicrobials for elective orthopaedic surgery either!

Goris and Draaisma [180] retrospectively analysed the cause of death in 89 patients with multiple trauma who did not die of burns, primary head injury or isolated fracture of the femur. They found that patients dying more than a week after the injury died primarily of remote organ dysfunction secondary to sepsis in 88%, but the role that wound sepsis may have played in this is not discussed.

Schimpff et al [181] analysed the incidence of nosocomial infection in severely traumatised patients admitted to a trauma centre. They showed that the organisms responsible for secondary infections in such patients were organisms not regarded as pathogenic in patients with normal host defences. They were able to identify a leg wound as the source of nosocomial infection in only 1 of 25 patients who developed such infections, the remainder being urinary tract infections, pneumonias or catheter related bacteraemias.

CHAPTER 6 THE AETIOLOGY AND INFLUENCE OF NOSOCOMIAL INFECTION IN THE ICU

The aetiology of secondary hospital-acquired infection is multi-factorial, depending on a number of host factors, the site where infection occurs, the organisms responsible and their intrinsic properties such as pathogenicity and invasiveness, the size of the inoculum of the organism and exposure of both host and organism to an environment which suitably predisposes to the development of infection. These factors are often inter-dependent and, while it is not difficult to appreciate the association between them, it is far more difficult to prove that the relationship is causal. For example, it is well recognised that prolonged hospitalisation predisposes to the development of nosocomial infection, but nosocomial infection itself prolongs hospital stay and thus it is often difficult to distinguish the one from the other, particularly when attempting to interpret the literature where all the variables influencing each specific factor are not outlined.

Such factors apply both in the general hospital and in the ICU. Haley et al [161] identified the following risk factors for the development of nosocomial infection in the general hospital: age, sex, duration of total and preoperative hospitalisation, presence of previous community-acquired or nosocomial infection, the type of underlying disease, the duration of surgery, as well as treatment with invasive devices or immunosuppressive medication. They found that 75% of the nosocomial infections occurred among patients undergoing surgery.

Craven et al [10] used a multivariate analysis to identify predisposing factors for the development of nosocomial infection, when comparing the incidence in the medical and surgical ICUs at the Boston City Hospital. They identified a number of variables which were associated with the development of infection: age > 70 years, white race, coma on admission, an Acute Physiology Score > 20, prior antibiotics, steroids or chemotherapy, admission to the Surgical ICU, an ICU stay of > 10 days, or one of the following admission diagnoses: head trauma, multiple trauma, neurologic disease,

cardiopulmonary arrest, respiratory failure, acute myocardial infarction or pulmonary oedema.

Laboratory values such as a serum urea of $\geq$ 7.1mmol/l, creatinine $>$130 mmol/l or a serum bicarbonate of $<$ 20mEq /l were also univariately associated with a statistically significantly increased risk of secondary infection, as were the presence of invasive devices such as a urinary catheter, a ventilator, a central line, an arterial line or a pulmonary artery catheter.

Such factors are useful in highlighting a high risk group of patients - at risk of both nosocomial infection and death, however, they do not themselves necessarily point to the root cause of the problem. Many of the variables merely serve to emphasise the severity of the underlying disease, although, in the case of invasive monitoring devices, they also may independently add to the risk of infection.

Such factors as shock, days in the ICU, admission to the surgical ICU, steroid or chemotherapy and renal failure were the factors most strongly associated with nosocomial infection, not only in Craven's and Haley's studies, but also in other reviews of the incidence and outcome of nosocomial infection, both involving the general hospital such as the studies by Gross et al [151], Bryan and Reynolds [152], the elderly as shown in a study by Harkness et al [182], or specifically in patients in the surgical wards as reported by Kinnear, Finch et al [183]. It is difficult to decide whether these factors cause infection by altering host immunity or merely serve as markers of severity of illness. These studies really serve to highlight the importance of the association, rather than to prove cause and effect.

Craven was able to show that the presence of invasive devices increased the risk of infection, and the longer the devices remained in situ, the greater the risk of infection became. The duration of ICU stay was also associated with an increasing incidence of nosocomial infection, but actuarial life tables were not used to analyse the time

relationship to the development of pneumonia in this study. Such analysis,as used by Langer et al [66], might have shown that the length of respiratory assistance and the associated device-related risk are contributory, rather than the primary cause of infection. The analysis of data in this area warrants further evaluation, possibly using actuarial life tables, to bring much needed clarity and hopefully some meaningful conclusions to this field.

The incidence of infection occurring in the different ICUs would suggest that there must be particular host factors characteristic of the populations in the different ICUs which predispose to the development of specific infections. While it is not difficult to understand why wound, or intra-abdominal infection should be more common in a surgical ICU, the discrepancy in the incidence of central nervous system infections, also reported to be higher in the surgical ICU by Craven's group, is more difficult to explain. The higher incidence of urinary tract infections was explained by the more prolonged placement of such catheters in the surgical patients.

In spite of the higher incidence of infection in the surgical ICU in Craven's study, the fatality rate was higher in the medical ICU, and the fatality rate due to secondary infection was similar in the two units. This poses the question as to whether the patients who died, died with, or of, their secondary infections. From the data in this study, it would appear that the medical ICU patients were older, more critically ill, with a higher incidence of coma, or other neurological disease, acute respiratory failure, shock or infection; all these factors would suggest that while doubtless contributing to the fatal outcome, most of the patients would ultimately have succumbed, irrespective of the development of nosocomial infection.

The undisputedly poor prognosis that untreated severe community acquired infections, requiring ICU admission, are known to have, may have been over-simplistically extrapolated to apply to nosocomial infections; the natural history of nosocomial infection is much less well established and less easily defined, because of all the other

factors which tend to be occurring simultaneously. It is well known that bacteraemias with *Klebsiella pneumoniae*, and other highly pathogenic aerobic Gram negative bacilli, are associated with a much higher mortality in community-acquired infections than secondary hospital acquired bacteraemias [184]. Might all nosocomial infections be rather a manifestation of severe illness than its cause? Similarly, may death not be due to the severity of the underlying disease with a variable contribution from secondary infection, rather than postulating that nosocomial infection is the final common pathway and cause of a fatal outcome? There is clearly no one answer to this question, although its relevance, when planning expensive strategies to prevent nosocomial infection, needs to be considered.

Rello et al [155] asked much the same question in their multi-institutional study in Spain. They identified a number of host risk factors which predisposed to the development of nosocomial pneumonia in a group of predominantly surgical (76%) and multiple trauma patients (29%) ; while the list is similar to that of Craven, there are a few notable differences: shock, immunosuppression and renal failure showed little correlation with the predisposition to develop secondary infection, but steroids, prior trauma or surgery, and coma were closely associated with nosocomial pneumonia. The mortality in the 25.7% who developed pneumonia was 42%, compared with 37% in those who did not develop secondary infection, suggesting that the role played by nosocomial pneumonia in determining a fatal outcome was not of major importance. Similar findings were reported by Nielsen et al [154].

Gross et al [151] noted that 50% of the nosocomial infections which were related to death in their survey of nosocomial infection throughout a general hospital, occurred in the ICU. They found that the usual hospital risk factors for infection such as intravenous catheters, indwelling urinary catheters and respiratory therapy equipment were not present more often in those who died with nosocomial infections than in their counterparts, in whom such infections did not develop. The use of more invasive

procedures, such as one finds in the more acutely ill however, such as intraarterial and central venous pressure monitoring devices and nasogastric tubes, appeared to be significantly associated with the development of nosocomial infections, and a risk factor for death. The findings of this study would again support the theory that critically ill patients are at risk of both infection and death, and that while the two occur together may indicate an association, it does not necessarily prove cause and effect.

Chandrasekar et al [157] similarly found the acquisition of infection in the ICU to be associated with a poor prognosis, with an outcome far worse than that of matched controls, but the patients who developed such infections again were noted to have greater severity of underlying disease and to have been subjected to more invasive procedures.

6.1 Nosocomial Pneumonia: Aetiology and significance

Celis et al [185] performed a multivariate analysis of risk and prognostic factors in 129 episodes of nosocomial pneumonia in 118 non-neutropaenic patients in the general hospital. The overall mortality rate for these patients was 36.6%. The diagnosis of nosocomial pneumonia was made on clinical and microbiological criteria using confirmatory fiberoptic bronchoscopy with a plugged telescoping catheter or transthoracic ultrathin needle aspiration. Each patient who developed pneumonia was paired with an unmatched control subject. Using univariate analysis, 8 factors were identified as being associated with a higher fatality rate: age > 60 years, place of hospitalisation (medical wards or ICU), ultimately or rapidly fatal underlying condition, "high-risk" pathogen, chest X-ray showing bilateral pulmonary involvement, shock, respiratory failure and inappropiate antibiotic therapy. The following factors were associated with a higher mortality, although this was not statistically significant: male patients had a higher mortality than female (39.5% vs 29.4%), chronic lung disease was associated with a higher mortality (42.9% vs 31.3% for those without it),

and a leukocyte count of > 20 000 /cu (42.9% of such patients died compared with 34.1% of those whose white cell count was less than 20 000/cu).

When performing univariate analysis on the data, the presence of a nasotracheal or orotracheal tube, depressed level of consciousness , chronic lung disease, thoracic or abdominal surgery, a previous episode of aspiration and age > 70 years were factors significantly predisposing to the development of pneumonia. However, such variables as the place of hospitalisation, smoking status, the presence of a tracheostomy, nasogastric intubation or previous antibiotic therapy failed to retain significance after adjusting for confounding factors. The same difficulty in further dissecting the problem of the role of infection in mortality was experienced.

Possibly the two most important points to emerge from this very carefully performed study are: 1) the importance of appropriate antibiotic therapy - 91.6% of those who received inappropriate antibiotic therapy died, and only 25% of these patients had ultminately or rapidly fatal underlying disease; this is also the only prognostic factor identified which is amenable to intervention. 2) The relevance of "high-risk" organisms in the aetiology of nosocomial pneumonia.

Similar findings are reported in papers by Torres et al [158], Jimenez et al [149] both emanating from the same centre, and, possibly, using the same raw data.

Leu 'et al [75] attempted to identify the morbidity and mortality attributable to nosocomial pneumonia in a general hospital setting. They identified 1 001 consecutive episodes of nosocomial pneumonia in 901 patients, in whom they confirmed the excess of previously discussed risk factors, such as the time from admission to the development of pneumonia, prior mechanical ventilation, and neoplastic disease were all associated with mortality. By multiple regresssion analysis, factors associated with increased length of hospitalisation were shown to include post-tracheostomy status, ventilation, immunosuppression, nasogastric intubation and prior bacteraemia. By using

a sampled, individually matched cohort study they determined the proportion of mortality attributable to secondary infection to be 33%, which was of only marginal significance, and the excess hospital stay which they showed to be prolonged by a statistically significant seven days.

Mosconi et al [186] studied the risk factors associated with nosocomial pneumonia in 1475 patients collected from 23 ICUs in Italy, who had no previous history of pulmonary infection, without irreversible/ ultimately fatal underlying disease, and who stayed in the ICU $\geq$ 48 hours. The incidence of pneumonia was 15% (220 cases). 239 patients died, with a mortality which was significantly higher in the patients who developed pneumonia ($p<0.0001$). Multivariate analysis of seven risk factors for pneumonia, showed a significantly higher risk in patients with neuromuscular disease, impairment of airway reflexes on admission, $\geq$ 24 hours of respiratory assistance, age $>$ 60 years and emergency surgery. This study again gives fairly convincing evidence of the relationship between impaired airway reflexes, with the associated increased risk of aspiration, mechanical ventilation and the development of pneumonia, but, more importantly, is extremely convincing that there is a strong relationship between nosocomial pneumonia and mortality. It is interesting to note however that no relationship between impaired airway reflexes and death could be demonstrated. A criticism of this study might possibly be that there is no accurate definition (perhaps one is not possible, as it is too subjective) or attempt at quantitation, of impairment of airway reflexes, which might only be a reflection of the severity of the underlying disease. Severity of illness scores might have been useful in assisting further evaluation. Harkness et al [182] in their study of risk factors for nosocomial pneumonia in the elderly, similarly found aspiration to be of particular importance.

6.1.1 Invasive Devices

The role of respiratory assist devices in the development of nosocomial pneumonia is so well established, that it hardly warrants comment. Virtually all of the above-mentioned studies have included this as a significant risk factor for the development of pneumonia. Cross and Roup [29] in 1981 reported a prospective study of 13 086 patients over 11 months, of whom 914 had a respiratory assistance device for at least 24 hours, specifically to document this risk factor. There were 108 episodes of pneumonia - a 0.82% overall incidence; in those without a respiratory assistance device the risk was 0.3% (35% of the total hospital associated pneumonia), versus 1.3% in those with endotracheal tubes and respirators (11% of hospital acquired pneumonias), 25% with tracheostomy (12% of hospital acquired pneumonia) and 66% in those with tracheostomy and a respirator (9% of hospital acquired pneumonias). The relationship with duration of ventilation was once again convincingly demonstrated in that no patient who was ventilated for <24 hours developed pneumonia, but the risk increased significantly after 5 days.

Deppe et al [187] evaluated the incidence of colonisation and nosocomial pneumonia when comparing closed and open suction systems for tracheal toilet. They found that the closed system was, perhaps not surprisingly, associated with a higher incidence of tracheal colonisation than the open system in which toilet was more adequate. The demographic features and severity of illness parameters were similar for both suction catheter systems. However, using clinical and radiological criteria to diagnose pneumonia, no difference in the incidence of nosocomial pneumonia between the two groups could be found and the probability of survival seemed to higher in those who were treated with the seemingly less effective closed system. Unfortunately, although this study casts doubt on the previously described pathogenetic mechanisms for the development of nosocomial pneumonia, the results need to be interpreted with caution,

because the actual number of patients with infections is too small for the conclusions of this study to be justified.

There are no studies particularly evaluating tracheostomised patients in the ICU, who have undergone this procedure to facilitate ventilation. Yet, as the above study suggested, such patients are recognised to be at particularly high risk of nosocomial pneumonia. In the only study of its kind in the literature, Rogers et al [188] documented the incidence of, and risk factors for, secondary pneumonia following tracheostomy for varying indications, in 139 patients. Pneumonia was diagnosed on clinical and radiological criteria. Patients with pneumonia, or at risk of pneumonia because of mechanical reasons at the time of tracheostomy, were excluded from the final analysis of 83 patients. The incidence of pneumonia was 20.5%, and occurred most commonly in the first 8 to 12 postoperative days. Interestingly, the incidence of other infections whilst the tracheostomy was present was twice as great amongst those who developed pneumonia as in the other patients in the study. The organisms isolated from other infected sites, excluding grossly infected tracheostomy wounds, showed a striking correlation with the tracheal flora. Patients with central nervous system derangements (encephalitis, brain tumours, strokes, fat embolism, etc) again formed the majority of patients requiring tracheostomy who developed pneumonia, whereas patients undergoing tracheostomy for facial fractures and upper airway obstruction (idiopathic tracheolaryngitis, recurrent juvenile papillomatosis) did not develop pneumonia. 59% of the pneumonias following tracheostomy occurred on the neurosurgical service. The overall in-hospital mortality, of the 82 patients studied, was 25.3%; 65% who developed pneumonia died, in whom the pneumonia was thought to be the primary cause of death in 64% of the deaths.

The incidence of pneumonia and other hospital-acquired infections has been shown in a number of studies to vary with the type of patients or ICU being studied [8,9,157]. Donowitz et al [162] analysed the differing infection rates in patients belonging to

different services who were cared for within the same ICU. They showed that the highest rates of secondary infection occurred in patients from the obstetrics and gynaecology, orthopaedic and general surgery services. The types of infection also varied with the services: the highest incidence of pneumonia and urinary tract infections were in the orthopaedic patients. Urological patients had the highest incidence of postoperative wound infection and general surgery patients the highest incidence of bacteraemia. It is difficult to surmise why this should be, particularly as no patient characteristics are given.

Craven et al [30], in another study in patients who required mechanical ventilation, using the populations in the medical, surgical and coronary care ICUs at the Boston City Hospital, identified by univariate analysis the following eight risk factors for the development of pneumonia and a fatal outcome: the presence of an intracranial pressure monitoring device, craniotomy, coma or head trauma, treatment with cimetidine or steroids, changing of the ventilator circuitry every 24 hours as opposed to every 48 hours and admission to hospital during the autumn or winter months. However, when stepwise logistic regression analysis was performed on these risk factors, only the presence of an intracranial pressure monitoring device, treatment with cimetidine, hospitalisation during the autumn/winter and 24 hourly changing of the ventilator tubing remained statistically significant.

The two-fold increase in pneumonia during the winter is difficult to explain; the investigators attribute it to infections with agents such as possible prior or concurrent viral or *Mycoplasma*, for which they did not routinely test, and which they postulate may have predisposed to bacterial pneumonia by altering nasopharyngeal colonisation and host defences. Such a seasonal difference in incidence of nosocomial pneumonia has not been reported elsewhere - perhaps it has not been looked for?

It is certainly easier to understand the increase in incidence attributed to frequent changing of the ventilator circuitry, and this study has served to change the policy in

relation to this, in most ICUs across the world. The more frequent manipulation of the patient, the endotracheal tube, or the ventilator tubing, must frequently and inevitably lead to the inadvertent flushing of condensate into the patient, and tend to cause increased leakage of bacteria around the endotracheal tube into the trachea, just as manipulation of other devices eg the urinary catheter, has been shown to lead to an increased incidence of bladder infection. There have been several reports in the literature of the dissemination of organisms, particularly *Pseudomonas aeruginosa* causing outbreaks of pneumonia secondary to the contamination of ventilatory devices and tubing [73].

The population that Craven studied were all at risk for secondary infections on a number of criteria mentioned previously. They all had significant underlying disease: 42% had chronic cardiovascular disease, 35% chronic respiratory disease, 32% were alcoholic, and notably 30% were admitted following a neurological event, 20% following cardiopulmonary arrest, 18% following head trauma. Further immunocompromising factors included the fact that 12% had diabetes mellitus, 8% had malignancies, 9% were bacteraemic, 7% had renal failure and 12% had sustained multiple trauma. 46% of the patients were comatose when admitted to these ICUs. The in-hospital mortality of the patients studied was 41% (including both those who developed pneumonia, who formed only 21% of the patients studied, and those who did not).

The presence of an intracranial pressure monitoring device as an independent predictive risk factor for the development of nosocomial pneumonia and mortality, is possibly synonymous with the finding of Mosconi et al [186] that neurological disease, particularly when associated with impairment of the upper airway reflexes, was the most important risk factor for the development of nosocomial pneumonia. However, it is difficult to distinguish the independent effect of a single parameter, from a whole host of other important factors that clearly must have operated in every patient who

required an intracranial pressure monitor. All patients who underwent placement of such devices were treated with steroids, and 89% of them were in coma at the time of placement, furthermore 41% were in shock and 63% had had a craniotomy, presumably under general anaesthetic. As mentioned in the study, further predisposing to the development of infection in such patients, was the fact that chest physiotherapy and suctioning were avoided to prevent any increase in the intracranial pressure, which these procedures might have induced; 52% of this population were paralysed with pancuronium, further hindering the clearing of secretions.

Similarly, when evaluating the data pertaining to the independent risk of secondary infection associated with cimetidine in this study, there are so many other variables in operation that possibly no amount of statistical manipulation of the data can definitely prove cause and effect. Craven found that 37% of the patients given cimetidine developed pneumonia, compared with 18% of those who received antacids, and only 8% of those who received no ulcer prophlaxis. These patients, to a significant extent, were the same ones who were already at risk of pneumonia by virtue of their head injuries, intracranial pressure monitoring devices (41% of those with intracranial pressure monitors received cimetidine) and steroid therapy.

Unfortunately all studies in the critically ill are, and are likely to be, equally hindered by the same problems so that while studies like that of Craven are extremely useful and important in encouraging audit of daily practice, and generate important conclusions, some of the data must at least be viewed with caution.

6.1.2 Gastric pH

Gastrointestinal bleeding is a recognised problem in all critically ill patients as a result of "stress ulceration", particularly in those with neurological injury or following burns. Cimetidine and other H-2 blockers inhibit the histamine type 2 receptors in all tissues, including the stomach. The role that histamine may play in initiating and modulating

the inflammatory and immune responses to infection is thought to be of importance; what the effect of blocking this may be is still not clearly established. Cimetidine may also have effects on host cellular and humoral defences, but the data in this area is again still not available.

Many studies have implicated the increased gastric pH as an important factor in the pathogenesis of nosocomial pneumonia, whether due to antacids or histamine antagonists, because it has been shown to lead to an alteration in the colonising flora of the stomach, promoting overgrowth by Gram negative bacilli. The stomach is believed to act as a source of organisms which then colonise the respiratory tract [52,54,56,61,62,154]. Cook et al [63], in a meta-analysis, were unable to confirm that, with the available evidence, stress ulcer prophylaxis with agents that raise gastric pH increased the incidence of nosocomial pneumonia; the use of sucralfate was, however, associated with a lower incidence of secondary pneumonia, when compared to antacids or H-2 antagonists.

While meta-analyses have failed to demonstrate that antacids or cimetidine increase the incidence of nosocomial pneumonia, the use of sucralfate has been shown to be associated with a lower incidence of nosocomial pneumonia [63]. Sucralfate is a weak buffer that probably acts through pepsin adsorption, mucosal protein binding and cytoprotection, without affecting the gastric pH significantly [189]. Tryba et al [59] demonstrated that in addition to maintaining a low gastric pH, sucralfate also exhibits anti-bacterial effects against both Gram positive and Gram negative bacteria, which may help to explain its more favourable profile with respect to the incidence of nosocomial pneumonia. The efficacy of all three agents in preventing acute stress bleeding would appear to be equivalent [55]. Although Tryba comments that there were, in this study, significantly fewer cases of nosocomial pneumonia in those who received sucralfate prophylaxis; such respiratory infections as occurred were of more minor

significance, and associated with a lower morbidity and mortality, than those that developed in the patients receiving antacids.

Driks et al [62] reported a study comparing the incidence of nosocomial pneumonia in intubated patients treated with sucralfate, antacids or histamine type 2 blockers. They found that nosocomial pneumonia occurred twice as frequently among those who received agents that raise the gastric pH as in those who received sucralfate. The mean duration of ventilation and ICU stay in those who received antacids or H-2 blockers, was also more prolonged, this contrasts with the study by Bresalier et al [189] who did not show any difference in morbidity (although there were more side-effects experienced in those who received antacids), or mortality between those receiving antacids or sucralfate. Although the mortality, in the study by Driks, for the group who received antacids/cimetidine was also higher than in those treated prophylactically with sucralfate, the authors comment that this may be related to a number of factors such as the patients' underlying disease and medical condition and there is insufficient evidence to implicate pneumonia alone. They found a lower gastric pH and lower concentrations of Gram negative bacilli in the stomach, pharynx and trachea of patients in the sucralfate group; importantly, they also noted that Gram negative bacilli were not often isolated in the tracheal aspirates of the patients who received sucralfate and who developed pneumonia.

Lacroix et al [190] added fuel to the fire regarding which agent to use for stress ulcer prophylaxis with their meta-analysis of studies using antacids and/or cimetidine, which have been shown to be as effective in preventing bleeding elsewhere as sucralfate [55,189]: they were unable to demonstrate any benefit in reducing morbidity or mortality with the use of any prophylaxis compared with no therapy.

Possibly the conclusion to draw from the above must be that, while awaiting further, better conducted studies to demonstrate conclusively whether any prophylaxis is indeed better than none, the motto "not to do any harm" should apply. In high risk cases such

as burns, head injuries and patients with liver failure, where enteral feeding is not possible, sucralfate should be used in preference to the other agents. However, it should be remembered that sucralfate binds to other enterally administered drugs and may thus inactivate them, which unfortunately may curtail its spectrum of application [64].

6.1.3 Nutrition

While enteral feeding is known to be effective prophylaxis against stress ulceration, simultaneously providing nutritional support, it is also recognised to elevate the gastric pH and may increase the risk of nosocomial pneumonia [62]. There are, however, few reports in the literature on the risk of nosocomial pneumonia associated with such a feeding regimen.

In a small study from Saudi Arabia, Jacobs et al [103] analysed the effect of continuous enteral feeding versus intermittent feeding, on the incidence of secondary pneumonia in 24 patients in their ICU. They reported an incidence of pneumonia, following three days of continuous enteral feeding and mechanical ventilation, of 54%, in whom they documented initial cultures of the pathogenic organism from the stomach, oropharynx and then trachea before the pneumonia ensued. The initial cultures from all these sites did not grow any organisms. Criteria used for the diagnosis of secondary pneumonia were only clinical and sputum culture. Antacids and H-2 blockers were not routinely used unless there was evidence of gastrointestinal haemorrhage. The 07h00 gastric pH in those receiving continuous enteral feeding was persistently documented at greater than 3.5, and 92% of these patients went on to develop pneumonia , while in the other patients who were fed intermittently the incidence of pneumonia was only 9% which was highly significant, and they were documented to have an intragastric pH intermittently of less than 3.3 (an intragastric pH of <2.7 is bactericidal, while a pH ≥ 3.65 is bacteriostatic within 2 hours). The mortality amongst those who had a higher

07h00 gastric pH was 46% as compared with only 18% in those with an intermittently lower pH, but this did not achieve significance.

There must be certain reservations about this study, because the patient sample size is too small to be meaningful, and the diagnostic criteria used to diagnose secondary pneumonia are poor; nevertheless, it makes compelling reading and is an area which requires further evaluation. The philosophy of intermittent feeding must be nearer the physiological norm of intermittent meals; the idea of permitting rest periods, so that the intragastric pH can fall within the bactericidal range, would appear to be a logical next step.

A further complication associated with nasogastric feeding and which may add to the infectious complications associated with it, is the potential for such feeds to become contaminated by a break in the cold-chain, or other breaches of hygiene, in the preparation and administration of the feed. Although often such infection is more likely to manifest with gastrointestinal disturbances, there is the potential for enteral feeding to act as a source for respiratory infection, particularly if the load of microorganisms is large, or the aspiration cannot be effectively cleared as may occur in patients with depressed consciousness [53].

6.1.4 Bacterial Translocation

Fiddian-Green et al [95] have also recently published work suggesting that nosocomial pneumonia may be the result of bacterial translocation rather than the aspiration of contaminated secretions. He showed [191] that monitoring of the intramucosal gastric pH may provide early evidence of impending gut ischaemia; gastric tonometry has been suggested as one of the best ways of detecting early, compensated shock at a stage when anticipatory management can improve outcome and prevent complications. The possibility of ischaemic mucosal injury, as demonstrated by gastric mucosal tonometry, which appears to be fairly common in the critically ill, may allow the translocation of

bacteria and their toxins into the bloodstream and serve as an important cause of multiple system organ failure and possibly nosocomial pneumonia. Goris [192] has attempted and failed to produce an animal model which would support such a mechanism, and there would appear to be little evidence to support this rather attractive hypothesis at present.

6.1.5 The Micro-organisms

The aetiology of hospital-acquired pneumonia differs from community-acquired pneumonia where the responsible pathogens are recognised to be *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella spp.*, *Chlamydia pneumoniae* and a variety of viral agents most commonly, with variations in the incidence regionally, with the seasons, and depending on host factors. *Legionella pneumophila* has been linked to outbreaks of pneumonia in hospitals around the world; the mode of spread of this organism within the hospital has been shown to be via the cooling towers used for the airconditioning plants, and shower heads [193]. Patients who are elderly and immunocompromised are again the most at risk of contracting this type of infection, and the mortality for nosocomially acquired Legionnaires' disease is reported to be of the order of 33%, compared with approximately 1% for community-acquired disease [69].

Chlamydia pneumoniae is a more recently identified agent of acute respiratory infection. Grayston et al [194] in a retrospective survey identified it as the possible aetiological agent by postive serology in 10% of 198 cases of pneumonia. In 9 patients the infection was thought to have been acquired in hospital; all these patients were in the ICU and intubated, having undergone major surgery or sustained multiple trauma, however Bates et al [127] recently identified the *TWAR* agent in 4% of nosocomial pneumonias in the general hospital, and almost 10% of community-acquired cases, so that the significance of this agent appears to be becoming more important, as it is more actively looked for.

With all the caveats of different diagnostic methods and criteria, the pattern of the microbial species isolated in association with nosocomial pneumonia reported in the National Nosocomial Infection Survey in the U.S. [195] is important in providing a basic profile of the spectrum of pathogens. It is interesting to contrast this with the spectrum of pathogens in community acquired pneumonia identified in a prospective survey by Andrews et al [196]. (See Table Two)

Table Two: Aetiology of community acquired pneumonia [196] and nosocomial pneumonia [195]

	Community-acquired	Nosocomial
Bacterial species	%	%
Streptococcus pneumoniae	34	4
Mycoplasma pneumoniae	18	0
Influenza A virus	7	0
Haemophilus influenzae	6	8
Chlamydia psittaci	3	0
Legionella pneumophila	2	0
*Enterobacteriaceae**	1	*
Staphylococcus aureus	1	14
Pseudomonas spp	0	15
*Klebsiella spp**	*	14
*Enterobacter**	*	10
*Escherichia coli**	*	8
*Proteus spp**	*	
Morganella morganii	*	7
Providencia stuartii		
Other *Streptococci*	1	2
Serratia marcescens	0	6
Others	3	4
No organisms	33	0

The incidence of community acquired pneumonia due to Gram negative organisms is of the order of 1% to 5% and again, patients who are immunocompromised with diabetes mellitus or alcoholism, or liable to aspiration from epilepsy or inebriation are most

susceptible to this, as their oropharynx has been shown to harbour a higher percentage of these organisms [36].

The spectrum of pathogens responsible for nosocomial pneumonia in the ICU differs considerably from that in the community and even the general hospital [141], because the emphasis in aetiology becomes still more predominantly Gram negative [38] and is more often found to be polymicrobial [127].

Using a baboon model, Johanson et al [197] investigated the accuracy of a variety of different techniques to determine the microbiological aetiology of nosocomial pneumonia, following prolonged mechanical ventilation. By using a bacterial index calculated from the log sum of the colony counts for the individual organisms, they found that nosocomial pneumonias were predominantly polymicrobial (in 50 - 87% of instances) in the absence of antibiotic therapy. Organisms included in this index included those grown at only very low concentrations which might have been considered to be merely colonising agents or contaminants in other studies. The stipulation of a threshold such as 10 000 cfu/ml in lavage fluid for any individual organism, or bacteraemia, would have yielded a much lower incidence of polymicrobial infections. Where there is failure of response to seemingly appropriate antibiotic therapy for a single aetiological agent, the possibility of a polymicrobial infection should nonetheless be considered.

In their multi-institutional analysis of pneumonias requiring ICU admission , Ruiz-Santana et al from Spain [150], contrasted the organisms identified in cases of community-acquired and hospital-acquired pneumonia. They showed a similar difference in the spectrum of microorganisms: with a 34% incidence of *Streptococcus pneumoniae* causing community- acquired pneumonia requiring ICU admission, compared with only 5.6% of hospital-acquired cases. 31.1% of secondary pneumonias in the ICU were due to *Pseudomonas aeruginosa*, compared with 2.1% of community-acquired infections.

Risk factors for Gram negative airway colonisation include previous antibiotic therapy, coma, uraemia, diabetes, advanced age, pre-existing lung disease, smoking, surgery, serious illness, malnutrition, gastric acid neutralisation, steroid therapy, and instrumentation of the airway either with endotracheal intubation or tracheostomy [5,33].

The possible predisposition to pneumonia by neutralisation of gastric acid by antacids and cimetidine has already been alluded to, as well as the fact that in patients receiving sucralfate, the organisms were isolated in lower concentrations, than in the antacid/H-2 group, possibly due to an independent anti-bacterial property of sucralfate [59]. Driks et al [62], attempted to demonstrate that such therapy alters the spectrum of organisms causing secondary pneumonia by showing that, in the seven patients who received sucralfate and developed ventilator-associated pneumonia, the organisms isolated were both fewer and included only mixed Gram negative bacilli in one, and *Haemophilus influenzae* in another; whilst in the sixteen receiving antacids or H-2 blockers who developed this complication, there were 7 cases of mixed Gram negative bacilli, including *Pseudomonas aeruginosa* in 5 cases, *Escherichia coli* in one, *Proteus spp* in two, and *Serratia* and *Enterobacter* in one each. *E.coli* and *Staphylococcus aureus* were also involved in a further 5 cases.

du Moulin et al [54] and Atherton and White [52] similarly showed increasing colonisation by aerobic Gram negative bacilli in patients treated with antacids, with clear evidence of oropharyngeal colonisation and airway colonisation secondary to this. Snepar et al [61] showed higher titres of organisms in post prandial gastric aspirates in those taking antacids and cimetidine. While they were unable to show any difference in the degree of colonisation when comparing antacids with cimetidine, there did appear to be an increase in the fasting titres of organisms in those taking cimetidine, compared with their pretreatment levels.

While such evidence is suggestive, it is of course far from conclusive, as the spectrum of organisms exactly mirrors that recognised to cause secondary pneumonia in the

critically ill, and gastric colonisation by such Gram negative bacilli is recognised to cause nosocomial pneumonia [56] regardless of the use or type of antacid therapy.

The majority of nosocomial respiratory infections are thought to be due to colonisation of the stomach, oropharynx and trachea by microorganisms, whose growth is promoted by alterations in the host defences and environment, and the aspiration of such organisms into the lower airway. Many of the above-mentioned risk factors for colonisation by Gram negative bacilli are thought to operate by causing alterations in bacterial adherence. However, Schwartz et al [39] showed that the pattern of colonisation leading to infection differs for different organisms. While oropharyngeal colonisation preceded tracheal colonisation and infection for the *Enterobacteriaceae*, the pathogenesis of tracheal acquistion of non-*Enterobacteriaceae* was completely different. Although the non-*Enterobacteriaceae* formed the minority of organisms isolated in the hypopharynx, they constituted about two-thirds of the Gram negative bacilli colonising the trachea after intubation or ICU admission. Their appearance in the trachea took place without their having been isolated previously in any other site, suggesting an exogenous route of acquisition from the environment.

The Gram negative organisms isolated from patients with nosocomial pneumonia are often divided into "endogenous" or "exogenous", according to the presumed origin of the organism. Typical exogenous species include *Pseudomonas aeruginosa* which is a common constituent of the flora in the hospital environment, but uncommonly found as part of the normal human flora. *Escherichia coli* which is a common component of the normal intestinal flora would be regarded as an endogenous organism. In the ICU, this classification falls away somewhat, as the flora undergoes such changes that even species regarded as exogenous, such as *Pseudomonas aeruginosa*, may transiently form part of the intestinal flora.

Bartlett et al [140] studied the bacteriology of nosocomial pneumonia prospectively in a general hospital, using microbiological samples taken by transtracheal aspirate, pleural

fluid and blood cultures only. The diagnosis of pneumonia was made on clinical and radiological criteria. They isolated Gram negative bacilli in 47%, anaerobic bacteria in 35%, *Staphylococcus aureus* in 31% and *Streptococcus pneumoniae* in 26%, but found that nearly half the specimens yielded a polymicrobial flora, with more than one potential pathogen. The difficulties with achieving an accurate diagnosis of nosocomial pneumonia, let alone a microbiological diagnosis, have been discussed previously. This study is one of a very few that reports the incidence of anaerobic organisms as potential nosocomial pathogens. The problem with obtaining an accurate value for the incidence of anaerobic microorganisms as pathogens, is that these organisms are fastidious and difficult to culture. There is a problem with obtaining suitable specimens, and getting them rapidly enough to the laboratory to yield any growth at all; furthermore, these organisms are all presumed to be sensitive to penicillin or metronidazole, and therefore of little interest as they are easily treated, and thus not worthy of further attention.

The aetiological agents responsible for nosocomial pneumonia vary with the timing of such infections [107]. In cases where the pneumonia occurs within two to four days of admission, the organisms resemble more closely those responsible for community acquired infections: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella* catarrhalis all being frequent pathogens. The *Enterobacteriaceae*, *Acinetobacter spp*, *Serratia marcescens*, *Pseudomonas spp* and *Staphylococcus aureus* are isolated as the causative organisms with increasing frequency, as the patient's hospital stay becomes more prolonged. Particularly after five days, the isolation of such organisms can be anticipated.

Prior antibiotic therapy, before the onset of pneumonia, was identified by Fagon and his group [123] to be the only risk factor with a statistically significant effect on mortality. They assessed the risk factors for the development of pneumonia in 52 patients in whom they were able to prove the diagnosis, and then tried to subdivide them according to the aetiological agent responsible. However, they were unable to

show much difference between the patients' risk factors in this way, except that 83% of those who died with nosocomial pneumonia had received prior antibiotic therapy compared, with only 48% of those who had not. Previous antibiotic therapy increased the probability of being infected by *Pseudomonas aeruginosa* or *Acinetobacter spp.* 100% of those patients who were infected by coagulase-positive staphylococci resistant to methicillin had received prior antibiotics, whereas this occurred in only 33% of those staphylococcal infections who had not. The mortality in those who developed nosocomial ventilator associated pneumonia was double that of those who did not develop this complication, although the frequency of poor prognostic factors such as those enumerated in the previously mentioned studies was similar. The mortality for those who had received prior antibiotic therapy was 83%, compared with 48% in those who had not received prior antibiotics.

As has already been discussed, part of the difficulty in making the diagnosis of nosocomial pneumonia lies with the fact that the lower airway in intubated patients is no longer sterile, and it thus becomes both more important and more difficult, to distinguish between organisms that are merely colonisers from those that are actually causing infection [113].

Crouch et al [198] using a baboon model demonstrated that colonisation of the oropharynx occurred within 24 to 48 hours of instrumentation of the respiratory tract. This was followed by aspiration of the colonising organisms into the tracheobronchial tree; however, specimens from the lower airway remained sterile for at least 24 hours longer than the proximal airway. They showed in the majority of these cases, who all received antibiotic therapy, that ,despite the presence of multiple organisms in the tracheobronchial secretions, pneumonias were usually due to a single species, selected from the organisms colonising the more proximal regions. The most common colonising organisms were *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Staphylococcus aureus*.

Salata et al [137] in their study evaluating the examination of tracheal aspirates for elastin fibres, went to great lengths to differentiate between colonisation of the respiratory tract and true infection. However, in spite of this, there is a considerable overlap between the two groups in their study, which unfortunately detracts from it, by its resultant low specificity. They identified the pathogens responsible for colonisation and infection, and showed a very similar profile of prevalence; apart from a much higher incidence of infection than colonisation by *Pseudomonas aeruginosa*, and much greater levels of colonisation by yeasts and *Streptococcus species*. They reported that *Pseudomonas aeruginosa* and *Serratia marcescens* accounted for more than 50% of the organisms causing infection, while *Staphylococcus aureus* and *epidermidis* accounted for a further 28%.

When evaluating the Gram's stain and quantitative tracheal aspirate cultures in colonised and infected patients, they found a higher Gram's stain grading for the presence of polymorphonuclear leukocytes and bacteria at the time of development of the pulmonary infiltrate in those who developed infection, compared with colonised patients with and without a pulmonary infiltrate. They noted that, patients who developed definite criteria for pneumonia, frequently demonstrated a rapid and marked rise in bacterial colony counts before the appearance of new or progressive pumonary infiltrates and clinical manifestations of infection. The importance of this finding is that it confirms what one intuitively expects: that by serial monitoring of the tracheal aspirate, one should be able to predict the evolution from colonisation to infection. Such serial monitoring should help limit the number of occasions that it is necessary to resort to more invasive diagnostic techniques. However, as mentioned previously, Schwartz et al [39] could not confirm this finding for non-*Enterobacteriaceae* Gram negative organisms.

Salata also evaluated demographic, clinical, microbiologic and diagnostic differences between those with infection compared with colonisation. No difference between the

two groups could be found for age, smoking or alcohol consumption, mortality, cardiopulmonary disease, diabetes melllitus, neoplasia, renal failure, hepatic failure, previous antibiotic therapy, steroid usage, duration of hospitalisation before intubation, or previous episodes of pneumonia. Although the mortality rates were similar, death was attributed to pneumonia in 63% of infections, as opposed to only 9% of those who were merely colonised. The frequency of underlying illnesses was similar in the two groups apart from neurological disease which was highly significantly more common in those who were colonised. Only longer duration of intubation was associated with a greater risk of infection in this study.

While different diseases may predispose to colonisation by differing organisms, the organisms in different ICUs might also be expected to affect the aetiology of nosocomial infection. In their survey of the differing infections occuring in different ICUs within the same hospital, Brown et al [8] analysed the different frequencies of distribution of the various organisms in the ICUs. They found a fairly uniform incidence of *Staphylococcus aureus* in the different units of approximately 10%, while the incidence of *Enterobacteriaceae* varied from 17.4% in the medical/surgical ICU to 3.3% in the neonatal unit. The incidence of *Pseudomonas aeruginosa* was again highest in the medical/surgical unit at 10.4%, but similar incidences were recorded in the neonatal and paediatric units, the incidence being lowest in the coronary care unit at 5.9%. The incidence of *Haemophilus influenzae* was uniformly low: 3.5% in the medical/surgical ICU and 1.3% in the neonatal unit. The overall incidence of *Enterococcus* was 5.6% and the incidence of *Candida sp* was surprisingly high at 8.7%. Such findings are for all infections and not only pneumonias. The incidence of primary bacteraemias, skin and wound infections was similar in all units and possibly accounts in part for the similarity in the incidence of staphylococcal infections. The higher incidence of pneumonias in the medical/surgical unit may be surmised to have been due to the *Enterobacteriaceae* and *Pseudomonas aeruginosa* which predominated

there, while nosocomial pneumonias are far less common in such areas as coronary care.

Chandrasekar et al [157] found a similar distribution of organisms when comparing the infections in the medical and surgical ICUs that they studied.

Craven et al [10] compared the prevailing organisms isolated by the site of infection in their medical and surgical ICUs. The infections in the surgical unit were predominantly urinary tract infections, bacteraemias and wound infections, while those in the medical ICU population were more prone to develop pneumonia. The aetiological agents isolated are shown in Table Three.

Table Three: The aetiological agents causing pneumonia in different ICU populations (Craven [10]).

	Medical ICU	Surgical ICU
Gram Negative organisms	%	%
Escherichia coli	7	8
Klebsiella, Enterobacter Serratia	30	38
Pseudomonas aeruginosa	16	27
Other	42	40
Haemophilus spp	9	13
Gram positive organisms	%	%
Staphylococcus aureus	16	19
Enterococci	0	0
Other *streptococci*	18	14
Candida	2	8
Other/not identified	5	5

Some infections had more than one organism isolated. There was a general similarity in the organisms isolated in the two units.

In their multicentre study of nosocomial infections in the ICU, Daschner et al [9] identified the most common organisms causing pneumonia as being *Pseudomonas aeruginosa* (30%), *Escherichia coli* (20%), *Staphylococcus aureus* (20%), *Klebsiella pneumoniae* (17%), enterococci (9%), *Candida albicans* (6%) and *Serratia marcescens* (6%). The total of 108% being due to the polymicrobial aetiology in some cases. They

also identified a differing spectrum of pathogens and differences in their pattern of occurrence between the ICUs in this study. They point out that each ICU needs to be aware of the prevailing microorganisms in the local environment, and how they vary, as this will determine to a certain extent the infection control methods which need to be applied. Unfortunately, the definitions of infections and the techniques used to obtain specimens are not specified in this study, so that the results must be interpreted with some reservations, nevertheless the spectrum closely resembles that from studies where these details are mentioned.

Rello et al [155] assessed the aetiology of nosocomial pneumonia in 1000 consecutive admissions to a medical/surgical ICU. They used more specific diagnostic techniques than Craven [10] to obtain representative specimens, and their diagnostic criteria were much more clearly specified than those of Chandrasekar [157] or Brown [8]. The predominant pathogens isolated notwithstanding, were Gram negative bacilli in 62.6% although the incidence of *Staphylococcus aureus* was higher than in the other mentioned studies at 23.2%. Interestingly, they found that patients with underlying chronic obstructive airways disease were at greatest risk for colonisation (and presumably infection) by Gram negative bacilli, whereas neurosurgical patients were at greatest risk of Staphylococcal pneumonia. They were unable to explain this discrepancy, which has also been reported from elsewhere [199].

Espersen et al [200] prospectively studied the incidence of pneumonia (the diagnostic criteria of which are not mentioned) due to *Staphylococcus aureus* in mechanically ventilated patients. They identified 17 cases out of 295 patients ventilated in their general ICU. Neurosurgical patients again had a significantly higher frequency of both colonisation (27.8%), and infection (25.9%) due to this agent than other categories of patients, which they attributed to therapy with hypothermia and steroids. This study is however very poorly reported, as they make no attempt to define diagnostic techniques or criteria and the overall incidence of pneumonia in their unit is not even mentioned.

The accuracy of diagnostic procedure to distinguish between colonisation and true infection was the object of studies by Chastre and his group. In a study carefully designed only to identify true pathogens, Chastre et al [121] compared the cultures obtained by protected specimen brush and bronchoalveolar lavage. While obtaining polymicrobial growth by both techniques, they felt able to distinguish between colonisation and infection by the number of colony forming units obtained. Fagon et al [123] using the protected specimen brush as the "gold standard" for diagnosis, isolated 111 microorganisms associated with 52 episodes of pneumonia, of which 84 were cultured in significant quantities to be regarded as significant. 61% were Gram negative bacilli, and 38% Gram positive organisms, anaerobes accounting for only 1%. *Pseudomonas aeruginosa*, *Acinetobacter spp* and *Proteus spp* accounted for 63% of all Gram negative bacilli and 39% of the total organisms isolated, while the most common Gram positive organisms were *Staphylococcus aureus* and nonpneumoniae streptococci. 75% of all episodes included at least one Gram negative bacillus and 48% were due to such organisms alone; *Pseudomonas aeruginosa* and *Acinetobacter spp* being involved respectively in 31 and 15% of such cases. Only 13% of patients with pneumonia caused by *Pseudomonas aeruginosa*, *Staphylococcus aureus* or *Acinetobacter spp* survived, whereas a statistically significant 31% of patients with pneumonias due to other organisms survived.

A similar spectrum of pathogens was demonstrated in an earlier study by this group [112], when they compared specimens obtained by protected specimen brush with lung cultures of specimens taken immediately after death. The high yield of *Acinetobacter spp* and *Staphylococcus aureus* in these studies is rather unusual; as most of the studies in the literature give little attention to the importance of these organisms and report much lower rates of incidence. Graybill et al [38] in their early study of nosocomial pneumonia in the general hospital, attributed 3% of cases to *Staphylococcus aureus* and, as in many studies, do not even mention identifying *Acinetobacter spp*. The more

recently reported experience of the French group, however, reflects very closely the local ICU spectrum of organisms [141,148].

The differing mortality rates associated with different organisms causing nosocomial pneumonia was a phenomenon already described in the ICU by Stevens et al [201] in a paper published in 1974, reporting their experience in the late 1960s. Their diagnostic techniques included clinical examination, sputum bacteriology and chest radiographs. They reported similar findings to later studies: patients with Gram positive pneumonias who did not go on to develop Gram negative organisms during the period of symptoms and signs involving the lower respiratory tract, had a mortality that did not differ from patients without pneumonia; however, they were younger, had less duration of prolonged mechanicial ventilation, and lacked other indices of severity of illness (such as a low serum albumin, or a large A-a oxygen gradient). The other patients who developed pneumonias due to Gram negative organisms had a much higher mortality, were older, had a higher proportion of underlying lung disease, more severity of illness parameters, and more prolonged ventilation.

In the following study by Celis et al [185], the incidence of these organisms, using specific diagnostic techniques, is again much lower with incidences more representative of most reports. In their analysis of risk and prognostic factors associated with nosocomial pneumonia, they identified infection with *Pseudomonas aeruginosa*, *Enterobacteriaceae*, and other Gram negative bacilli, *Streptococcus faecalis*, *Staphylococcus aureus*, *Candida sp*, *Aspergillus sp* and episodes of polymicrobial pneumonia, by a stepforward logistic regression analysis, as independent factors which worsened the prognosis. The mortality rate of the polymicrobial episodes was 66.6%. For those due to *Pseudomonas aeruginosa* (sixteen patients) the mortality was 75%, while the mortality was 40% with the *Enterobacteriaceae* (five patients). However, such organisms as *Acinetobacter baumanii* (one patient), *Streptococcus faecalis* (two patients), *Staphylococcus aureus* (two patients), *Candida sp* (two patients) and

Aspergillus sp (one patient) were associated with a 100% mortality. Although the numbers are small, this is one of the few studies that has specifically evaluated the prognosis related to individual microorganisms. Organisms such as *Streptococcus pneumoniae*, *Streptococcus viridans*, *Bacteroides fragilis*, or *Haemophilus influenzae*, which more closely resemble community-acquired pathogens, were categorised as "low risk", because all patients with pneumonias due to these organisms survived.

In 60% of the patients in this study, no pathogen was identified, despite extensive and invasive diagnostic procedures, probably because only those organisms that were isolated from the lower respiratory tract were accepted to be definitely proven pathogens; it is difficult to know how many of these patients may have had a non-infectious diagnosis. The outcome in those where no organisms were isolated was relatively benign.

Similar results are reported from the same centre in studies by Torres et al [158], Jimenez et al [149].

Silver et al [202] in a study designed to look specifically at nosocomial pneumonia due to *Pseudomonas aeruginosa*, reviewed the records of 34 patients, admitted to their ICU over a 2.5 year period. 59% survived the initial episode of nosocomial infection; however, half of those who survived the initial episode went on to develop a recurrent episode, and only 50% of these went on to survive hospitalisation; however, 90% of those who did not develop recurrent episodes survived. They identified the patients who developed recurrent bouts of Pseudomonas as being significantly sicker, as measured by the APACHE II and APS scores, more likely to have underlying chronic pulmonary disease, younger, and also to have received more prolonged ventilation and to stay for longer both in the ICU and hospital.

The poor outcome reported in this study, in those with recurrent episodes of infection is possibly not unexpected. It might have been easier to assess whether *Pseudomonas*

aeruginosa was "a high risk pathogen", if the outcome and other parameters were contrasted with other causes of nosocomial infection in the same unit. It is difficult to draw conclusions from this study as it is well known that patients with chronic lung disease are at risk of colonisation by *Pseudomonas aeruginosa*. Patients with more severe underlying disease are also likely to spend longer in the both the hospital and the ICU, and those who develop pneumonia will require more prolonged ventilation. Once again, it is difficult to be certain which process initiated the whole course of events.

Johanson et al [5], in an early study of nosocomial respiratory infections, suggested that the pathogenicity of an organism was probably more the result of host factors than the result of virulence or invasiveness of the organism. They identified a similar spectrum of organisms in both those who were colonised and infected: *Klebsiella pneumoniae*, *Escherichia coli*, species of *Enterobacter* and *Pseudomonas aeruginosa* being the most commonly isolated organisms. They found that no single bacterial species showed exceptional invasive potential, and that the frequency of isolation of a particular organism from patients with clinical infection, was similar to its isolation from patients who were merely colonised.

Bryan and Reynolds [152] in their study of bacteraemic nosocomial pneumonia identified a similar spectrum of organisms, with a slightly increased mortality in those where the blood culture yielded a polymicrobial result. They identified a high incidence of underlying disease in those who developed this complication and felt unable to attribute death solely to the infection, but rather that it was the culmination of the severity of the underlying disease and its inevitable consequence. This rather serves to confirm the impression created by Johanson that it is not the virulence of the organism, but the lack of host responsiveness which determines whether disease develops and what the final outcome may be.

Tran et al [203] in their review of the relationship between mortality and a number of risk factors, similarly found that underlying disease, particularly the presence of organ

failure, was the major determinant of mortality. While the severity of underlying illness, age, etc, predisposed to sepsis, sepsis alone was not an independent contributor to overall mortality.

The importance of host factors in determining outcome is illustrated in a study by Seidenfeld et al [204], who studied 129 patients with ARDS (from a variety of causes), of whom 29% survived. Necropsy was performed in 51% of non-survivors. The authors did not attempt to differentiate between primary and secondary pneumonia in this report, although by implicating colonisation as the main factor to explain the predominance of Gram negative infections, there is a suggestion that the majority must be presumed to have been acquired in the hospital.

The difficulty in diagnosing pneumonia in patients whose chest radiograph already has a diffuse pulmonary infiltrate has been discussed, and the difficulty of making an aetiologic diagnosis is well illustrated in this study. No infective cause could be identified in 67% of patients who survived (of whom 24% were clinically septic), compared with only 33% of non-survivors (in whom there was clinical evidence of both pulmonary and non-pulmonary sepsis in 76%). Two or more organisms were simultaneously implicated in 45% of all the infected patients. 27% of patients with pulmonary infections were bacteraemic. 58% of respiratory infections (both primary and secondary) were due to Gram negative bacilli, 12% to Staphylococci, 20% to other Gram positive organisms, predominantly enterococci, and 10% to a miscellaneous group. Pneumonia associated with the development of ARDS occurred in 22% of survivors. In those who did not survive, pneumonia was found at autopsy in 20%, but was thought clinically to have developed in 53% as a further complication. The overall survival rate for patients with ARDS and pneumonia was only 12%.

The authors attribute this poor outcome to inadequate tissue penetration by aminoglycosides, which are known to penetrate respiratory secretions poorly, and may be inactivated in the presence of a purulent exudate. When the adequacy of treatment

by site and organism was assessed, 70% of pneumonias were considered to have received adequate therapy in that they had received the appropriate antibiotic; however, the dose may have been inadequate as the outcome in such patients was poor. The better outcome in those patients who received inadequate therapy is difficult to explain: the authors attribute this to less severe infection, which is possibly a little unconvincing. More of the inadequately treated infections were due to *Pseudomonas aeruginosa*, in which Stevens et al [201] previously showed the mortality to be unaffected by antibiotic therapy (although their patients did not have ARDS). The dilemma of whether cause and effect exists in the relationship between pneumonia and mortality is still unanswered by this study, which illustrates all the difficulties associated with ARDS, infection and outcome.

Coalson et al [160] from the same group did attempt to answer this question in their study on the effect of bacterial superinfection on lung function in ARDS in a baboon model. They induced acute lung injury by means of intravenous oleic acid infusion and demonstrated that in the absence of bacterial superinfection, the resultant effect on lung function was mild; however in those that went on to develop infection, 80% deteriorated and died of complications of their infection. Thus in the presence of lung injury, acquired infection, either in the form of nosocomial pneumonia, or infection at another site may markedly worsen lung function. The current understanding of the septic syndrome and definitions of sepsis and the mediators of multiple organ dysfunction, possibly shed greater light on this issue [205].

6.2 The Aetiology and Significance of Nosocomial Urinary Tract Infections

Gross et al [151] analysed the incidence of nosocomial infection in the general hospital and identified the urinary tract as the most common site for infection and which did not appear to lead to death. As in all the other studies looking specifically at this type of infection, the presence of an invasive device, the urethral catheter, was the greatest risk factor for the development of infection.

For urinary tract infections, the most common organisms isolated were *Escherichia coli*, *Proteus spp* and *Pseudomonas spp*; *Serratia spp*, enterococci and yeasts, although less frequently isolated, were also common.

Haley et al [161] in their analysis of nosocomial infections occurring in 338 hospitals across the U.S.A., estimated that 61% of all patients with nosocomial infection had at least one urinary tract infection. This study evaluated a large number of the potential risk factors for infection at the various sites, but unfortunately did not attempt to look at the spectrum of organisms responsible for such infections. Although such data would undoubtedly have illustrated a marked variation between centres, such information, apart from being interesting, might have been useful in determining preventive methods, if patterns of organisms associated with the various risk factors could have been highlighted. The incidence of urinary tract infection, as with infection at other sites, was shown to increase with increasing age, and unlike infection at other sites, was more common in women than in men. Such infections occurred more commonly in neurosurgical and urological patients, with orthopaedic and thoracic surgery patients showing an intermediate risk of infection. In patients receiving any form of immunosuppressive therapy, the risk of contracting a nosocomial infection at the four most common sites, viz: bladder, lower respiratory tract, wound and primary bacteraemia, was lowest for the urinary tract. The incidence of infection was shown to increase linearly with increasing duration of hospital stay, but a prior community-

acquired urinary tract infection, doubled the risk for the subsequent development of a further urinary tract infection. The presence of a urinary catheter was yet again shown to be the most important factor for the development of infection: the risk of infection without a catheter was 1.4% compared with 9.9% for those with indwelling catheters; 67% of infections occurred in patients with catheters. The incidence of infections was also shown to be higher if the patient was mechanically ventilated, although there are obviously a number of factors such as the severity of the underlying disease, etc which must contribute to this phenomenon.

Very little has been written about the aetiology of urinary tract infections specifically pertaining to the ICU. Most of the patients are catheterised for the greater part of their duration of stay, either as an adjunct to the management of fluid balance, or to facilitate nursing management, which must contribute significantly to the risk of infection in these patients. Whether there are indeed organisms that predominantly cause infection in the ICU setting is not clear, but the sheer volume of urinary tract infections, and the relative ease with which they are usually both diagnosed and treated, as well as the lack of many studies to show any relationship between such infections and mortality, has made this an area which has not been particularly well studied.

Urinary tract colonisation and infection in the catheterised patient, both in the general hospital and ICU, is often polymicrobial. The organisms best recognised to cause urinary tract infection in the catheterised patient are *Escherichia coli* and *Providencia stuartii*. The mechanisms for infection of *E.coli* are the adhesin type 1 pilus, which has been well studied, and also Tamm-Horsfall protein. For *Providencia stuartii*, the adhesin is MR/K and this is thought to mediate adhesion to the catheter surface itself [78]. Both these organisms are thus well-suited to colonising and infecting the catheterised patient, particularly if such catheterisation is long-term.

Other organisms which are common uropathogens, particularly in patients who are catherised for less than a month, include *Pseudomonas aeruginosa*, Proteus mirabilis,

Morganella morganii and *Klebsiella pneumoniae*. The enterococci and staphylococci also may account for a small proportion of bacteriuria [78]. More importantly, *Candida albicans* and other yeasts may colonise the bladder and urinary tract in catheterised patients, who are immunocompromised by severe illness, have received previous antibiotic therapy, or who are diabetic.

Only 1-5% of all patients with catheter associated bacteriuria are thought likely to develop bacteraemia in the general hospital setting [76]. Whether this risk increases in the ICU is not known. Men with catheter associated bacteriuria are at greater risk of developing bacteraemia than women. Certain bacteriuric organisms such as *Serratia marcescens* are also thought more likely to result in bacteraemia than others [76]. The mortality attributed to bacteraemia from nosocomial bacteriuria is 13%, although again most deaths occur in patients with severe underlying diseases. Even without overt evidence of systemic disease, catheter associated bacteriuria is thought to be related to an increased risk of death [78].

Table Four: The spectrum of organisms isolated from catheter bacteriuria and its relationship with the duration of catheterisation [78]

Organism	Short-term %	Long-term %
Providencia stuartii	0	24
Proteus species	6	15
Escherichia coli	24	14
Pseudomonas aeruginosa	9	12
Enterococcus	7	8
Morganella morganii	0	7
Klebsiella spp	8	4
Coagulase negative staphylococci	8	3
Other Gram negative bacilli	7	6
Other Gram positive bacteria	4	4
Yeasts	26	0

Daschner et al [9] in their multicentre study of infection in ICUs in Europe, reported that urinary tract infections were the most common cause of nosocomial infection. All patients who developed urinary tract infections, with the exception of neonates, were catheterised. The organisms most commonly isolated in such infections were *Escherichia coli* (28%) and the enterococci (22%), while other Gram negative organisms were *Pseudomonas aeruginosa* (5%), *Klebsiella pneumoniae* (5%), *Proteus mirabilis* (8%), *Enterobacter* (3%), *Serratia marcescens* (0.5%) and a miscellaneous group comprising 11.5%. *Candida albicans* accounted for only 6% of isolates, as did both *Staphylococcus aureus* and *Staphylococcus epidermidis*.

While Donowitz et al [162] reported an increasing incidence of Gram positive infections in his study of infections in the ICU, Chandrasekar et al [157] were unable to confirm this in their study where Gram negative bacilli predominated. Both these studies noted that fungal infections usually followed prolonged antibiotic therapy, but were relatively uncommon.

Craven et al [10] reported a high incidence of urinary tract infections, particularly in their surgical ICU. The organisms isolated from the patients in the surgical ICU followed much the same pattern as reported above: *Escherichia coli* 23%, *Klebsiella*, *Enterobacter* and *Serratia species* 34%, *Pseudomonas aeruginosa* 11%, other Gram negatives 7% (including *Citrobacter freundii*); enterococci 7%, other Gram positive cocci 5% (including *Staphylococcus epidermidis*, *Bacillus species* and *diphtheroids*), and a much higher incidence of *Candida* than in the other studies mentioned above at 20%, while in 4% the organism was not identified. The pattern in the patients in the medical ICU was virtually the same, apart from a slightly higher incidence of *Pseudomonas aeruginosa* and a lower incidence of *Candida species* (16%). Almost all the patients who developed urinary tract infections in both ICUs were catheterised.

This experience with fungal urinary tract infections is similar to our local experience, but the wide discrepancy between the incidence of such infections reported in these studies is difficult to explain.

Brown et al [8] reported that *Klebsiella*, *Enterobacter* and *Serratia* were the most common organisms encountered causing nosocomial infections in the four categories of ICU in their hospital, followed by *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas* (all species) and *Candida* (all species). While noting the most common types of infections and the organisms most prevalent in each unit, they unfortunately did not analyse this data according to the site of the isolate, so that the spectrum of pathogens causing their 25.8% incidence of urinary tract infections is not clear.

6.3 The Aetiology of Nosocomial Bacteraemias

Nosocomial bacteraemias are largely thought of as device-related infections, and as such the staphylococci are well recognised to be the most frequently isolated pathogens, accounting for one half to two thirds of all episodes. Although *Staphylococcus aureus* is a common cause, the coagulase negative staphylcocci have more recently become increasingly important ; it is thought that they may have a selective advantage in such infections, by being able to adhere more aggressively to plastic catheters than other organisms. The other pathogens most frequently encountered in device-related infections are: *Klebsiella spp*, *Enterobacter spp* and *Serratia marcescens*, although a contaminated infusate may also be the cause of such bacteraemias. *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *Citrobacter freundii* may also be isolated in these infections; however, they are still more unusual and contamination of the infusate should be excluded, if such organisms are isolated. *Candida albicans* and the *Candida spp* are seen most frequently in patients who have received prolonged therapy with broad spectrum antibiotics; and are most commonly encountered amongst patients who are receiving total parenteral nutrition. Such infections are thought to arise from contamination at the catheter entry site, although there have been reports of fungal contamination of the T.P.N. solution [81]. Bacteraemia due to the *Corynebacteria species* occurs almost exclusively in severely immunocompromised patients, who are, or have been, receiving broad-spectrum antibiotics, and who have indwelling intravascular devices.

The most frequent source of the bacteraemia depends on the population that is being studied. Eykyn et al [184] in a large study of almost 4000 cases of bacteraemia in London, showed that 40% of episodes were community-acquired and 60% nosocomial. Nosocomial septicaemias were usually of lesser severity than were the community-acquired septicaemias. Unfortunately they did not report the actual mortality

attributable to septicaemia in this survey, although they noted that the mortality was lower for a nosocomial than a community-acquired bacteraemia.

The primary site for both community-acquired and hospital- acquired bacteraemia was the urinary tract, the second most common site for community acquired bacteraemia being the biliary tract. The most common organism isolated was *Escherichia coli*, although its proportion of the total number of causative organisms was lower in hospital (20%) than in the community (25%). In the general hospital setting, they noted that after the urinary tract, intravascular devices were the second most common source for bacteraemia; together these two sites accounted for more than 50% of nosocomial bacteraemias. *Escherichia coli* was never associated with infected intravenous lines; however, the second most common organism in the hospital setting, *Staphylococcus aureus* (19%), which was isolated almost as frequently as *Escherichia coli*, was detected in almost half the episodes of infected intravenous access sites. Other important nosocomial pathogens causing bacteraemia were (in descending order of frequency): *Klebsiella spp* (9%), *Pseudomonas spp* (8%), coagulase negative staphylococci (8%), *Proteus spp* (5%), and then a miscellaneous assortment of other organisms including anaerobes (5%) and yeasts (1.5%), while the isolates were polymicrobial in 11%. These infections were largely related to instrumentation, either of the urinary tract, or more rarely after surgery or other manipulation; the other main source being surgical wounds, particularly sternal wounds after cardiac surgery, or abdominal wound infections after emergency Caesarean section and hysterectomy. Certain underlying diseases were associated with particular isolates in community-acquired bacteraemias: *Escherichia coli* was found to occur twice as commonly in diabetics as in non-diabetics, *Streptococcus pneumoniae* was three times more common in alcoholics; however, this pattern was not detected in nosocomial bacteraemias.

Interestingly, Forgacs et al [93] in their prospective study of bacteraemias from the ICU in the same hospital, over a remarkable fifteen year period, noted that the most

common source of bacteraemic infection in the ICU (66%) was the intravenous line. Despite the previous study by Eykyn, one must conclude that the intravenous line is a more important source for bacteraemia than the urinary tract, since 17% of all bacteraemias occurred in the much smaller ICU population (1.2% of the hospital beds). Forgacs noted a male predominance of 64.9%, with a mean age of 51.8 years. 25% of bacteraemias in the unit, were community-acquired and largely related to pneumococcal pneumonia (38.5%); 22% occurred in medical patients and 53% in surgical patients.

The pattern of microbial isolates was similar to that encountered in the rest of the hospital, apart from a higher incidence of *Pseudomonas spp* (11% vs 5.6%)and fungal septicaemias (3.8% vs 0.4%). The commonest nosocomial organisms to be isolated were staphylococci, and the source of these organisms was an infected intravenous line in 66% of cases. The mortality from bacteraemia in the ICU was 60.4% compared with only 13.1% in those without bacteraemia.

Forgacs divided the site of infection into medical and surgical, and while there more than twice as many surgical as medical episodes, showed that 40.8% of all medical bacteraemias were related to intravenous lines, compared with 30.6% of surgical bacteraemias; the respiratory tract accounted for 17.5% of medical and 7.3% of surgical bacteraemias, peritoneal dialysis 21.4% of medical cases and wound infections for 32.7% of surgical cases. The urinary tract was the source of only 8.7% of bacteraemias in the medical patients and a similar 7.7% in the surgical patients.

The differing effects of an organism depending on the environment and host are probably best characterised by *Streptococcus pneumoniae*. Mylotte et al [206] compared the differences between community and nosocomial bacteraemias due to this organism. They showed a mortality for community acquired bacteraemia of 26.9% compared with community acquired pneumococcal pneumonia with bacteraemia where the mortality was 18.2%; however, the mortality of nosocomial pneumococcal bacteraemia was significantly higher at 75.8%, and the mortality of nosocomial pneumococcal

pneumonia with bacteraemia was also much higher at 66.7%. Patients with nosocomial bacteraemia were more likely to have received previous antimicrobial therapy, than those with community acquired disease; there were also the usual risk factors associated with hospitalisation including sedation, the use of respiratory assist devices. The patient population was also older, with co-existing, often ultimately fatal, underlying disease. Alcoholism was identified as a risk factor for community-acquired, but not nosocomial pneumococcal infection.

When reviewing the aetiology of nosocomial bacteraemias, once again the problem of cause and effect arises . Haley et al [161] in their study of nosocomial infections in hospitals across the U.S.A., highlighted a number of risk factors for all types of nosocomial infection. While convincingly demonstrating an association between severity of illness and susceptibility to infection, there was possibly no causal relationship between the majority of factors identified, and the infectious complications which developed. They estimated that 5.6% of all nosocomial infections in the general hospital were primary bacteraemias, but that, when such infections were analysed specifically among surgical patients who had undergone a surgical procedure, the incidence increased to 9%. These patients experienced 54% of all bacteraemias, of which 45% were primary and 60% secondary. As with other secondary infections, the risk of infection increased with the patient's age and duration of hospital stay, it was higher for men than women, and highest in thoracic surgery patients, but lowest in gynaecological patients. The risk for acquiring a nosocomial bacteraemia increased 10.3 times if the patient received steroids or other immunosuppressive therapy; the risk for subsequent nosocomial infection was highest amongst patients who had presented with an initial community-acquired or secondarily acquired nosocomial bacteraemia, particularly if the infection had been acquired in hospital. The risk for nosocomial bacteraemia appeared to be related to the duration of surgery, although this probably only gives some indication of the severity of illness, or the likelihood of bacterial contamination from complications during surgery, such as spillage or

ischaemia. The risk of bacteraemia increased sixteen fold in patients who received ventilatory support, and 14% of the bacteraemias developed in the 1% of patients who were mechanically ventilated. This observation is probably just a further indicator of severity of disease. There is no comment on the predominant pathogens causing bacteraemias in hospitals in the U.S.A..

Gross et al [151] found a similar incidence of 9% for nosocomial bacteraemias, in their comparative study of the incidence of nosocomial infections in a university and community hospital. When death was associated with nosocomial infection, they found that more than 50% of the deaths had occurred in the ICU. There was no specific microbial aetiology identified for the bacteraemias. Virtually all patients, with or without nosocomial infections, had intravenous catheters placed, but in those who developed infections, other more invasive devices were present such as central venous catheters, intra-arterial monitoring devices and nasogastric tubes. Yet again, the severity of disease necessitating the placement of such devices, may obscure a causal relationship; however, the authors observed that such devices were not present more often in patients who developed infections than in those in whom such infections did not occur.

Donowitz et al [162] studied the risk of nosocomial infection in their ICU which admitted predominantly surgical patients. They found an incidence of nosocomial bacteraemia of 5.2%, which was significantly higher than the incidence in the general hospital. Patients from the general surgical service were most prone to this complication, with an incidence of 12% compared with thoracic surgery, where the incidence was only 2%, or otorhinolaryngology and plastic surgery, where the incidence was reported as 0%. These incidences contrast markedly with those of Haley et al [161] where the thoracic surgery patients were at highest risk of such infection, but we are not given sufficient detail about either patient population to be able to draw further conclusions. The organisms most frequently isolated from the blood were

Staphylococcus epidermidis, *Staphylococcus aureus*, and *Serrratia* and *Pseudomonas spp.*

When comparing the prevalence of infections in the different intensive care units within the same hospital, Brown et al [8] identified the neonatal ICU as the intensive care unit where primary bacteraemias were most prevalent (14.5% of all infections), with an incidence 50% higher than any other unit. There was a significantly higher rate of infection in which no pathogen was isolated, and they noted that the high prevalence of aerobic Gram negative bacilli encountered in all the other ICUs, was not a feature. The mortality attributable to nosocomial bacteraemia in this study was 27% compared with 6% in non-bacteraemic controls. However, overall only 46% of the infections in this study were ICU acquired, and there is no attempt to differentiate the source of the pathogens in the analysis.

Chandrasekar et al [157] do not comment specifically on the incidence of nosocomial bacteraemias in their study of nosocomial infections in their various ICUs, suggesting that such infections were of only limited importance in terms of incidence and sequelae.

Daschner et al [9], in their multicentre European review, identified septicaemia as causing between 21.8% and 14.2% of all nosocomial infections, the incidence varying markedly between centres and for different categories of patients. They found venous catheter thrombophlebitis to be associated with a high risk of secondary septicaemias; this factor was identified in 77.5% of patients who developed this complication. The frequency of isolation of the organism responsible for these episodes of nosocomial bacteraemia did not vary significantly between the centres: *Staphylococcus aureus* 48%, *Staphylococcus epidermidis* 10%, other Gram positive cocci 10%, *Escherichia coli* 9%, *Pseudomonas aeruginosa* 7%, *Klebsiella pneumoniae* 6%, *Serratia marcescens* 2%, *Proteus mirabilis* 3%, *Candida albicans* 1% and other bacteria 4%, accounted for the organisms isolated in Freiburg, while the spectrum was very similar

in the Swiss hospitals, excepting for one unit where there was a higher incidence of *Serratia marcescens*.

Craven et al [10] noted a higher incidence of bacteraemia (8%) in their surgical ICU than in the medical ICU (5%). Nosocomial infections were noted to develop in 48% of those who had a central line placed, 51% of those with an arterial line and 56% of those with a pulmonary artery catheter. The rate of infection was related to the duration such devices were in place. The site of the infections in relation to the devices however was not specified. Yet again the role of the invasive device as a risk factor for infection is uncertain, as it may serve more as an index of susceptibility to infection and severity of disease, than as its direct cause. There was a considerable difference in the spectrum of organisms isolated in the two units although in both units, 64% of the pathogens were Gram negative. There is no immediately obvious explanation for this difference, although the higher incidence of *Enterococci* and *Enterobacteriaceae* (other than *E.coli*) in the surgical patients might be presumed to be related to bowel surgery, or the underlying disease.

Table Five: Organisms causing bacteraemia [10]

Organisms	Medical ICU	Surgical ICU
Gram negative	%	%
Escherichia coli	28	17
Klebsiella, Enterobacter		
Serratia spp	12	27
Pseudomonas aeruginosa	4	9
Other	20	11
Haemophilus influenzae	0	0
Gram positive		
Staphylococcus aureus	16	15
Enterococci	4	21
Other streptococci	16	5
Other Gram positive cocci	0	17
Candida species	0	5

The local experience with nosocomial bacteraemia in a respiratory ICU, reported by Potgieter et al [148], was limited in that the overall incidence of nosocomial infection was only 23.6%, and only 13% of these infections were bacteraemias, effectively only eight patients. In three of these, generalised septicaemia was attributed to an infected intravenous line; in one, the infection followed nosocomial pneumonia. There were a further eleven patients in whom positive catheter cultures were obtained, but without evidence of infection. The incidence of such catheter tip colonisation has not been reported in most of the studies assessing the incidence of nosocomial bacteraemia, nor

do the definitions make allowance for the often questionable significance of an isolated positive blood culture, particularly of an organism such as *Staphylococcus epidermidis* [94]. Such discrepancies make the drawing of comparisons and conclusions difficult.

In a study designed to assess nosocomial bacteraemia, unrelated to colonisation and catheter related sepsis within the general hospital, Bryan et al [152] analysed episodes of bacteraemia attributed to nosocomial pneumonia over a five year period in four major hospitals. Although they acknowledge the difficulty in accurately determining the source of the bacteraemia by the epidemiological methods that they used, they argue that their findings are in agreement with other studies, and that they were able to validate their findings by autopsy in 26 cases. In this way, they identified 1 551 episodes of bacteraemia in 300 547 patients, but of these, only 172 episodes in 168 patients were attributable to nosocomial pneumonia. A male predominance of 62% was identified. All the patients in whom bacteraemic nosocomial pneumonia developed had underlying diseases such as neurologic disease, tumours, chronic heart or lung disease, renal failure and alcholism . which would have predisposed to the development of secondary infection. The findings of this study indicate that bacteraemic nosocomial pneumonia is a complication of the critically ill, but the authors were unable to demonstrate cause and effect. The same organism was isolated from both sputum and blood in 49% of instances, Gram positive organisms being isolated from both sites more frequently than Gram negative. The mortality was also significantly higher for Gram negative bacteraemia (45%), than for episodes associated with Gram positive bacteraemia (26%). 12% of the blood cultures were polymicrobial, and in such cases the organisms were most commonly *Staphylococcus aureus*, *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*. These episodes were associated with a greater mortality than in those in whom a single pathogen was cultured (68% vs 57%). The same organisms, either individually or in combination, were the most common pathogens in patients whose death was attributed to nosocomial pneumonia; the authors suggest that

empirical antimicrobial therapy, in patients suspected of having this complication, should include agents effective against these organisms.

Smith et al [163], in a study designed to evaluate the mortality attributable to primary nosocomial bacteraemia in the ICU population, identified *Staphylococcus aureus* in 39% of the isolates, Gram negative bacilli in 24% (*Pseudomonas aeruginosa* 10%, *Klebsiella pneumoniae* 5%, *E. cloacae* 5%, *P. cepacia* 2%, *Proteus mirabilis* 2%) and *Candida albicans* in 15%; *Streptococcus sp* (10%), *Enterococcus* (7%) and *Staphylococcus spp* (5%) accounted for the remainder. The spectrum of pathogens would suggest that the primary source for these infections would have been an infected intravenous catheter. In an attempt to differentiate between the mortality due to the severity of the underlying disease from that of the complication, the mortality of these patients was matched with a control population of equal disease severity, but without this complication; in this way, an excess mortality of 28% was ascribed to the bacteraemia.

In a large study of 331 catheters, specifically designed to evaluate diagnostic techniques for detecting catheter related sepsis by quantitative culture, Brun-Buisson et al [90] identified the organsisms obtained by this method according to whether they resulted in contamination, colonisation or infection. The spectrum was similar to other studies: there were 99 isolates of which 54 were thought to be contaminants (34 coagulase negative staphylococci, 6 *Acinetobacter spp* and a miscellaneous spread of the other organisms), 7 isolates were thought to be colonisers only (3 *Acinetobacter spp*, 1 *Staphylococcus aureus*, 1 *Proteus spp* and 1 other), there was catheter sepsis, but no bacteraemia associated with 18 isolates (5 *Staphylococcus aureus*, 8 *Staphylococcus spp*, 1 *Pseudomonas aeruginosa*, 2 *Acinetobacter spp*, 1 *Klebsiella spp* and 1 *Candida spp*), while there were 20 isolates with catheter-related sepsis and bacteraemia (13 *Staphylococcus aureus*, 2 *Staphylococcus spp*, 2 *Klebsiella spp*, 1 *Escherichia coli*). The predominant organisms causing infection were therefore Gram positive cocci with

Staphylococcus aureus in 42% of episodes, followed by *Staphylococcus spp* 22%; the Gram negative bacilli caused 18.4% of infections, while *Acinetobacter spp* and *Pseudomonas spp* were analysed separately, and thought to have caused 13.5% of episodes, and *Candida* 4.5%. The patients in this study were all critically ill and the overall incidence of central venous catheter infection was high at 11%. The authors identified a prolonged duration of catheterisation, the presence of another septic focus, or bacteraemia, to be associated with an increased risk of both catheter infection and contamination. A significant number of infections in this study were attributed to haematogenous seeding of the catheter. which then acted as a metastatic septic focus responsible for persistent clinical sepsis and positive blood cultures. Bacteraemia due to *Escherichia coli* and other Gram negative organisms, although common, was thought unlikely to result in secondary catheter infection. Most infections occurring either from the initial insertion, or subsequent manipulation of the catheter, were due to staphylococci.

Other studies looking specifically at aspects of catheter related sepsis [80,84,87,89] demonstrated a similar spectrum of pathogens both colonising and causing infection in the intensive care unit; the risk factors for colonisation being very similar to those already mentioned [85].

There is surprisingly little specific detail on the septic complications of total parenteral nutrition, where infection is acknowledged to be a major hazard [164]. One of the earlier studies by Ryan et al [81] identified catheter-related sepsis in 11% of all patients receiving T.P.N., and 7% of all catheters used for this purpose became infected. There was a 2.1% incidence of fungaemia identified in this study, with 61% of the organisms recovered from confirmed cases of catheter-related sepsis being due to *Candida spp* or *Torulopsis glabrata*. These patients had all previously received broad spectrum antibiotics and half of them had also received steroids. Such factors as the catheter care

provided, and the duration of placement of the catheter were important in determining whether sepsis occurred.

In the most recent and comprehensive reviews on the subject [98], infectious complications were identified to occur more commonly in those who were borderline or mildly malnourished and received T.P.N.. The major infectious complications were largely unrelated to the intravenous catheter, generally being postoperative infections such as pneumonias, empyemata, abscesses etc and only one death in the 192 patients who received T.P.N. was attributed to catheter-related sepsis.

6.4 The Aetiology of Nosocomial Wound Infections

Bacterial contamination of a wound is inevitable, even under the most stringent conditions of asepsis, with the best use of aseptic technique and the use of laminar flow[170]. The presence of devitalised and traumatised tissue, haematomas and foreign material are all recognised to increase the risk of wound infection, as are host factors such as malnutrition, extremes of age, diabetes mellitus, concomitant steroid therapy and severe obesity [170]. The routes of wound contamination remain largely undefined[181]. Nasal carriage of staphylococci has been recognised to predispose to the subsequent isolation of such organisms from the wound site. Despite adequate skin disinfection, the resident flora located in the sebaceous glands and hair follicles is largely unaffected, and the organisms are easily carried into the wound by the scalpel. Airborne contamination is also recognised to be of importance, although its importance relative to direct contamination via hands, skin and surgical instruments is uncertain. However, quite remarkably in view of the above preamble, wound infection is the exception rather than the rule, although in all the studies reported in the literature, surgical patients are at greater risk of nosocomial infection than medical patients.

In their study of the relationship of death to nosocomial infections in the general hospital, Gross et al [151] omitted to specify wound infection as a category in its own

right, choosing rather to categorise such infections which were clearly regarded as of limited significance only, as part of "other".

Green et al [175] assessed the increased duration of hospital stay and direct cost attributable to post-operative wound infection in a controlled study. They found that such infection tended to double the duration of hospital stay, and significantly increased the associated costs; however, there was no mortality among any of the patients in this study.

Haley et al [161] in their review of nosocomial infections in 300 major U.S. hospitals, identified wound infections as one of the four most important sites. They estimated that of all patients with nosocomial infection, 30% had at least one surgical wound infection, with 14.5% having multiple infections at the same site; the risk of a previous infection increasing the risk of a recurrence four times. When analysing the nosocomial infections in the surgical patients separately, they identified wound infection as the cause of 40% of hospital-acquired infections in this group, It was particularly frequent in the obstetrical and general surgical patients. Immunosupressive therapy increased the risk of infection three-fold, while mechanical ventilation was associated with a five times increased risk. There was an almost linear increase associated with increased duration of preoperative stay, as well as the duration of surgery. The same phenomenon of the severity of underlying disease predisposing to the development of complications was encountered, and other host factors such as age, diabetes and other underlying disease also appeared to add to the risk of infection at the wound site.

Haley et al [28] developed a simple multivariate index of patient susceptibility and wound contamination, to identify patients at high risk of surgical wound infection. Such factors as abdominal surgery, an operation which lasted more than 2 hours, a contaminated or dirty-infected operation, or the presence of at least three diagnoses were all found to be highly significant risk factors predictive of the development of infection.

The pathogen responsible for wound infection depends not only on the site of the wound, but also on whether the surgery was elective or emergency and whether the operation was clean, clean-contaminated, contaminated or frankly dirty. Gil-Egea et al[27] identified additional risk factors in their large prospective study of infections in clean wounds. The drainage of clean wounds significantly increased the incidence of infection and the skill of the surgeon accounted for up to a tenfold difference. The scheduling of the surgery also affected the chance of infection, with operations scheduled last being least likely to lead to infection. The authors explained this phenomenon as being due to the fact that longer procedures, which are recognised as higher risk, are usually performed first. The microbiology of the wounds showed that the causative organisms were 29% coagulase negative staphylococci, 28% *Staphylococcus aureus*, 21% *Enterobacteriaceae*, 3% *Pseudomonas spp*, anaerobes comprising the remainder.

While because of the implied severity of underlying disease, the incidence of wound infection might be expected to be higher in the ICU than in the general hospital population, Donowitz et al [162] found no significant difference in incidence between the two settings. They assessed the risk for nosocomial infection according to the services admitting the patient to the ICU; obstetrical and gynaecology patients were identified as having the highest incidence of wound infection (9%) compared with otorhinolaryngology and medicine where the incidence was 0%. The organisms in this study were not analysed according to the site at which they were isolated.

Chandrasekar et al [157] compared the nosocomial infection rates between the different patient populations admitted to the different types of ICUs within the same hospital. They found a significantly higher rate of wound infections in the ICU compared with the ward; however, the data that they used included a burns unit where the overall incidence of infection was 30% and, although no further details are provided, the

authors comment that all post-operative wound infections emanated from this and the surgical ICU. Again no analysis according to site of the organisms is provided.

Craven et al [10] analysed the incidence of nosocomial infection specifically in their medical and surgical intensive care units, where they found an overall incidence of hospital-acquired infection of 31% in the surgical ICU compared with 24% in the medical unit. Similar risk factors for the development of infection at this site were identified: duration of admission, shock, hospitalisation in the surgical ICU, steroid therapy, chemotherapy and renal failure and the use of invasive devices. 25% of surgical patients were infected on admission compared with 44% of medical patients, but the incidence of wound infections in the surgical ICU was 10% compared with only 2% in the medical ICU. There were many underlying reasons predisposing the surgical ICU patients to wound infection: 21% of the patients in the surgical ICU were multiple trauma patients, 12% had head trauma, 8% had intra-abdominal abscesses or trauma and such diagnoses did not occur in the medical ICU. There was also a higher proportion of patients with gastrointestinal disease (21% vs 15%) and malignancy (15% vs 8%). The incidences of diabetes mellitus (18% in the medical patients vs 12%)and alcoholism (34% vs 26%) were however higher in the medical ICU. The organisms causing wound infection in this study are shown in Table Six

Table Six: Bacterial isolates causing wound infection

Organisms	Medical ICU	Surgical ICU
Gram negative	%	%
Escherichia coli	0	17
Klebsiella, Enterobacter, Serratia spp	9	29
Pseudomonas aeruginosa	27	23
Other	9	20
Haemophilus influenzae	0	1
Gram positive	%	%
Staphylococcus aureus	36	20
Enterococci	0	6
Other streptococci	9	14
Other Gram positive cocci	18	14
Candida spp	0	6
Not identified	9	3

(The total percentages add up to more than 100 because many of the isolates were polymicrobial)

There was a difference in the organisms causing wound infection in the two ICUs, with *Staphylococcus aureus* being isolated more frequently in the medical ICU. Unfortunately the site of the wounds in the medical patients is not specified - possibly they were mainly septic intravascular catheter sites? The aerobic Gram negative bacilli

formed the large majority of isolates in the surgical ICU. Despite these apparently adverse factors, including the type of organisms being associated with complications of disease requiring admission to the surgical ICU, the mortality was higher in the sicker patients in the medical ICU.

Daschner et al [9] in their multi-centre study in European ICUs, similarly found nosocomial infections to occur more commonly in surgical patients. They identified the presence of a surgical wound as the cause of hospital-acquired infection in 5.2% of instances in Swiss hospitals, compared with 7.3% in Freiburg. The organisms causing wound infections in this study were predominantly Gram positive cocci, with *Staphylococcus aureus* in 40%, *Staphylococcus epidermidis* in 8%, *Enterococcus* in 6% and *Group B Streptococcus* in 2%. Gram negative bacilli were less frequent: *Escherichia coli* 16%, *Pseudomonas aeruginosa* 12%, *Enterobacter* 2%, *Klebsiella pneumoniae* 6%, *Serratia marcescens* 2%, *Proteus mirabilis* 4%, other bacteria comprised 2%, while *Candida albicans* caused 2% of infections. Secondary bacteraemia was identified as being due to nosocomial wound infections in 47%, which demonstrates that such infections should not be too easily dismissed as of minor importance only.

Wound infection in surgical patients resulted in 33% of all cases of bacteraemia, and was identified as the most important site for secondary bacteraemia in surgical patients in the ICU by Forgacs et al [93]. The most common pathogens isolated from the blood in these cases were the Gram negative *Enterobacteriaceae* accounting for 31%, *Staphylococcus aureus* 28%, *Pseudomonas spp* 7%, *Streptococcus spp* and anaerobes 31%, with a variety of unspecified organisms causing the remainder. The authors point out that although Staphylococcus was the most common organism causing bacteraemia, this was not so if the episode was wound related, unless the infection followed cardiac surgery.

Infection in the severely traumatised patient forms another important part of the spectrum of wound and other infections encountered fairly commonly in the general or surgical ICU. The host defence mechanisms in the traumatised patient closely resemble those of patients with severe, chronic underlying disease. The patients' susceptibility to infection and the spectrum of organisms encountered are thus often different from what might be expected in young and previously fit individuals. Almost all infections in this category of patients are nosocomial, and related to the multiple invasive procedures required to resuscitate and manage these cases. Although such patients almost invariably have sustained a variety of wounds, it would appear from the literature that the wounds themselves are of fairly limited significance in terms of morbidity and mortality.

Schimpff et al [181] in their review of infections in severely traumatised patients admitted to their trauma centre identified a high percentage of nosocomial infections in patients who stayed in hospital for more than 48 hours as a result of their injuries. There were no infections in those whose stay was shorter than this. In 135 patients who developed nosocomial infection, there were 35 bacteraemias, 8 wound infections, 40 urinary tract infections and 7 peritoneal infections. The most prevalent organisms included: *Pseudomonas aeruginosa* (24%), *Candida spp* (16%), *Klebsiella spp* (10%), *Enterobacter* (8%), *Escherichia coli* (6%) and coagulase negative staphylococci (6%). Nearly 50% of the bacteraemias were due to organisms such as *Candida* spp, staphylococci and *Serratia marcescens*. The organisms encountered in the secondary infections were similar to those previously described as common causes of device related infections of the urinary tract, vascular catheter-related or ventilator associated infections. Wound infections related to trauma were uncommon in this study.

Caplan and Hoyt [207] identified infection as the second most common cause of death in multiple trauma patients, after head injury. In their survey of 2 348 severely traumatised patients admitted to a trauma unit, the incidence of infection was 27%.

Overall, 44% of infections were associated with bacteraemia, and 14% of the infected patients were thought to have died as a result of their infections. 37% of patients who developed nosocomial infections had multiple episodes, with 9% having at least four episodes of secondary infection. The most common sites of infection were the urinary tract (18%), pneumonia (15%), empyema (11%), phlebitis (12%), primary bacteraemia (10%), surgical wounds (10%), intra-abdominal abscesses (7%), central nervous system related (7%), sinusitis (5%) and catheter related (2%). Fourteen percent of infections and 21% of bacteraemias were attributed to the use of vascular devices. The surgical wound infections were mostly due to coagulase negative staphylococci, which also caused IV catheter infections, infections related to chest tubes, and intraventricular catheters; however, the isolates from the intra-abdominal abscesses, which were usually deep-seated and related to major intra-abdominal trauma were polymicrobial, and required extensive surgical drainage.

Goris et al [180] retrospectively analysed the cause of death in 89 patients who had sustained blunt trauma. They found that, in the group who died more than 7 days after their injury, death was due to sepsis in 88%. The only factor which seemed to differentiate survivors, with similar severity of injury, was the absence of injury to the extremities. Although the exact details of these injuries are not provided, it would seem that again it was not the presence of wound sepsis, but rather the associated lack of mobility, which resulted from limb injuries, that lead to complications; nosocomial pneumonia possibly being the final event.

Allgower et al [179] again emphasised the importance of early mobilisation to prevent complications of nosocomial infection, in patients who had sustained polytrauma. The mortality of the patients who developed overt sepsis was 65%. The main causes of fatal sepsis being: nosocomial pneumonia 28% (100% of nosocomial pneumonias were fatal), subphrenic abscesses 28%, wound infections 8% (these patients sustained major injuries with traumatic amputations of legs, and the mortality was 100%), urinary tract

infections 12%, brain empyema 4%, the site not being identified in 8%. They found that 4% of post-traumatic wounds became infected, with an incidence of 12.3% of trauma patients developing wound infection - an incidence of wound infection which was higher than in their surgical patients. Traumatic wounds contrasted with surgical wounds in that the incidence of Gram positive and Gram negative organisms isolated was similar, whereas in the surgical incisions, the infections were predominantly caused by Gram negative organisms.

Machiedo et al [208] reviewed the patterns of mortality in their surgical ICU. 41% of admissions to their unit followed trauma. The overall mortality rate in the unit was 6%, with 37% of the 101 deaths in the study period being due to trauma : 81% of the deaths in the trauma patients were as a direct result of the injury, 19% dying as a result of severe, uncontrolled infection, resulting in septic shock or multiple organ failure. However, in the non-traumatic group of patients, 62% of the deaths were the result of sepsis.

Thus while trauma predisposes to infection which remains a late and important cause of morbidity and mortality in these patients, the initial wound infections in themselves are not regarded as important sites or sources for the development of nosocomial infection, as they are usually easily managed with debridement, the early administration of antibiotics and appropriate surgery.

CHAPTER 7. THE PREVENTION OF NOSOCOMIAL INFECTION

Introduction

The prevention of nosocomial infection within the intensive care unit environment can be divided simplistically into the prevention of exogenous,or cross-infection, and the prevention of endogenous infection. The importance of nosocomial infection has been highlighted in the previous sections dealing both with its aetiology, incidence and the attributed morbidity and mortality. The development of infection either by endogenous or exogenous mechanisms requires the acquisition of the organism, colonisation of a susceptible site and the subsequent progression to tissue invasion and infection. Although many so-called "endogenous" infections are thought to be acquired from colonisation of the patient's own gastrointestinal tract. the organisms must first have been acquired from the hospital environment. Thus. the prevention of the exogenous spread of infection should aim to prevent the development to some extent of both routes of infection.

Under normal circumstances, the endogenous colonising microbial flora consists largely of anaerobic organisms, while other organisms such as *Moraxella catarrhalis*, *Klebsiella spp*, *Serratia spp*. etc are unable to colonise in sufficient quantities for sufficiently prolonged periods to cause infection. In the critically ill patient however, all these organisms can cause infection. and it has been estimated that nosoocmial infection is due to endogenous colonisation in 30% to 50% of instances [209]. Techniques aimed at preventing endogenous infection have included the use of disinfectant solutions on skin and mucosae. the irrigation of cavities, total gut sterilisation in leukopaenic patients, topical antimicrobial prophylaxis and more recently selective decontamination of the digestive tract.

The control of the immediate environment surrounding the patient is important in preventing nosocomial infection. It is thought however that the aerogenous route plays

a minor role in the transmission of microorganisms. Techniques such as laminar flow are accordingly no longer deemed necessary in the general ICU [209], although infection with airborne microorganisms is still an important consideration in patients with burns or extensive open wounds, and in the severely immunocompromised leukopaenic and transplant patients.

The effect of nosocomial infection on patient outcome in the ICU, although not clearly established as one of cause and effect, clearly contributes to both morbidity and mortality, and thus significantly increases the cost of hospitalisation. Pneumonias, septicaemias and wound infections are the most expensive nosocomial infections to treat and it is estimated that the average episode of hospital-acquired infection cost between $1 800 and $42 000 in the USA in 1986 [11]. These infections in the intensive care unit setting are thought to be a leading cause of death which should be preventable - at least to a certain extent.

The continuous microbiological surveillance of all patients and infections within the hospital is probably not justified, as it requires vast quantities of time, manpower and money; however, surveillance with goal-directed objectives is important in identifying problem areas and effectively controlling the sources of infection.

Cost-containment in the area of infection prevention is also extremely important and includes the education of all involved in hospital administration and patient care. For example, it has been shown to be unnecessary to change dressings within 24 hours of an aseptic surgical procedure, as wound infections are not recognised to occur within this early period. The use of protective gowns for all entering the ICU is unnecessary if the person is not going to be in direct contact with patients. Except for certain ventilation systems, improvements in architectural design have not been shown to have any effect on the incidence of nosocomial infection [11]. However, the importance of a spacious and good working environment should not be underestimated, as its influence on staff morale is carried over into all aspects of patient care. Even in this important

area, there needs to be a guidance and some measure of realism in setting achievable targets for reducing the incidence of nosocomial infection.

7.1 The Infection-Control Team

Hospital-acquired infection has been recognised to be a problem of sufficient magnitude to justify the development of specific infection control programmes. Their aim is to minimise the risk of infection to patients, staff and visitors, by maintaining constant surveillance. The Centre for Disease Control in Atlanta has established that the efficacy of nosocomial infection control depends on the degree of surveillance activity, and where such levels increased, the infection rate progressively declined [210]. A good infection control programme needs a broad multidisciplinary approach with consideration of the medical, administrative, economic, legal, social and ethical implications. Although cost contraints are foremost in the minds of all concerned with hospital management, the medical and ethical aspects must not be allowed to be overshadowed.

In order to permit efficient, streamlined and economic functioning, most hospitals have developed infection control committees, who are responsible for the administration of this important problem; such committees may vary depending on the staff structure and size of the hospital, as well as the available resources. To ensure maximum co-operation, such a team needs representation from all sectors involved in any aspect of infection prevention. Ideally those participating should be interested, influential within the hospital and endued with tact and other socially endearing qualities! In most hospitals, the team would consist of clinicians, especially infectious disease specialists, microbiologists, epidemiologists, pharmacists, pharmacologists, administrators, nurses involved in infection control and surveillance, and infection control practitioners. As is often the case, as the size of the committee expands, its efficacy diminishes.

The existing policies need continuous review by the infection control committee, so that problems can be identified and appropriately managed. The infection control committee must be required to be accountable to the administration for their findings, and to be sufficiently empowered to be able to implement the necessary changes.

The functions of an infection control team are:

1) the education of the staff in practices to prevent nosocomial infection, and their motivation to carry these out to the best of their ability on a daily basis.

2) surveillance, investigation and reporting of outbreaks of infection.

3) the formulation of an antibiotic utilisation and prescribing policy, and the monitoring of antibiotic resistance patterns.

4) the screening and protection of staff and patients from transmissible diseases.

Daschner [9] reported a 17% reduction in the rate of nosocomial infections in his hospital in Freiburg when an infection control programme and team were introduced. Where cost constraints limit the scope of such programmes, the high risk areas in the hospital must be prioritised. Possibly the area which deserves most attention is the intensive care unit. The ICU has the highest rate of nosocomial infection in the hospital, with more device related infections than elsewhere, and is where antibiotic resistance most commonly originates.

A recent survey of infection control in the intensive care units in the United Kingdom [211] showed that in 13% of the units, there were no isolation facilities, 60% had fewer than one washbasin per ICU bed and some units used open urinary drainage systems. While there appeared to be fairly adequate accessibility to microbiologists for advice on infection related problems, excessive numbers of specimens were being submitted for microbiolgical surveillance, without any co-ordinated response to problems. This study

revealed a disturbing lack of awareness of methods of infection prevention and control and a need for greater education.

Education

It is essential that the importance of preventing and controlling nosocomial infection is conveyed to all concerned, by both the visibility and accessibility of the infection control team. The participation of the staff in regular meetings at which the guidelines for infection prevention can be presented, specific areas of concern highlighted, and new aspects of policies in management of procedures or drugs explained, help both to educate and motivate all concerned by the creation of a sense of involvement and team spirit.

The results of educational programmes are often disappointing in the carry-over of the procedure into the daily practice in the unit [43]. It is thought, nonetheless, that units with educational programmes do have lower infection rates than those without any form of in-house education, probably by the demonstration that these matters really are of concern to all those involved. Constant cajoling does serve as motivation!

The organisms that cause nosocomial infection are frequently transmitted by the hands of the hospital personnel, and hand-washing is considered to be the single most important procedure in preventing nosocomial infection. Hand-washing has been recommended after contact with every patient by the Centers for Disease Control, particularly in the ICU where patients are highly susceptible to nosocomial infection [212]. Handwashing is described as " a vigorous rubbing together of all surfaces of lathered hands, followed by rinsing under a stream of water"[213]. However, adherence to recommendations of frequent hand-washing has been demonstrated in several studies to be poor, even during studies where there was careful monitoring and motivation of the staff [41,212].

In controlling an outbreak of nosocomial infection, the team needs firstly the ability to identify the reservoirs of colonised and infected patients and the contaminated areas in the environment; secondly, to halt the spread of infection by improving handwashing and aseptic technique, isolating colonised and infected patients, and eliminating any identified common environmental sources for the outbreak. Susceptible patients need to be separated and protected if at all possible, while those who are colonised may need to be treated, depending on the nature of the pathogen. In many centres, the outbreak of a resistant organism has prompted the closure of the unit to new admissions. Finally, antibiotic usage needs to be controlled to prevent further resistant strains from emerging.

Surveillance

Continuing microbiological surveillance is an area of extreme importance. The quantification of the problem by this method not only helps in the setting of realistic goals and providing feedback for motivation to improve problem areas, but surveillance cultures also fulfill an important role, both in the management of the patients in intensive care, and in the overall "housekeeping" of the ICU. Surveillance cultures may be used to help detect early breakdowns in the general maintenance of hygienic standards, air-conditioning, environmental control, sterilisation of equipment, and the adherence by staff to aseptic technique and other hygienic precautions.

From an epidemiological point of view, such cultures may serve to reveal an outbreak of resistant microorganisms. However they are more often of value in assisting in the determination of the most appropriate antibiotic use, and are helpful in the early detection of the emergence of resistant strains.

Microbiological sampling has become a routine part of patient care in the ICU, usually being performed twice or three times weekly in all patients. Samples of tracheal aspirate, samples from all wound sites and urine are sent for microscopy, culture and

sensitivity from all patients in the ICU on specifically designated days, regardless of whether infection is clinically suspected or not. It is possible that with routine surveillance cultures, the use of more invasive diagnostic techniques to obtain a pathogenic microorganism may be reduced to a minimum. The phemonenon of the isolation of a colonising organism gradually becoming predominant on repeated samples, and then becoming associated with the presence of pus cells and systemic signs of infection, should render further investigation superfluous. The diagnosis of nosocomial infection may be pre-empted in this way; so that if infection is clinically suspected, clues are already to hand as to where the most likely site of infection may be, and what pathogenic organisms and their antibiotic sensitivity patterns should be expected, so that therapy can be initiated appropriately and expeditiously.

It is for this reason that it is important to differentiate between "bronchial" infections and "nosocomial pneumonias": there can be no justification for awaiting a deterioration in gas exchange and a new radiological infiltrate, when surveillance cultures indicate that colonisation by a predominant organism is leading to infection.

7.2 Antibiotic policy and the monitoring for drug resistance

Selection pressure caused by antibiotic use is the main factor responsible for the emergence of antibiotic-resistance; the best ways of curbing the spread of antibiotic resistance are through the adherence to an antibiotic policy, and preventing and controlling outbreaks of infection [214].

Part of the duties of an infection control commitee is to monitor the levels of antibiotic resistance and antibiotic usage in the hospital; guidelines for the prescribing of drugs in the hospital can be formulated from this, in an attempt to curtail further antibiotic resistance, contain costs and assist clinicians in selecting the most appropriate empirical therapy for nosocomial infections. The development of antibiotic policies, if effectively implemented, may, with the use of "drug holidays", over time, allow the

reintroduction of agents to which the hospital flora had previously become resistant. However, the institution of such policies requires careful follow-up as these therapeutic manoeuvres are not always successful, and may promote further antibiotic resistance [34]. With the development of new antibiotics, the problem of resistance has become increasingly serious, resulting in a desperate race between the use of higher doses and newer antibiotics on the one hand, and the development of resistance on the other.

Certain organisms have been recognised to be susceptible to the development of high level antibiotic resistance; these organisms include methicillin-resistant *Staphylococcus aureus*, high level penicillin-resistant *Streptococcus pneumoniae*, carbenicillin-aminoglycoside resistant *Pseudomonas aeruginosa* and, more recently, aminoglycoside resistant *Acinetobacter baumanii*.

Weinstein et al [215] reported efficacy in controlling epidemic outbreaks of antibiotic resistance by the restriction and rotation of antibiotics, thereby decreasing selective pressure for "plasmid outbreaks". They also recommended the careful dosing of antibiotics to prevent subinhibitory levels from selecting resistant subpopulations. As last resort manouevres they suggested the control of antibiotics which select sensitive precursors of resistant organisms eg cephalosporins selecting for *Pseudomonas spp*, or even the total suspension of all antibiotic usage.

Other techniques for the control of epidemic resistance include the use of prophylactic topical antibiotics (vide infra), and the largely experimental use of bacterial interference.

7.3 Staff and patient screening

The screening of the personnel in the hospital serves both to improve communication and to identify the sources of, and prevent the transmission of infection either to or from, the one to the other. The control and organisation of staff health includes: routine chest radiographs, to ensure that staff are not serving as a source of infection, either to

their colleagues or patients; education about the need for protective techniques to protect against exposure to transmissible and highly infectious diseases and the implementation of routine vaccination. A periodic review of the techniques currently being employed in treating patients with transmissible diseases is also essential in maintaining a healthy, motivated work force.

7.4 Sterilisation, Disinfection and Waste Disposal

It is not the purpose of this thesis to review the techniques of sterilisation, disinfection and waste disposal in any detail; however, although it is often taken for granted, the safe performance of these procedures should not be underestimated and is essential to the prevention of all nosocomial infections and of extreme importance.

According to the CDC [213], patient care objects can be divided into three categories, based on the level of disinfection or sterility necessary for the object. Items which have access to the blood such as surgical instruments, intravenous fluids, catheters, irrigation fluids etc, for which sterility is required, are termed "critical objects", while those objects such as bronchoscopy and gastroscopy equipment, that are only in contact with mucous membranes, but require a high level of disinfection, are termed "semicritical", and should be kept free of vegetative bacteria. "Noncritical objects" are those such as bedpans and electrocardiogram leads, which require a low level of disinfection. It is thought that the cleansing of the fomites surrounding the patient once a day is sufficient.

The other well-recognised medium by which infection is spread is through the animate environment comprising the hospital personnel, particularly on the hands. While there is general agreement on the important role that the animate environment plays in the aetiology of nosocomial infections, proper quality control and the maintenance of appropriate procedures and techniques should virtually eliminate the inanimate enviroment as a potential source for nosocomial infection.

In a study by Weber et al [216], manual ventilation bags were demonstrated to be a source for bacterial colonisation of ventilated patients, particularly by coagulase negative staphylococci and *Acinetobacter spp*. This study, and others already mentioned [29,217] serve to highlight the importance of adhering to strict protocols for the sterilisation of ventilatory equipment. It also shows how such contaminated equipment may serve as a source for colonising the hands of personnel, who may then cross-transmit such pathogens directly to other patients, or to colonise respiratory or other medical equipment. Contaminated equipment can also be a source of nosocomial infection, by acting as a direct source for introducing the pathogens into the patient. The importance of hand-washing following any contact with patients, or potentially contaminated equipment, and high-level disinfection of ventilatory apparatus between patients would appear to be self-evident, but is, nonetheless, worthy of emphasis.

Cross and Roup [29] prospectively studied the role of respiratory assist devices and techniques in the pathogenesis of nosocomial pneumonia. They found the incidence of contaminated respiratory devices to be reassuring low, so that they were unable to recommend the routine monitoring of these devices while in use . They also did not find any positive cultures of nebuliser fluid, however, they did demonstrate a correlation between the cultures of respirator effluent, tracheal suction fluid and the respirometer, with subsequent nosocomial respiratory infection by the same organism. 65% of cases with hospital-acquired pneumonia in this study occurred in patients who had used respiratory assistance devices; they also showed that manipulation of the respiratory tract greatly increased the risk of infection. Some of the recommendations formulated are easier in theory than in practice: the earliest possible discontinuation of intubation and respiratory assistance being the most obvious, but most difficult to implement. The authors recommended the changing of respiratory tubing at 24 hourly intervals, which has since been overtaken by the recommendation of Craven et al [30] that 48 hourly changes actually reduced the incidence of secondary respiratory tract

infections. They also suggested that equipment that cannot be adequately sterilised should not be used.

7.5 Isolation techniques

The theory of patient isolation to prevent infection owes its origins to the quarantining of patients with contagious diseases. Although the technique of separating infected from non-infected patients has persisted, the isolation of patients is mainly confined to those with certain categories of highly infectious diseases, highly resistant organisms or more commonly as practice to protect the patient from the normal hospital environment. In an effort to promote the awareness of both potential susceptibility to and the infectivity of all patients, universal precautions in the management of all patients have been introduced. By this means it is hoped that the provision of health care can be made both safer and more efficient. Handwashing again is of prime importance in all patient contact, and the use of protective clothing when in contact with all bodily secretions is recommended. Similar attention is given to the handling and disposal of all contaminated equipment.

Techniques such as reducing the number of patients in a room, reducing the nurse to patient ratio, improving the facilities for hand washing are all recognised to reduce the incidence of nosocomial infection. Elaborate forms of protective isolation used in combination with antibiotic prophylaxis have been extensively studied [13] and have had a significant effect on reducing the incidence of infection in granulocytopaenic patients. In general, the use of simple barrier nursing without antibiotic prophylaxis has shown no benefit [218], possibly because the infections in these patients are caused by microorganisms already colonising the patients at the time of admission. Few infections appear to be related to invasive devices or procedures, where an improvement in infection control practice could further reduce the incidence of infection. However, in patients with burns, the use of a protected environment alone has been demonstrated to

have significantly reduced the very high incidence of wound and other infections by organisms which are acquired exogenously from the hospital environment [219].

In the general intensive care unit setting, many of the pathogens causing nosocomial infection are extrinsically acquired after admission to hospital, often being transmitted on the hands of staff or equipment, or caused by invasive devices or surgery. The period at which such patients are most susceptible to exogenously acquired infection is while devices are still in place, and it is for this reason that environmental control is of the utmost importance in the prevention of ICU-acquired infection.

Weinstein et al [215] reported the use of selected barrier type antibiotic resistance precautions to control and prevent the emergence of multiple drug resistant nosocomial infections throughout the hospital, following an outbreak of multiply resistant aerobic Gram negative bacilli. They highlighted the following mechanisms as being of importance in leading to the development of multiply resistant organisms:

(1) The admission or readmission of patients with pre-existing gastrointestinal, genitourinary, respiratory or wound colonisation or infection with resistant strains. In their hospital 25% of aminoglycoside resistant Gram negative bacteria were isolated from patients on admission. (2) The transmission of bacteria between persons, often indirectly, via transient carriage on the hands of the personnel, or due to environmental contamination such as urine measuring devices. (3) Antibiotic pressure, both suppressing the sensitive flora with sequential colonisation by more resistant bacteria, and selecting a resistant subpopulation of bacteria from a larger sensitive population. (4) Other more controversial mechanisms of transmission of mulitply resistant Gram negative organisms include food-borne and air-borne contamination.

Based on the above, they employed the use of the following barrier-type precautions in all patients who were colonised with multiply resistant aerobic Gram negative bacilli: the use of isolation cubicles with no more than two beds per room and no sharing of

such rooms by two patients both with drainage tubes or Foley's catheters; the wearing of gloves for all patient or secretion contact, and the allocation of individual urine measuring devices to each patient. The wearing of gowns and gloves however, was not deemed to be necessary. Such precautions were applied to all patients who were identified as persistently shedding resistant bacteria, while cultures were being processed from patients admitted or readmitted with a history of colonisation or infection with resistant organisms, or in patients with indwelling urinary catheters.

Klein et al [220] reported a prospective randomised trial of 70 non-immunosuppressed patients who required mechanical ventilation in a paediatric ICU, to determine whether simple protective isolation, using disposable high-barrier gowns and non-sterile gloves could reduce the incidence of nosocomial infection. The number of contacts between patients and the ICU personnel and family members was monitored. The protective isolation was well accepted by patients and their families; more than 90% of the observed contacts with the isolated patients were in compliance with the isolation protocol, which seemed to be well tolerated in the majority of instances. The frequency of contact with patients by personnel and family was comparable in the two treatment groups.

The definition of nosocomial infection was an infection that was not clinically apparent on admission, and required the isolation of a pathogen from a site of culture with clinical criteria not specified further but which included fever.

The 32 patients who were randomised to isolation were comparable in terms of sex ratio, age, severity of illness and underlying disease with the 38 who received standard care. Nosocomial colonisation by *Staphylococcus aureus*, methicillin-resistant coagulase negative staphylococci, Gram negative bacilli or fungi occurred in comparable numbers of patients in both groups (31% of those isolated vs 42% given standard care); however, colonisation occurred significantly earlier in those receiving standard care. 44% of the isolated patients and 55% of those receiving standard care

developed nosocomial infections, but 12 patients receiving standard care had multiple infections compared with only 1 in isolation. The incidence of infection in the isolated patients was not affected by whether they received care in a private room or in the open area of the ICU. Those given standard care were febrile for more days in the ICU (21 days), than the isolated patients (13 days). The mortality rate in those who received standard care was 13% compared with 9% in the isolated patients, but the deaths were not considered to be directly related to nosocomial infections in any patients. The use of antibiotics and the mean duration of stay in the ICU were also reduced in the isolated patients.

While there may have been some added vigilance in the implementation of a new protocol in the treatment of the isolated patients as part of the trial, the authors argue that such enthusiasm would have been unlikely to have been sustained for over two and a half years. The high rate of observed compliance with maintaining the isolation protocol in a busy ICU was seen as confirmation that such precautions could be implemented as part of routine prophylaxis; particularly as such a technique did not seem to lessen the amount of care and contact that the patients received.

The reduction in the infection rate encountered in this study was attributed by the authors as being largely due to the use of gloves, as compliance with hand washing procedures by medical personnel are recognised to be notoriously poor [41,212]. Clearly further work is needed to assess the cost efficacy of such a technique, its efficacy in an adult ICU, and whether gloves alone might suffice in achieving the same result.

A recent study [221] in paediatric wards. found that a significant reduction in the incidence and transmission of *Respiratory Syncytial Virus* could be achieved by the combination of cohort nursing, and the wearing of both gloves and gowns, but that none of these prophylactic methods was sufficient alone.

The wearing of non-sterile gloves at every contact with mucous membranes, secretions and "moist body substances", as an alternative, or in addition to, the difficult to enforce hand-washing, has been developed as part of the technique of body-substance isolation, should serve to prevent the transmission of microorganisms between patients [42]. Such a technique, which should not be confused with universal precautions, adds considerably to the cost of patient care. The danger still remains that gloves may provide a false sense of security: staff may move from patient to patient without changing gloves, handwashing may become neglected and hands can become contaminated through leaks in the gloves or when the gloves are removed.

7.6 The effect of drugs on the immune response and the importance of mobilisation

An area not often addressed in the literature regarding the incidence and management of nosocomial infections, is that of the method of patient management within the ICU. While it is evident that invasive devices play a major role in promoting the development of secondary infection, management is often not directed at achieving decanulation as quickly as possible. This important aspect of infection prevention should be encouraged and, while the ability to judge the correct timing requires experience, over-hasty removal of supportive care may compromise patient care or necessitate the replacement of devices which have been removed too soon, and should be deplored; this balance is often difficult to achieve.

Techniques of patient care vary markedly between units, depending on the philosophies of those in charge. In many ICUs, the ventilation of almost all patients is performed by means of an orally placed endotracheal tube. As discussed previously, there are both advantages and disadvantages associated with this method of intubation. One of the possible disadvantages is that there is poor tolerance of an orally placed tube by an awake patient, and, for this reason in the ICUs where this method of ventilation is preferred, the patients are kept fairly heavily sedated. There have been several studies

recently suggesting that even in awake patients, the recall of the time spent in the ICU is scanty and generally neither unpleasant or frightening [222]; so that the argument that the use of sedation is kinder to the patient may not be valid. It would appear that the early mobilisation of patients in the ICU reduces the incidence of secondary infection, both because the drugs that are used for sedation may themselves exert immunosuppressive influences [26] and because with mobilisation [223], it is often possible to wean and extubate patients sooner, and thereby remove the invasive devices which are so well recognised as being associated with the development of nosocomial infection.

Seibel et al [70] reported a study in which patients who had sustained blunt multiple trauma with fractured femurs were randomised to: immediate internal fixation with post-operative ventilation and mobilisation by 30 hours (20 patients), 10 days of femoral traction before fixation which was followed by ventilatory support (20 patients), immediate extubation following fixation and thereafter 30 days of femoral traction (9 patients) and a group who were particularly predisposed to the development of pulmonary complications (7 patients). The patients were fully comparable on admission to the trauma unit in terms of severity of injury and demographic features.

They found the incidence of "pulmonary failure septic state", which was defined by the presence of an alveolar arterial oxygen tension difference greater than 100mmHg, with fever and leukocytosis, in those who underwent 10 days of traction, was doubled compared with those who underwent immediate fixation to a statistically significant level. In those patients who underwent 30 days of traction, the incidence of pulmonary complications was still higher being 3 to 5 times that of those who underwent immediate fixation and mobilisation and two patients developed advanced multiple organ system failure, many patients having episodes of bacteraemia. The course of the patients in the various groups was reported to be radically different in terms of magnitude and severity of the pulmonary failure septic state, which was very closely

associated with the days of femoral traction. The authors suggested that fat emboli, the enforced supine position, increased pain with fracture motion and a large fracture haematoma and retained necrotic tissue, probably all serve as reasons favouring early fixation. Early surgery to prevent the spiral into multiple organ failure by removing all necrotic foci, which serve as potential sources of sepsis, and ongoing sites of cytokine release, was thus advocated in trauma patients. Similar findings on the early mobilisation of trauma patients have been reported by Goris [180] and Behrman [71].

The enforcement of the supine position can be extrapolated to all sedated patients in the ICU. In this position, the weight of the abdominal viscera prevents the efficient movement of the diaphragm in those who are not fully ventilated; the presence of fractured ribs, abdominal wounds and gastrointestinal distension as well as generalised malaise, all inhibit normal deep respiration and promote the development of atelectasis and retained secretions, with ventilation-perfusion mismatches. The use of mechanical ventilation with positive end expiratory pressure has been designed for this scenario to improve gas exchange, and is essential to the management of critically ill patients. However, it would appear that mobilisation of the patient to an upright position should be attempted as soon as possible, if adequate analgesia without sedation can be achieved, so that aspiration can be prevented, with early weaning and removal of all the associated "hardware" [223].

Stevenson et al [26] reviewed the effect of anaesthetic agents on the immune response. This is an area in which little work has been performed to date and clearly will need to advance as our understanding of immunology increases. While it would appear that specific humoral impairment of immunity is more related to the degree of surgical trauma than to the specific anaesthetic agent employed, there is nonetheless evidence already available which suggests that the use of anaesthetic related drugs may significantly affect the host immune response. The prolonged postoperative use of

narcotics and other sedating drugs should therefore be avoided unless it is essential for patient management.

There have been in vitro studies demonstrating a decrease in gamma interferon following halothane exposure, and a decrease in lymphocyte migration towards chemical attractants following exposure to anaesthetic agents. Regional anaesthesia has, however, been shown to block the post-operative T-cell impairment associated with general anaesthesia. The lysis of tumour cells and the production of alpha interferon by monocytes has been demonstrated to be decreased by thiopentone.

Patients with neurological disease requiring ICU admission are recognised to be at high risk of developing secondary infections, because of the loss of upper airway protective reflexes predisposing to aspiration, and their usually protracted duration of admission and immobility. Beale et al [224] reported 44 cases of Guillain-Barre syndrome admitted to the Baragwanath ICU, 43% of whom received steroids, possibly further contributing to their immunocompromised status; the mortality was 18% and in 62.5% of those who died, the fatal outcome was attributed to respiratory complications and infection.

Patients with tetanus form another group with neurological disease who require prolonged ICU admission, often with sedation and paralysis. In a study from Leeds, Edmondson et al [225] reported the course of 100 patients admitted to their ICU. There were 8 deaths, 6 of which were attributed to respiratory complications (they cite retained secretions, atelectasis and infection as the main problems) associated with the prolonged ventilation of a paralysed patient. Trujillo et al [226] reported 233 cases of tetanus admitted to their ICU in Caracas, Venezuela; 34.5% of them developed infectious complications and sepsis accounted for 12 of the 26 deaths.

7.7 The prevention of nosocomial pneumonia

Although some hypothesise that ischaemic mucosal injury with an associated translocation of enteric bacteria and toxins may be the most important mechanism in the

pathogenesis of nosocomial pneumonia in the critically ill [95], the aspiration of oropharyngeal organisms [36] is still generally believed to be responsible for initiating the majority of cases of nosocomial pneumonia, with haematogenous dissemination from a distant site or the inhalation of aerosolised bacteria being much less common.

Other potential, although sometimes controversial risk factors for the development of pneumonia in the ICU, have been discussed in previous sections. The association of pneumonia with colonisation of the stomach by Gram negative bacilli [56] and the enhanced risk for pneumonia associated with the use of antacid or H-2 antagonist therapy [227] has been alluded to. Although the last word on this relationship has not been said, it would seem reasonable to avoid the use of agents which may increase the gastric pH unless the need for them exceeds the potential risks associated with them. Pingleton et al [58] and Jacobs et al [103] have demonstrated that enteral nutrition can be associated with gastric flora colonising the trachea and causing nosocomial respiratory infection; although the frequency with which the gastric flora may contribute to the development of nosocomial respiratory infection is uncertain, and this potential source for infection should not prevent enteral feeding, it is important that the preparation and administration of enteral feeds should be performed in such a manner as to reduce this risk, and that the clinician should be aware that the risk exists.

The Study of the Efficacy of Nosocomial Infection Control (SENIC) in the USA found that 3 out of every 4 definite or probable cases of nosocomial pneumonia occured in patients who had had surgical operations, being particularly high in those who had undergone thoracic and abdominal surgery [228]. This association is thought to result from impairment of normal swallowing and respiratory clearance mechanisms (by instrumentation of the respiratory tract, anaesthesia and the use of narcotics and sedatives and pain from the operation) allowing bacteria to enter and remain in the lower respiratory tract.

In the pre-1970 era, aerobic Gram negative bacilli and Gram positive cocci were each reported to account for approximately 40% of instances of nosocomial pneumonia; however by 1980 the National Nosocomial Infections Study in the USA reported that aerobic Gram negative bacilli were now the cause of 68% of cases of nosocomial pneumonia, with a dwindling incidence of only 24% of cases being attributed to Gram positive cocci.

The patients at highest risk for the development of nosocomial pneumonia are those who have had surgery, or have other conditions which predispose to aspiration [182], are exposed to contaminated respiratory therapy equipment, have aerobic Gram negative bacilli colonising the oropharynx, or have impaired immunological function. Stoutenbeek et al [229] described three mechanisms by which colonisation of the respiratory tract by Gram negative bacilli could occur: from direct contact with environmental pathogens such as *Pseudomonas aeruginosa* (exogenous colonisation), colonisation of the oropharynx by the normal resident gastrointestinal flora, usually the *Enterobacteriaceae* (endogenous colonisation), or lastly colonisation of the gastrointestinal tract by environmental pathogens, with these organisms eventually extending to involve the upper respiratory tract (secondary endogenous colonisation).

Efforts to prevent nosocomial pneumonia therefore need to be directed at the above. The risk for developing nosocomial pneumonia is dependent on the individual, the reason for hospitalisation and the presence of underlying or predisposing factors. It is important to identify the high risk patients so that prophylactic measures can be targeted at those most likely to benefit: those who are elderly (more than 70), obese, immunocompromised, have underlying chronic obstructive airways disease, a history of smoking or abnormal pulmonary function tests; the patient who has a tracheostomy or requires prolonged intubation and mechanical ventilation, the patient who is undergoing abdominal, particularly upper abdominal, or thoracic surgery are all at greatest risk. While unfortunately it is not possible to modify these risk factors by the time patient

presents to the ICU, careful preoperative preparation might considerably reduce the need for major supportive care postoperatively and its associated morbidity.

Ventilatory therapeutic strategies have been devised to minimise the risk of nosocomial lower respiratory tract infection. The use of physiotherapy, including mobilisation of the patient out of bed and into a chair with maintenance of erect posture and the early encouragement to walk, the use of breathing exercises, postural drainage, percussion, and efforts to stimulate coughing and the mobilisation of secretions are all recognised to be extremely important. Early mobilisation and the recent introduction of positive end expiratory pressure with physiotherapy are possibly the most important modalities in reducing the incidence of post-operative pulmonary complications. The use of intermittent or continuous positive airway pressure ventilation is thought to assist in maintaining lung expansion and prevent the development of areas of atelectasis which may more easily become infected by retention of secretions.

The humidification of the gases supplied during anaesthesia and whilst receiving mechanical ventilation may be important in preventing pneumonia, as the prolonged breathing of dry gases dehydrates the respiratory mucosa, impairing ciliary function and the respiratory defence mechanisms. The maintenance of a high level of disinfection of the ventilatory equipment to prevent contamination and equipment-related outbreaks of infection, is also of importance.

The nebuliser is one of the principal reservoirs of infection from contaminated respiratory equipment. It can easily become contaminated by the introduction of non-sterile fluids, air, by manipulation of the nebuliser cup and by retrograde flow of condensate and tracheal secretions that collect in the respiratory tubing. Reinarz et al [67] found that the reservoir nebuliser jet was the source of bacterial aerosols and served as a nidus to inoculate the reservoir fluid in which the organisms propagated. The organisms isolated from the aerosols varied between institutions, but the major contaminants were all Gram negative and included *Pseudomonas spp*, *Flavobacterium*

spp, *Herellea spp*, *Alcaligines spp* and *Achromobacter spp*. Moiraghi et al found that the filling of bubble humidifiers or underwater chest drains with tap water was a potential hazard for the development of nosocomial pneumonia due to *Legionella pneumophila* and should be avoided [193].

Patients who require endotracheal tubes or tracheostomies for prolonged periods, are at high risk for the development of pneumonia for many reasons and the colonisation of the oropharynx with Gram negative bacilli in such patients may be as much a manifestation of the severity of the underlying disease, as a risk factor for the development of pneumonia. Techniques directed at reducing this colonisation are discussed below.

Simmons et al [228] published the CDC guidelines for the prevention of nosocomial pneumonia which, in broad outline, include the following:

1. Perioperative measures for prevention of postoperative pneumonia: pulmonary function testing in those with pulmonary dysfunction undergoing abdominal or thoracic surgery; treatment and resolution of pulmonary infections; efforts to remove pulmonary secretions; the discontinuation of smoking by the patient before surgery; the institution of pre and postoperative physiotherapy with education about breathing exercises; the provision of sufficient analgesia to permit coughing and deep breathing.

It has been suggested that the indications for the prophylactic measures outlined above are restricted to too narrow a category of patients - possibly all surgical patients should receive this form of care.

2. Handwashing after contact with respiratory secretions, whether or not gloves are worn.

3. Fluids and medications : only sterile fluids preferably in single dose vials should be used for nebulisation, and these fluids should be dispensed aseptically.

4. The maintenance of in-use respiratory therapy equipment : fluid reservoirs should be filled immediately before use and fluid should not be added to replenish partially filled reservoirs, without first having discarded the residual fluid; the water that has condensed in the respiratory tubing should be discarded and not allowed to drain back to the reservoir; the respiratory tubing and breathing circuits should be changed between patients, and replaced with sterilised or disinfected ones every 24 hours.

5. Disposable equipment : No pieces of disposable respiratory therapy equipment should be re-used. Re-usable equipment should be sterilised or disinfected to remove all blood, tissue, food, or other residue and should be decontaminated before or during cleaning. Equipment that touches mucous membranes, breathing circuits (including tubing, exhalation valves), medication nebulisers and their reservoirs, venturi wall nebulisers and their reservoirs, and cascade humidifiers and their reservoirs should be sterilised before use between patients, or at least receive high-level disinfection.

The internal machinery of ventilators and breathing machines should not be routinely sterilised between patients.

Respirometers and other equipment used to monitor several patients in succession should not directly touch parts of the breathing circuit, but extension pieces should be used between the equipment and breathing circuit and these should be changed between patients; otherwise the equipment should be sterilised between patients.

Once they have been used for one patient, hand-powered resuscitation bags eg Ambubags, should be sterilised or receive high level disinfection before use on other patients.

6. Microbiologic monitoring: In the absence of an epidemic or high endemic rate of nosocomial pulmonary infections, the disinfection process for respiratory therapy equipment should not be monitored by cultures; and routine microbiologic sampling of

respiratory equipment while it is in use by one patient is not recommended, because of the difficulty in interpreting results.

7. Patients with tracheostomy: Tracheostomy should be performed under aseptic conditions in an operating room, except where there are strong clinical indications for emergency or bedside operation. Until the wound has had time to heal or from granulation tissue around the tube, "no touch" technique should be used. When a tracheostomy tube requires changing, a sterile tube or one that has received high-level disinfection should be used under aseptic technique.

8. Suctioning of the respiratory tract: There is a risk of cross-contamination and excessive trauma with frequent suctioning; this should therefore only be performed when needed to reduce substantial secretions, which may be indicated by increased respiratory difficulties or easily audible gurgling sounds, and not as a routine procedure. Suctioning should be performed using "no-touch" technique or gloves, although the gloves need not be sterile. A sterile catheter should be used for each series of suctioning. If tenacious mucus is a problem, sterile fluid should be used for flushing.

Suction collection tubing should always be changed between patients.

Suction collection cannisters when used on one patient need not be routinely changed or emptied. Once they have been changed, reusable suction collection cannisters should be sterilised or receive high level disinfection. Unless in short term care units , suction collection cannisters chould be changed between use on different patients.

With portable suction devices, which may discharge contaminated aerosols, high efficiency bacterial filters should be used between the collection bottle and vacuum source.

9 Protection of patients from other infected patients or staff: Personnel with respiratory infections should not be assigned to the direct care of high-risk patients.

Although the role of airborne cross-contamination is controversial and not generally thought to be of much importance in the transmission of infection, as organisms are rarely isolated at more than three metres' distance from the patient, an outbreak of *Acinetobacter spp* was attributed to this mode of spread recently [230].

Cobley et al [44] reported a small study in which total colony counts from air sampling before and after tracheal suctioning using either a routine suction catheter or a closed suction system were compared. They demonstrated environmental contamination up to one metre away from the suction port when the conventional system was used, with the obvious implications of contamination of not only the bed linen, but also equipment and staff, with the potential that contaminated secretions may persist as potential sources of infection for days and result in cross-infection. This potential mode of spread was reported to be reduced with a protected suction catheter, but further large studies need to be undertaken to confirm these findings.

Notwithstanding the efforts at environmental infection control, education about handwashing and the rigorous enforcement of antibiotic policies, nosocomial infection has continued to be a problem. It has gradually become apparent that, although none of the techniques directed at controlling the environment and preventing the exogenous transmission of infection should be de-emphasised, the endogenous reservoir of organisms harboured by the patient in the ICU is possibly an even more important source of secondary infection. Critically ill patients have seriously impaired immune defence mechanisms against colonisation and infection, particularly if they are undergoing mechanical ventilation. It is thought that colonisation of the oropharynx and gastrointestinal tract almost always precedes colonisation and infection of the lower airway, urinary tract, and wounds in these patients.

Further attempts to reduce the incidence of nosocomial infection have therefore been directed at protecting the patient against colonisation by potentially pathogenic organisms, by maintaining the normal flora and eliminating nosocomial colonisers.

Such prophylactic strategies have involved the administration of intravenous, topical and topical aerosolised endotracheally administerd antibiotics and selective decontamination of the digestive tract.

i)The Prevention of nosocomial pneumonia with intravenous antibiotics

Mandelli et al [17] reported a multicentre, randomised clinical trial of 1319 patients in 23 ICUs to prevent the development of ICU acquired pneumonia within the first 4 days following admission, which accounted for more than 50% of their overall incidence of pneumonia. The patients who were enrolled in the study received either prophylaxis with cefoxitin 2g IV 8 hourly for three doses , penicillin G 2 million units IV 6 hourly for four doses or no antibiotic prophylaxis at all in the control group. The diagnosis of pneumonia was made on the basis of a new radiological infiltrate, clinical parameters (including fever, worsening hypoxaemia, leukocytosis and purulent tracheal secretions) and microbiological specimens obtained by bronchoscopy, if possible, or from the tracheal aspirate.

The overall incidence of pneumonia was 6.1% in those who received prophylactic therapy compared with 7.2% in the controls, and no statistically different rates of pneumonia or death were found among the groups. They concluded that patients without impaired oropharyngeal and upper airway reflexes should not receive prophlaxis, and that, even in those at greater risk because of impaired reflexes, the evidence of benefit from the use of prophylaxis was not conclusive. Even short term prophylaxis was found to alter the resident flora, induce and select resistant species, result in toxicity, or alter the clinical manifestations of an incipient infection, without resulting in a cure.

ii)The prevention of nosocomial pneumonia by the use of an antimicrobial pharyngeal nonabsorbable paste

Rodriguez-Roldan et al [231] reported a prospective study comparing the incidence of lower respiratory tract infection in patients requiring longterm mechanical ventilation for non-infectious reasons. 28 patients were randomly allocated to receive a nonabsorbable paste containing tobramycin, amphotericin B and polymyxin E which was topically applied to the pharynx (13 patients), or a control placebo paste (15 patients). The diagnosis of pneumonia was made on the basis of clinical criteria (including fever, purulent tracheobronchial secretions, leukocytosis and hypoxaemia), radiological criteria and quantitative tracheal culture.

There were 3 episodes of tracheobronchitis in those who received the study paste, compared with three patients who developed tracheobronchitis and 11 patients who developed pneumonia in the placebo group, which was highly significant. No difference in mortality between the groups was noted. No alterations in bacterial resistance patterns were observed during the short study period. While acknowledging the small number of patients in the study, the authors conclude by recommending the efficacy of such a regimen in preventing the development of nosocomial pneumonia.

iii)The Prevention of Gram-Negative Pneumonia using topical aerosolised endotracheally administered antibiotics

Colonisation of the upper respiratory tract by pathogenic bacteria is thought to be the initial step in the pathogenesis of nosocomial pneumonias caused by Gram negative bacilli; attempts at prophylaxis have thus been directed at preventing colonisation from developing. The risk factors for colonisation with Gram negative bacilli are poorly understood.

Valenti et al [45] analysed the factors predisposing to colonisation in the elderly and found that the levels of colonisation by Gram negative organisms increased with

increasing debility, including the development of incontinence, incapacitation due to underlying neoplastic, cardiac or respiratory disease, and immobility. Even in the young and otherwise healthy, following an episode of viral upper respiratory tract infection, the colonisation of the oropharynx by aerobic Gram negative bacilli has been observed to increase from baseline values of between 12% to 18%, to levels as high as 60% [46], with colonisation by *Staphylococcus aureus* also increasing to up to 43%; it is thought that this may serve as a factor predisposing to post-viral bacterial pneumonia.

Parenterally administered antibiotics do not prevent pneumonia and may actually increase the frequency of colonisation of the upper respiratory tract, because while the low antibiotic levels achieved by this means of administration in the bronchial secretions are sufficient to eradicate the normal colonising flora, they fail to eliminate the more pathogenic Gram negative bacilli.

Topical administration of antibiotics achieves very high levels at the local site, but such a form of administration is thought to be associated with a much greater potential for the development of antimicrobial resistance.

Klick et al [232] retrospectively analysed the incidence of nosocomial infection in their Respiratory-Surgical ICU over a 30 month period. They found that *Pseudomonas aeruginosa* was the most common respiratory pathogen accounting for 50% of episodes of bacterial pneumonia, with a mortality of 75% compared with only 25% for other bacterial pneumonias; this contrasted markedly with the mortality of only 3.8% in patients who did not develop pneumonia. They then monitored 640 patients and the ICU environment to assess the reservoirs of *Pseudomonas aeruginosa*; 71% of the sputum or throat swab isolates of the organism were found to have been hospital-acquired and the only environmental source identified were the sinks. The authors accordingly then embarked on a prospective study to assess the efficacy of preventing colonisation of the upper airway to prevent the development of pneumonia. They monitored the effects of aerosolised polymyxin or placebo, used in 2 month alternating

cycles, sprayed 4 hourly into the posterior pharynx and tracheal tube of all of 744 patients admitted to their unit in a double-blind study. Aerosol treatment with polymyxin B had previously been shown not to contaminate the culture media so as to inhibit the growth of viable organisms deposited in the plate.

There was intensive microbiological surveillance performed throughout the study with daily culture of tracheal aspirates, and bi-weekly culture of the hand basins. The diagnosis of colonisation was the isolation of a new organism from throat or sputum on more than one consecutive culture. The overall rate of colonisation with *Pseudomonas aeruginosa* of the upper airway was 5.6%; during the placebo cycles, the upper airways of 9.7% of patients were colonised while during th polymyxin B cycles only 1.6% of patients were colonised, and this was statistically significant. The incidence of colonisation with other species of organisms sensitive to polymyxin B also declined significantly. The organisms resistant to polymyxin B (*Staphylococcus aureus*, *Flavobacterium*, *Serratia* and *Proteus spp*) were not observed to cause bacterial overgrowth as a result of the use of aerosolised polymyxin. Swabs from the environment including ventilatory apparatus, following the implementation of daily sink decontamination, were only rarely positive.

The diagnosis of pneumonia was based upon three separate opinions obtained from the house-officer, an independent physician and a group of paramedical personnel, and classified as "possible" or "probable" using the presence of: "persistent radiological evidence of an alveolar infiltrate on more than 2 consecutive days, associated with a positive sputum culture for potentially pathogenic organisms, an elevated alveolar-arterial oxygen difference while breathing 100% oxygen, an evaluation of the temperature course, daily weights, central venous pressure and pulmonary artery catheter data. Only "probable" cases were considered.

The incidence of pneumonia during the study was 18.1%, 35.5% of such cases being acquired in the ICU. There were 30 episodes of pneumonia during the placebo periods

of which 17 (4.6%) were due to *Pseudomonas aeruginosa*, and 4 of the latter group died. 18 patients acquired pneumonia during the cycles when polymyxin was used, but only a significantly reduced 3 (0.8%) of these episodes were due to Pseudomonas and only 2 patients died. There were 5 cases of pneumonia due to *Staphylococcus aureus* in the polymyxin cycles and only 2 in the placebo which was non-significant. The use of systemic antibiotic therapy during the different cycles was similar in both groups. Despite this significant reduction in the incidence of pneumonia due to this organism, there was no effect on the mortality: 12.2% in the placebo cycles and 12% in the polymyxin cycles.

Feeley and other authors from the same group [233], subsequently reported in the New England Journal of Medicine the same year as the above study, the effect of aerosolised polymyxin B administered prophylactically to the upper airways of 292 patients in a respiratory-surgical ICU over a 7 month period, without the benefit of 2 month periods when placebo was used. In neither of these papers is sufficient data about the categories of patients or their severity of illness parameters provided; however, these studies were performed before the advent of the APACHE II and other scoring systems. The definitions used were similar to those in the above-mentioned study. Colonisation by Gram negative organisms was observed in 24% of the patients, and 74% of the isolates were resistant to polymyxin. Previously when alternating cycles were used, there had been no difference in polymyxin resistance. 14% were colonised by yeasts, and 16% by Gram positive organisms, most commonly staphylococci. Colonisation of the respiratory tract preceded the development of pneumonia by the same organism in 10 of the 11 patients who developed nosocomial pneumonia.

The incidence of nosocomial pneumonia was 3.8%. Although only one of the patients studied acquired pneumonia due to *Pseudomonas aeruginosa*, there were 10 others where pneumonia was caused by an organism resistant to polymyxin; there were also seven cases of pneumonia due to uncommon, opportunistically pathogenic organisms

(*Flavobacteria*, *Serratia spp* and *Streptococcus faecalis*). The overall mortality in the ICU was 12%; however, the mortality in those who developed nosocomial pneumonia was 64%, which was higher than the mortality associated with this complication prior to studies where prophylactic therapy had been used (14% per annum for the preceding 7 years, with a mortality of 48% for nosocomial pneumonia).

Although the use of this prophylactic therapy succeeded with its primary aim and reduced the incidence of colonisation and infection due to *Pseudomonas aeruginosa*, it appears to be a potentially dangerous form of prophylaxis. It resulted in an increase in antibiotic resistance to the agent used for prophylaxis, the emergence of infections due to organisms seldom regarded as being pathogenic and, according to the authors, a trend towards an increasing mortality for hospital acquired pneumonia.

v) Combined intravenous and topical oropharyngeal antimicrobial prophylaxis

The efficacy of antimicrobial agents applied topically in the oropharynx and trachea, with and without the use of intravenous antibiotics, in the prevention of bacterial pneumonia during prolonged mechanical ventilation was assessed by Johanson et al[234]. They used a baboon model and studied 35 cases using a variety of prophylactic regimens (6 received no prophylaxis, 4 intravenous polymyxin B and gentamicin, 2 topical polymyxin B alone, 2 topical polymyxin B and intravenous penicillin , 6 topical polymyxin and intravenous penicillin/gentamicin, 4 topical gentamicin and intravenous penicillin/gentamicin, 5 topical gentamicin and intravenous penicillin, and 6 topical polymyxin and gentamicin with intravenous penicillin) which were ventilated for 7 to 10 days and then killed; the presence of pneumonia was determined histologically, and segments of lung were cultured.

They found that most animals that received topically administered gentamicin did not achieve measurable serum levels. The antimicrobial resistance patterns of oropharyngeal flora isolated from animals receiving prophylaxis with intravenous

penicillin and gentamicin did not show any change in sensitivity, but only 20% of animals receiving polymyxin B still had organisms sensitive to this agent at days 8 to 10, compared with 100% in those who did not receive this agent; however, the prevalence of polymyxin B resistant organisms increased over time. Organisms resistant to gentamicin were present in 71% of animals receiving topical gentamicin, compared with only 37% of animals not receiving topical gentamicin.

The antibiotic regimens that were judged to be effective by bacteriologic and histological criteria were: topical polymyxin B and intravenous penicillin ± intravenous gentamicin, topical gentamicin and intravenous penicillin ± intravenous gentamicin, and topical polymyxin and gentamicin with intravenous penicillin. 36% of the histological samples of those who received these regimens had no histologic evidence of pneumonia, 52% of the lobes being sterile; there being evidence of histologically severe pneumonia in 15%. Intravenous gentamicin had no independent effect on either culture or histological findings. All the other regimens were found to be ineffective and 81% of the histological samples in this group showed moderate to severe changes, only 2% showing no changes, and there were no sterile lobes on culture.

The pneumonias occurring in those who received no antibiotic prophylaxis were always polymicrobial, the most numerous organisms being those that comprise the normal oropharyngeal flora of the baboon. Such organisms are penicillin sensitive, and, in those to which it was administered, penicillin was extremely effective in eliminating these organisms from both the tracheal aspirate and lungs. The sensitivity patterns of such organisms were not often tested later during the course of therapy, and the authors point out that penicillin resistance might well have occurred and been missed.

Prophylaxis with topical polymyxin alone resulted in extensive pneumonias with very high tissue concentrations of penicillin sensitive organisms and lower concentrations of organisms resistant to polymyxin; when penicillin was added, the penicillin sensitive organisms were eliminated, and although small numbers of polymyxin-resistant

organisms persisted, such therapy was highly efficacious in preventing pneumonia. The authors indicate that, with more prolonged ventilation and in the presence of underlying disease, the resistant organisms might have resulted in the development of severe pneumonia.

Prophylaxis with intravenous penicillin and gentamicin was ineffective in preventing colonisation and pneumonias due to Gram negative bacilli. This was attributed to the poor penetration of the bronchial secretions by gentamicin, particularly in the presence of pus or an acidic environment.

Although the numbers in this study were small, on the evidence obtained from ventilating 23 baboons for 7 to 10 days, the authors concluded that a combination of topical polymyxin B, and/or gentamicin with intravenous penicillin was a highly efficacious method of preventing pneumonia. The authors do mention that the cost-effectiveness of such a regimen, the incidence of pneumonia in the population being studied, the incidence of side-effects and the possibility of the development of multiply resistant Gram negative organisms all need to be evaluated before embarking on such a method as routine prophylaxis for all patients requiring mechanical ventilation, a sentiment echoed by Faling [235] in an accompanying editorial.

While the use of topical aerosolised antibiotics has not gained wide acceptance for either the prophylaxis or the therapy of nosocomial pneumonia (v.i.), as a result of concern about the emergence of antibiotic resistance, the use of selective decontamination where the topical antibiotics are applied to the gastrointestinal tract, does not seem to be associated with this problem, and studies evaluating all aspects of this method of preventing nosocomial infection have now been carried out for almost a decade without any clear answers. This technique is reviewed below.

vi)Bacterial adherence mechanisms in the prevention of nosocomial pneumonia

The initial stage of most bacterial infections is thought to be the adherence of the pathogen to an epithelial surface. Johanson et al [4,5,48] established that Gram negative bacterial infections are usually preceded by oropharyngeal colonisation, and that this colonisation was associated with an elevated adhesion index for the attachment of Gram negative bacteria to the patient's buccal epithelium. Todd et al [24] demonstrated that the bacterial adhesion index paralleled the risk of patients acquiring bacterial pneumonia while in the ICU, although there was no correlation between this value and the duration of intubation.

The ability to influence the abnormal colonisation of the gastrointestinal tract, may hinge on the understanding of the basic factors that govern normal and abnormal bacterial attachment to the upper airway epithelium and techniques to modify this. This method of prophylaxis is still in its infancy, as the methods of bacterial adherence are unravelled; once the underlying mechanisms are understood, a new direction in the prevention of nosocomial infections may open.

Fibronectin normally covers the oropharyngeal epithelial cell surface receptors for Gram negative bacteria, thereby inhibiting bacterial-epithelial cell adherence. In patients colonised by Gram negative bacteria, for reasons that are poorly understood, fibronectin is digested and stripped away by elastase released into the saliva by polymorphonuclear leukocytes.

It has been noted in tracheostomised patients that higher sputum levels of IgA appear to inhibit the attachment of *Pseudomonas aeruginosa* to the tracheal epithelium [50]. This is thought to reflect an inhibitory activity of secretory IgA on the adherence process. The release of neutrophil elastase in tracheal inflammation can promote proteolytic fragmentation of the IgA, thus leading to enhanced bacterial-epithelial cell attachment, with the potential to enhance tracheal colonisation [23]. The experiments on the possible

effects that nutritional deficiencies might have on bacterial adherence have shown conflicting results [23,48].

Clearly the answers are not going to be available for some time, but the prevention of colonisation of the respiratory tract by these mechanisms may hold the key to preventing nosocomial pneumonia.

vii) Vaccination

Mylotte et al [206] found that patients who developed either community acquired or nosocomial pneumococcal bacteraemia. had a significant mortality associated with their illness. All the patients in their study who developed this complication were eligible for vaccination and the majority could have received immunoprophylaxis. It is important that such easily administered and accessible modalities of prophylaxis be considered early in all at-risk patients and sectors of the community, to reduce the incidence of preventable morbidity and mortality.

7.8 The prevention of urinary tract infections

The most common site of nosocomial infection is the urinary tract, particularly in the catheterised patient. The prevention of such infections is most easily achieved by removing the urinary catheter as soon as the patient's condition will permit. If the catheter can be removed before bacteriuria develops, this should largely prevent the development of infection. The removal of infected calculi, and the rapid recognition of obstruction and its treatment. should also assist in reducing the incidence of this complication.

The maintenance of a closed catheter system is also extremely important in preventing the transmission of infection. The system should only be opened at the bag drainage tube, and the staff should avoid allowing the end of the drainage tube from touching potentially contaminated containers. Urine specimens should be obtained without

opening the catheter-collection tube junction. Education in the techniques of catheter care and the collection of urine samples is essential for effective prophylaxis. It has been suggested that the urinary catheter should receive much the same attention as an open wound. Techniques such as handwashing between patients, the use of gloves, and attempts to segregate infected or catheterised patients from the others may all be helpful.

Patients with indwelling catheters used to receive meatal care with soap and water or a povidone-iodine solution once or twice a day; however, studies comparing these two forms of meatal care with a group of patients who received no meatal care demonstrated a higher level of bacteriuria in those in the treatment group [236]. Thus this form of preventative care has been abandoned. Methods of catheter irrigation using antiseptic solutions have not been shown to be effective in reducing catheter associated bacteriuria.

There have recently been reports of the use of silver-coated catheters, which have been shown to postpone the development of bacteriuria [237]. Although more expensive to use, it is thought that such catheters may rapidly pay for themselves in patients likely to require more prolonged catheterisation, by reducing antibiotic usage. Further studies on the efficacy of these catheters are needed before they are widely adopted.

Daschner [9] strongly advocated the use of suprapubic catheterisation in the intensive care unit. The rationale for this mode of catheterisation being that the concentration of bacteria on the anterior abdominal wall is considerably less, and thus that this should reduce the incidence of bacteriuria. This technique has not gained wide acceptance however, possibly because it is perceived as being too invasive.

The use of antibacterial substances in renal and bladder urine may also prevent the development of bacteriuria. The majority of patients with indwelling catheters will already be receiving antibiotics for their underlying diseases or procedures, during, but

not because of catheterisation. It has been shown in some comparative studies [237-239] that the use of antibiotics is associated with a lower incidence of bacteriuria, and the use of antimicrobial prophylaxis has also been shown successfully to postpone the development of this complication [239], although it does not prevent it. The prophylactic use of antibiotics is however, not generally recommended, because of their potential to promote the emergence of antibiotic resistance, the problems that may be caused by side-effects, as well as the additional cost involved.

The regular monitoring of urine samples of all patients in the ICU assists in the recognition of the development of colonisation, bacteriuria and infection. If an organism is detected to be present in high concentrations and pure growth on repeated samples, the removal and replacement of the catheter may be prudent, in anticipation of the development of infection. If colonisation of the new catheter occurs rapidly, treatment should be instituted.

In some centres, colonisation of the catheter or bladder by yeasts, which may occur quite commonly in patients receiving broad spectrum antibiotic therapy, and who are immunocompromised by critical illness, is treated with the early institution of Amphotericin B bladder washouts, to prevent the development of systemic fungal infection.

Once bacteriuria has developed, its consequences may extend to involve other patients, by contaminating the periurethral area with faecal bacterial flora, the surfaces of the catheter system, the collection containers, as well as the skin of the patient; these may all serve as potential sources for the contamination of the hands of personnel, and thus the transmission of bacteria to other patients. This may lead to the development of outbreaks of nosocomial bacteriuria, often due to resistant organisms. The use of surveillance cultures should reduce this problem, by allowing its early recognition and the institution of appropriate control measures.

7.9 The prevention of vascular-catheter related sepsis

It is estimated that over 25% of patients hospitalised in the USA will receive intravenous infusions [79], yet microbial contamination of this method of administration of drugs, nutritional solutions and blood, can result in serious illness and death. Almost half of all the nosocomial infections identified by Daschner [9] were procedure- or device-related, the majority being causally attributed to vascular and urinary catheters; Craven and many others [10,80,85] have shown that the risk of nosocomial infection is associated with the duration such devices are kept in place. In their study of bacteraemia in the ICU, Forgacs et al [93] identified the surgical patients as being at greater risk of this complication, than the medical patients; 31% of episodes were attributed to intravenous line sepsis. The mortality for patients who develop nosocomial bacteraemia, whether related to vascular access devices or other sources, is significantly higher than in patients who do not develop this complication, and thus this is yet another important area where effective prevention is needed.

The potential for the administration of intravenous infusions to cause infection extends from the techniques used in their preparation; the manufacture and use of the administration sets; through hand-washing and care of the entrance wound site; the techniques used for the maintenance and replacement of catheters, as well as the criteria used for deciding on catheter replacement. Techniques aimed at preventing such an array of potential sources thus need to be directed at ensuring that sterility and aseptic technique are maintained at each stage, and that the possibility that infection originating from this site is constantly considered.

Olson et al [240] recently published the results of a study evaluating various techniques of central venous catheter replacement in sheep. They convincingly demonstrated that the replacement of a catheter by using a guidewire over an existing catheter, the replacement of a catheter while a potentially infected catheter was still in situ, or the administration of antibiotics through an infected catheter were all ineffective in the

prevention, or eradication, of sepsis. These techniques were associated with a high incidence of endocarditis, septic pulmonary emboli and pneumonitis, as well as the presence of organisms within the vessel wall at the site of the catheter, at autopsy. They demonstrated that the organisms produce a slime-enclosed, antibiotic-resistant biofilm, which allows the organisms to both colonise the catheter and to then become detached to cause septic embolic dissemination. Only in the sheep where the removal of the initial catheter was followed by a 48 hour catheter-free interval and the subsequent insertion of a new catheter at a new site, was colonisation and infection of the second catheter prevented. These results are in direct conflict with those of Eyer et al [84] where no differences in the infection rates were found when the following three techniques of catheter maintenance were assessed: a routine weekly change of all longterm central venous catheters, the weekly change of the catheter over a guidewire using the same site, or the use of a new site and replacement of the catheter only when clinically indicated. It may be that the protocol for maintaining strict asepsis of the catheter site, the removal of catheters in cases where skin sepsis and positive blood cultures developed, or sepsis without another source occurred, allowed the earlier detection and prevention of catheter-related sepsis than an animal-model might permit. The clinical relevance of Olson's study needs further evaluation.

Also of importance was the observation by Olson [240] that, despite the presence of heavily contaminated central venous catheters, daily peripheral blood cultures failed to yield bacteria. This finding confirmed the clinical studies [92] of Hickmann catheters in patients with malignancies, where virtually all catheters were shown to be colonised by mixed populations of yeasts and bacteria, but in fewer than 5% were positive blood cultures obtained. The colonisation of the surface of the catheter by biofilm bacteria, therefore seemingly does not necessarily precede the development of overt bacterial infection, and, while it is essential to minimise the potential for infection, it is not yet certain that the removal of biofilm-colonised central venous catheters will reduce the

risk. Further studies will be needed to establish the conclusions from this study and the the clinical application of these important observations will need to be addressed.

Techniques of catheter insertion including the avoidance of cut-downs , which are associated with a higher rate of infection [80], and the use of percutaneous methods of insertion where possible, avoiding the unnecessary use of central lines, and if a central line is needed siting it preferably in the jugular or subclavian rather than in the femoral position, should help to reduce rate of sepsis. The cannulation of the lower limbs is also recognised to be associated with a much higher incidence of complications and should be avoided if at all possible [80].

Patients who harbour systemic bacterial or fungal infections before the insertion of catheters are recognised to have higher subsequent colonisation rates of these catheters [80], and, although often little can be done about this at the time of insertion, the shortest duration of insertion of the catheter, and the constant awareness of this potential risk for a further site of sepsis, need to be borne in mind. The loosely organised clot that forms around the intravascular catheter may seve as a trap for circulating microorganisms, and microscopic examinations have shown organisms deep within such thrombi. Microorganisms from anatomically distant sites of infection such as tracheostomies, the urinary tract or surgical wounds may become established on the cannula tip, in the absence of recognised bacteraemia. Such secondary bacteraemias are most frequently caused by *Escherichia coli*, although this organism is only rarely isolated from the catheter tip.

Manipulation of the catheter is associated with a far higher incidence of colonisation and infection [80]. Catheters removed because of phlebitis, leakage or infiltration also appear to have an increased incidence of culture positivity. Thus the irrigation or other manipulation of occluded, infiltrated or leaking catheters serves to provide a focus for introducing contamination and potentiating a focus for the development of bacteraemia, as well as dislodging small thrombi, some of which may be infected. Manipulation of

virtually every component of the intravenous delivery system may reult in contamination of the system. The addition of medication, injections of medications into the tubing, administration of blood products, the introduction of stopcocks, transducers, manometers and other devices into the line, the change of the bottles and administration sets and the use of the system to obtain blood samples are all potential risk factors for contamination to occur. However, while the additional manipulations likely to be associated with increased availability of venous access with a triple lumen central venous catheter, compared with a single lumen catheter system, might have been expected to increase the incidence of infectious complications, this has not been shown to be significantly different by Miller et al [87].

Factors known to decrease the incidence of sepsis associated with peripheral intravenous cannulae, include aseptic insertion, daily inspection and removal at 48 hours, or earlier in the presence of thrombophlebitis. The use of an effective, uncontaminated skin disinfectant during insertion is imperative, as the microorganisms found on the catheter tip are most commonly representative of the cutaneous microflora.

Iodine containing skin disinfectants have been shown to be highly effective as they are bactericidal, fungicidal and sporacidal. If used in a solution of 1% mixed in either water or 70% alcohol, their efficacy is maintained while skin burns should not occur. Before the application of the disinfectant, the site should be thouroughly cleaned and all foreign, organic matter that might interfere with the bactericidal activity of the disinfectant should be removed. Aqueous bezalkonium chloride should not be used for skin disinfection, as it is ineffective against some Gram negative organisms and contaminated solutions have been implicated in outbreaks of *Pseudomonas spp* and *Enterobacter spp* septicaemias [80]. There is no evidence that shaving of hair from the site of cannula insertion is helpful; the flora of the skin has little relation with the presence of hair and methods used to clean the skin are sufficient also to clean the hair.

The micro-abrasions that are produced during shaving are thought to alter the cutaneous flora, and if hair removal is desired, the use of a depilatory is recommended [80].

The skill and experience of the venipuncturist are inversely proportional to the number of infected catheters [85]. The development of dedicated teams of venipuncturists, and a strictly enforced intravenous access protocol by nursing staff, was shown to reduce significantly the incidence of intravenous cannula related sepsis compared to catheters inserted by resident medical staff [82]. Collignon et al comment that the single most important factor identified in reducing the incidence of catheter related sepsis was daily or even twice daily inspection of the intravenous site by the IV team. The implementation of careful and reliable hand-washing by all who deal with the catheter cannot be over-emphasised. Possibly this aspect is also more reliably performed by a dedicated team.

The colonisation of the site of insertion of the catheter is recognised to be one of the major sources of catheter-related infection. Reports of the use of a silver-impregnated subcutaneous cuff, for the prevention of infection with central venous catheters have been encouraging, and have shown significant reductions in the incidence of colonisation around the catheter site (Multicentre trial of an attachable silver-impregnated subcutaneous cuff for prevention of infection with central venous catheters, Maki D.G., Cobb L., Garman J.et al, 27th Interscience conference on antimicrobial agents and chemotherapy).

The topical application of both antibiotics and antimicrobials has also been attempted to prevent this source of colonisation and infection. There have been controlled trials that have shown that the application of a topical polyantimicrobial agent such as bacitracin, neomycin and polymyxin to the catheter insertion sites provided an element of protection against catheter-related infection [80,83]. Catheters treated with antibiotic ointment have also been reported to be less likely to be associated with septicaemia, but such studies have been too small for reliable conclusions to be drawn. The use of

antibiotic ointments has not been widely adopted as prophylaxis, because its efficacy was not well established in all studies, and it was noted that its use promoted the emergence of antibiotic resistant strains, as well as altering the flora isolated from the cannula tips. Most investigators have also found that the administration of systemic antibiotics has little effect on the incidence of positive cannula cultures [80]. With regular changing of catheters, the entire problem should be sufficiently minimised to make such forms of prophylaxis unnecessary.

Maki [83] reported an evaluation of four dressing regimens for the prevention of infection with peripheral intravenous catheters. The regimens included: sterile gauze which was replaced every other day, gauze, a transparent polyurethane dressing and an iodophor-transparent dressing. Cutaneous colonisation of the insertion site, contamination of the catheter hub, moisture under the dressing and prolonged catheterisation were all shown to be significant risk factors for catheter-related infection. While the iodophor dressing did not adhere as well as the others, moisture or blood accumulated more frequently under the transparent dressings than under gauze. It was not shown to be cost-effective to redress peripheral venous catheters at periodic intervals, and the use of either sterile gauze or a transparent dressing was recommended that could be used and left on until the catheter was removed. This recommendation was not designed to conflict with at least daily inspection of the catheter-insertion site, however.

In the same article, Maki [83] reported that 19% to 28% of hubs of the peripheral venous catheters were contaminated at the time of removal. Although the hub was contaminated in only half of the infected catheters, this contamination was significantly associated with catheter-related infection. There are, however, no studies reported in which the relative importance of this site of contamination has been compared with infection via the cutaneous site.

Evidence is accumulating that the synthetic material of which an intravascular device is made plays an important role in the pathogenesis of device-related infection - by determining whether the material provides a suitable surface for bacterial adherence by pathogenic organisms such as coagulase negative staphylococci or yeasts. Intravasular catheters made of teflon are more resistant to microbial adherence than catheters made of polyvinylchloride or polyethylene, and appear less prone to become colonised and cause bacteraemia [83]. Siliconised catheters are thought to be less thrombogenic than polyethylene catheters, but at autopsy, a fibrin sleeve was found to have formed on both types of catheters within 24 hours of insertion. The use of heparin bonded to the catheter material appears to reduce the incidence of thrombosis, and the systemic administration of low dose heparin is also recognised to reduce clotting on intravenous catheters. The use of metal needles is associated with a lower incidence of colonisation than that encountered with plastic catheters [85], but the obvious drawbacks with loss of flexibility and the potential to puncture the vessel if not completely immobilised have limited their widespread application. It is thought that the lower rate of colonisation observed with the use of steel scalp vein sets may be due to the smaller bore being less traumatic to the vessel, although the fact that they tend to infiltrate the tissues rapidly and thus require more frequent replacement may also be important.

The majority of intravenous infusions are manufactured and sterilised by pharmaceutical companies; the quality control in such plants is usually strictly enforced, as the vast medico-legal consequences of contamination are a sufficient enough incentive. Nonetheless, contamination of infusates still does occur, due to contamination either during manufacture, industrial sabotage, or defective containers.

Outbreaks of nosocomial infections secondary to intravenous fluids becoming contaminated during manufacture in the USA were identified as being due to organisms such as *E.cloacae* and *E. agglomerans* adhering to the elastomer liners of caps in previously unopened bottles, introduced during the manufacturing process. An outbreak

of *Pseudomonas thomasii* in London was traced to the use of deioinised, distilled water manufacture in the pharmacy; it was discovered that when used for cooling bottles of parenteral fluid and other sterilised fluids in the hospital's rapid-cooling autoclave, that the water often remained on the rubber stopper beneath a foil seal and entered the bottle when the closure was manipulated [80].

There may be breakdowns in the storage procedure of the fluid before it is administered, either at the site of manufacture, or at the place of administration. The method of preventing such infections is ongoing surveillance, and the maintenance of the strictest quality checks at each stage. The centralisation of mixing of all additives to solutions for administration within the hospital should help to reduce the incidence of contamination, as well as avoid the potential for drug incompatibilities and prescribing errors. However, if contamination should occur under these circumstances, the potential to expose a far larger number of patients to contaminated solutions exists. The solutions would also be more likely to be stored for longer periods before administration, thereby further increasing the potential for contaminants to proliferate. The relative merits of either system are not clearly established.

Unfortunately, clusters of contaminated infusion related bacteraemias and deaths continue to be reported, particularly in highly susceptible populations such as the very young or old, the highly immunocompromised or the critically ill.

Quercia et al [79] reported a double blind prospective study to determine the level of contamination associated with the admixture (except TPN) and administration of intravenous fluids, and whether intravenous filtersets were able to prevent bacteraemia. They evaluated 70 patients and found that 14.1% of real filtersets and 11.3% of the placebo filtersets were contaminated with microorganisms. Overall, 42.9% of all patients in the study were found to have extrinsically contaminated intravenous adminstration sets on at least one occasion. Coagulase negative staphylococci were the most commonly isolated organisms and it was demonstrated that this organism was

particularly suited to adhere to the plastic cartridge of all the filter sets. In 13 patients, (10 with placebo) the contamination of the filterset was associated with clinically significant bacteraemia. It was thought that the level of contamination of the filtersets, whether true or placebo, was probably a conservative reflection of the overall level of contamination of the intravenous fluids being administered. There was no evidence that the use of three-way extension sets increased the level of contamination.

In sharp contrast to the above, Maki [83] commented that the extrinsic contamination of intraveous fluid has been shown to be a very rare cause of nosocomial bacteraemia in the USA, and that it is therefore unnecessary to replace delivery systems routinely, more frequently than every 48 to 72 hours; he recommended that the infusion set be changed each time the catheter was replaced.

The composition of the fluid also determines its potential for contamination. The administration, or reflux of blood into the infusion system, may provide sufficient nutrients to broaden the spectrum of pathogens capable of proliferation, and it is generally recommended that infusion sets should be replaced after the administration of blood products. Although reports of clinical infection following the administration of blood are rare, 1% to 6% of individual donor units have been reported to be contaminated in the USA [80]. Malaria, cytomegalovirus infection, hepatitis and the human immunodeficiency viruses have all been transmitted by blood transfusions, despite careful screening; leukocyte transfusions have transmitted malaria and toxoplasmosis. It is thought that the rate of infection is low because of the small size of inocula, intrinsic antibacterial properties of the blood, refrigeration of the blood products, and the awareness of the necessity of prompt infusion of such products following their delivery from the blood bank. The infections that have been reported have been caused by organisms that are able to proliferate at $4^{o}C$ such as Pseudomonads and coliforms. The risk of infection with the administration of platelets

is higher, as these are pooled from several donors and often stored at a higher ambient temperature to prolong viability.

To minimise the risk of infection being caused by transfusion, blood products should be administered as soon as is possible after delivery, and the entire blood-administration set should be removed and replaced after completion of the transfusion. If sepsis is suspected, empirical antibiotic therapy should include broad cover against Gram negative bacilli.

The highly nutritious solutions used in total parenteral nutrition are particularly at risk for contamination. The catheters used for supplying TPN are often left in place for weeks at a time, which may further contribute to the associated high risk of infection. Most investigators have found that fungi, particularly *Candida spp*, are responsible for a remarkably large proportion of septicaemias complicating TPN - up to 54% in a survey by the CDC [80]. This has been attributed to the generally poor condition of patients requiring such therapy for prolonged periods - usually such patients are immunocompromised, malnourished, receiving broad spectrum antibiotic cover, and possibly steroids or immunosuppressants. The use of topical antimicrobials or occlusive dressings which alter the microbial flora of the skin, and provide a moist environment at the line insertion site, may also promote fungal colonisation.

Goldman [91] published guidelines for infection control in TPN, which, in slightly modified form, may be summarised thus: 1. TPN should only be initiated when clinically indicated by the patient's clinical requirements, and should be balanced against the well-recognised and significant risks for infection inherent in such therapy. 2. The administration of TPN should be under the supervision of a physician and a team of health care professionals who are responsible for the insertion, administration, and maintenance of the TPN, and are also fully conversant with the management of potential complications. 3. The TPN solution should be prepared using sterile or aseptic technique, when possible under a laminar flow hood. Once prepared the solution should

be stored at 4°C or infused immediately. Studies have demonstrated that *Candida spp* proliferates very rapidly in TPN fluid prepared with casein hydrolysates, and fluids containing these compounds should be discarded if they have not been used within 12 hours. Synthetic solutions are not associated with this problem and can be used for 24 hour administration. 4. Catheters should be placed, delivery systems maintained, and fluid administered according to strict aseptic technique with a carefully developed and approved hospital protocol. 5. The catheter placement should be considered to be a surgical procedure, performed with the use of drapes, gloves, and appropriate skin disinfection. 6. The catheter should be securely anchored to prevent irritating movement and to avoid the potential for bacteria to enter through the puncture site. 7. The catheter site should be regularly inspected and disinfected. 8. To avoid unnecessary contamination, the catheter should not be used to measure the central venous pressure or to administer blood products or "piggy-back" medications, and manipulation of the line should be kept to a minimum. 9. The administration set should be closely inspected to check for cracks in the tubing and bags. The infusate should also be discarded if there is evidence of turbidity or precipitate. 10. Other theoretical preventative measures of unproven value include: the routine application of antiseptic cream to the site of catheter insertion, routine changes of dressings, and skin preparation with antiseptics, routine use of semipermeable membrane dressing materials routine use of in-line membrane filters, use of silicone or other less traumatic, less thrombogenic catheters, use of heparin-locked catheters, or low dose heparin infusions, tunneling of the catheter to increase the anatomic distance between catheter insertion and point at which the catheter enters the vessel. 11. The TPN system should be immediately considered and removed if there are signs of infection and there is no other obvious site of infection.

The use of perioperative total parenteral nutrition was highlighted in the multicentre study reported by the Veterans Affairs Group [98]; their conclusion that its use is only justified in patients who are severely malnourished or who have other specific

indications, if carefully applied, should go a long way to preventing unecessary morbidity and mortality from the associated infectious complications .

7.10 The prevention of wound infections

Despite the advances in aseptic technique, the contamination of the surgical wound is inevitable, and the ability of the tissues to contain the contaminating bacteria depends on the existing local and systemic immune responses. Although there is often very little that can be done to modify them, host risk factors such as age, nutritional status, the severity of illness, the site of surgery, the number of surgical procedures, cigarette smoking, diabetes and steroid therapy are all recognised risk factors for the development of wound infection [28,169,241]. The role of the anaesthetist and surgeon in preserving and enhancing what host defences are present is important [170]. Surgical wound infection is an important cause of morbidity, doubling the duration of hospital stay and considerably adding to costs, although the associated mortality, while unknown, is thought to be low [175].

An effective infection control programme is essential to the prevention of wound infection. A surveillance system is needed to identify foci of infection and analyse the organisms responsible and their resistance patterns; in this way clusters of infection can be rapidly recognised and steps taken to prevent outbreaks. Gil-Egea et al [27] reported that the provision of periodic information on infections rates to the various surgical services, was associated with a decrease in the infection rate over time.

The use of asseptic technique, hand washing, effective skin decontamination, laminar flow and, post-operatively, the prevention of potential haematogenous seeding from other infected sites such as vascular catheters, are all important in the prevention of wound infection. The skill of the surgeon and the duration of the surgery are also factors which determine the likelihood of postoperative wound infection, as are such

factors as the presence of foreign material, traumatised or devitalised tissue, and haematomas [179].

The classification of wounds into clean, clean-contaminated and contaminated has been discussed previously, but its relevance has been lost to some extent by the development and use of perioperative antimicrobial prophylaxis, which has succeeded in dramatically reducing the incidence of wound infections. Of the studies that compared antibiotic prophylaxis with a placebo or non-antibiotic control, a literature review in 1983 demonstrated benefit with prophylaxis in more than 80% [166]. However, the margin of benefit is small for minor procedures, and the enormous potential costs involved as well as the emergence of antibiotic resistance and side effects, need to be considered[177].

Kaiser [166] recommends the use of the following "interventional" manouevres to reduce the risk of surgical wound infection:

a)pre-operatively: the preoperative avoidance of antibiotic usage, with minimum duration of preoperative hospitalisation, the elimination of nasal carriage of *Staphylococcus aureus*, and the treatment of remote sites of infection.

b)intra-operatively: careful skin disinfection, strict adherence to aseptic technique, the maintenance of high flow of filtered air, the irrigation of wounds with antiseptic solutions and the minimal use of drains, catheters and intravascular lines.

c)postoperatively: the maintainenance of adequate tissue perfusion, oxygenation and nutrition, should also be of value in reducing the incidence of wound sepsis.

There appears to be an "incubation period" for the development of wound infection[173]: once bacterial contamination of the wound has occurred there is an interval during which the bacteria are extremely susceptible to antibiotic administration; however, once the bacteria have become established within the wound, they become resistant to the use of antimicrobial prophylaxis. Thus the timing of the administration of prophylactic antibiotics is crucial, and for most procedures the administration of the antibiotic with

the induction of anaesthesia is seen as the most convenient and efficacious moment [177]. The duration of antimicrobial prophylaxis has also been a matter of controversy, and the pharmacokinetics of the agent used need to be considered when determining the time of administration and future dosing intervals.

Classen et al [178] recently demonstrated that prophylactic antibiotics are most effective if given during the two-hour period before the surgical incision, but that the infection rate increased if antibiotics were administered earlier than this, or post-operatively.

The selection of a prophylactic regimen depends upon the spectrum of infecting pathogens, and the prevailing degree of antimicrobial resistance within the hospital. The site and nature of the surgery to be undertaken also need to be considered when deciding on the most appropriate agents. Not all surgical procedures require the use of antimicrobial prophylaxis [167,169,176,177], but should be categorised preoperatively according to risk determined by the operative procedure and the state of the host. Patients at high risk of infection, or in whom the consequences of infection would be disastrous, should be selected to receive prophylaxis [167,174]. Although guidelines do exist for most surgical procedures, it is important that the regimen be individualised and tailored to the most recently available surveillance data from the particular hospital [171,176,177]. It needs to be remembered that the most prevalent contaminating organism does not necessarily correlate with the most likely infecting organism.

Neurosurgery: The evidence for the efficacy of antimicrobial prophylaxis is not well established [169], although many surgeons continue to use anti-staphylcoccal prophylaxis.

Cardiac surgery:In order to prevent the significant mortality rate associated with the development of prosthetic-valve endocarditis in the initial period of insertion, antimicrobial prophylaxis has become standard practice , despite the studies evaluating this form of prophylaxis being inadequate; again, the prophylactic regimen should be directed at preventing staphylcoccal infection.

Peripheral vascular surgery: wound infection may result in failure of revascularisation, and thus its prevention is extremely important; controlled studies have demonstrated a reduction in postoperative infection with the use of first generation cephalosporins. However, the use of prophylactic antibiotics is not warranted for vascular procedures on the upper limbs, or in carotid artery surgery.

Orthopaedics: open fractures require therapeutic rather than prophylactic antibiotics, but in joint replacement surgery their efficacy has been confirmed.

Urology: patients with sterile urine are not generally recommended to require antibiotic prophylaxis, but if bacteriuria is present prior to surgery, this should first be treated, or, if this is not possible, pre-operative therapy should be continued during the operation.

Biliary tract surgery: antibiotic prophylaxis has been demonstrated to be of benefit in high risk cases, such as patients with acute cholecystitis, in the elderly, or those with obstructive jaundice, or common duct stones. The agents of choice should cover the *Enterobacteriaceae*, but whether prophylaxis should be extended to include cover against *Enterococcus* and *Bacteroides spp* is not certain. Gastroduodenal surgery: the use of prophylactic antibiotics has been shown to reduce postoperative wound infection in the presence of diseases which decrease gastrointestinal motility, or acidity, or in the presence of bleeding, obstruction or malignancy; a first generation cephalosporin provides adequate prophylaxis.

Colorectal surgery: support for the use of prophylactic antibiotics here has precluded studies of their efficacy in this field; mechanical bowel preparation is insufficient alone, but should form part of the regimen for elective surgery. Intravenous antibiotics have been shown to be far more efficacious in preventing postoperative infection, than orally administered combinations.

Gynaecology: the incidence of infectious complications depends on the surgery and the route employed, being higher following an abdominal hysterectomy than when the vaginal route is used. Infections of the female genital tract are usually

and include anaerobic organisms, however, antimicrobial prophylaxis which does not include anaerobic cover has been shown to be effective: agents such as penicillin, ampicillin and the first generation cephalosporins are all effective.

The cephalosporins have been selected as the agents of choice for most surgical prophylaxis, because of their antimicrobial spectrum which covers the skin flora and the normal gastrointestinal flora, as well as their relative lack of toxicity. One of the major, recognised disadvantages associated with the use of surgical wound prophylaxis has been the increasing emergence of multiply-resistant infecting pathogens. The cephalosporins have been the antibiotics most commonly used for wound prophylaxis, and the concern has therefore largely focused on cephalosporin-resistant organisms. Cefazolin has been used in the United States most commonly [166], but failure to maintain adequate tissue levels throughout surgical procedures, which is thought to result in higher rates of infection, has lead to the introduction of agents with longer half lives. Oral agents are also effective in colon surgery, maxillofacial and reconstructive surgery, and are much less expensive than the use of routine parenteral antibiotics; both oral cephalosporins and newer agents such as the quinolones have been used successfully (Rohwedder R., Cerisola J.A., Chavanne J.M. et al. Perioperative antibiotic prophylaxis with a single oral dose of 750mg ciprofloxacin in maxillofacial and plastic or reconstructive surgery. June 1992, Poster at International Society of Infectious Diseases Conference, Nairobi).

The semisynthetic penicillins have been used as prophylactic agents in clean procedures including orthopaedic, vascular and cardiac surgery. The frequency of penicillin allergy has probably prevented these agents from assuming a more important role in general prophylaxis. The widespread use of vancomycin in clean surgery has not been adopted because of adverse reactions, cost and concern that this might potentially lead to resistance to this "last resort agent". The use of aminoglycosides in combination with beta-lactam antibiotics have not been adopted as first line prophylaxis, because of

concern about toxicity, the duration of effective tissue levels, which has not been clearly established, and their broad spectrum of activity. The use of metronidazole for colorectal and gynaecological surgery in combination with an antibiotic active against aerobic Gram negative bacilli has become one of the mainstays of prophylaxis, although its superior efficacy over the cephalosporins has not been established [166,174].

Surgical wound infections are increasingly being reported to be caused by methicillin-resistant *Staphylococcus aureus*, methicillin and cephalosporin-resistant coagulase negative staphylococci, cephalosporin and gentamicin-resistant Gram negative bacilli and fungi. Colonisation and infection with these multiply resistant bacteria is thought to follow exposure of the patient to the hospital flora, transmitted on the hands of the hospital personnel, and it is for this reason that it is recommended that patients undergoing elective surgery should have the shortest duration of preoperative admission possible.

The concomitant use of antibiotics has been thought to enhance the colonisation process by resistant organisms once exposure has occurred, by altering colonisation resistance. It is not certain what the effect of such changes of the colonising flora on the incidence and types of infection is likely to be. It is still felt that appropriately administered prophylaxis can actually result in less total antibiotic use and a shortened hospital stay [166]. The selection of resistant pathogens should not preclude the appropriate use of antimicrobial prophylaxis, but rather serve to discourage the use of prolonged therapy with multiple agents.

The patient with multiple trauma requiring ICU admission, should be recognised to have a marked impairment in host defenses and should be treated in much the same way as the highly immunocompromised [241]. The use of empirical, prophylactic antibiotic therapy is not generally recommended [207], although in the critically ill patient, it is often difficult to resist adding an antibiotic for a presumed, but as yet unidentified site of sepsis; again in such cases, the use of surveillance cultures are

extremely helpful. The organisms causing nosocomial infections in such patients are generally aerobic Gram negative bacilli, *Staphylococcus epidermidis* and *Candida albicans* [181]; the importance of reverse isolation, handwashing and scrupulous aseptic technique in preventing infection in such patients cannot be over-emphasised

7.11 Antimicrobial prophylaxis for Endogenous Infection

The use of antimicrobial prophylaxis, beyond the confines of perioperative prophylaxis, is an emotive area, generally regarded with scepticism and fear that the widespread resistance of organisms to antibiotics might be induced in this way. "In clinical use, antimicrobial prophylaxis usually combines inefficiency with unproved efficacy" [242]. Nonetheless, possibly aided and abetted by the pharmaceutical industry, there is constant research and exploration into new indications and areas where the prophylactic administration of antibiotics might have a role.

Shapiro et al [168] reported in the late 1970s that about 10% of all hospitalised patients, in some randomly selected short-stay general hospitals in Pennsylvania, received antimicrobial prophylaxis, either for surgical on nonsurgical procedures; this use of antibiotics amounted to 30% of the total antibiotic usage, and was largely inappropriate.

In the early 1980s, Jackson [242] reviewed the indications for antibiotic prophylaxis in nonsurgical high risk patients. He stated that the prevention of nosocomial acquisition of urinary tract infection, pneumonia, catheter sepsis and cutaneous infections by antibiotic prophylaxis was ineffective, yet within three years of this article, Stoutenbeek [14,243] had reported dramatic benefit in preventing just such infections with the use of selective decontamination; and this method of antimicrobial prophylaxis within the ICU has gained increasing popularity and acceptability ever since. Clearly an answer to the existence of a role for antimicrobial prophylaxis must lie somewhere between these two

opinions - largely still to be determined by carefully controlled clinical studies to determine indications, and contraindications, in this still very controversial area.

The experience with antibiotic prophylaxis is fairly extensive, but largely unevaluated, owing to poorly conducted studies . While there are theoretically enormous potential benefits to be derived, these are often difficult to prove. Such therapy is often given to large numbers of patients accepting a low rate of efficacy, because the drug is cheap and safe to administer, or in the hope that it might prevent, or at least delay, the development of infection. If infection does occur in the face of prophylaxis, a number of explanations can immediately be provided: including host factors, the endogenous and nosocomial flora, so that it is often very difficult to separate the subjective and objective data. Clinical and economic values rather than true efficacy thus often ultimately may determine whether antimicrobial prophylactic policies are adopted. Jackson commented cynically that prophylaxis is consistently most efficacious, or fails least frequently. when the exposure to an unusual risk of infection is brief. Where the required duration for efficacy is limited, a broad spectrum of potentially pathogenic organisms can be inhibited and prophylaxis may appear to have been successful.

The potential adverse effects of antimicrobial prophylaxis on the host include: an alteration of the normal host flora due to selective pressures with the loss of natural antibiosis and colonisation resistance, leading to colonisation by an abnormal flora, often containing resistant strains which may predispose to bacterial and fungal superinfection. There may be other more uncommon side-effects such as the development of pseudomembranous colitis from *Clostridium difficile* overgrowth, idiosyncratic reactions and vitamin deficiencies. Where the benefit of the regimen is difficult to prove, the added costs, particularly if prophylactic drugs are prescribed on a large scale are yet another disadvantage. The possibility for increasing numbers of resistant organisms to colonise and cause infections in patients who are not receiving prophylaxis, particularly if the benefit of prophylaxis is unquantified and uncertain, is

one of the major areas of concern with this form of therapy, and is thought to be more likely if the regimen is used generally, for prolonged periods, and is not of demonstrable benefit.

It is thus recommended that the indications for antimicrobial prophylaxis should be for extremely limited periods only, if the aim is to cover procedures or exposure to disease (such as would more commonly be encountered in the community), that prophylaxis for disease prevention, such as for bites or following contaminated trauma, should be continued for a period of 24 hours to not more than 5 days to a week , and that more prolonged regimens should only be used in high risk, immunocompromised patients. The regimen should ideally be used only in areas where sepsis is likely to result in significant morbidity and mortality, and the use of topical antibiotics or other practices that might promote the emergence of Gram negative organisms, should be avoided.

Infection prevention was initially most vigorously studied in the immunocompromised haematological patients, because infection has long been recognised to be the major cause of death in these patients, often sadly even in the presence of a "cure" for the underlying condition. The use of protective isolation and laminar flow was developed in the 1960s and was found to be expensive, cumbersome and difficult to maintain from a logistical point of view, as well as from the patient's psychological viewpoint. Virtually all patients who were treated with protective isolation also received prophylactic oral non-absorbable antibiotic therapy to eliminate the faecal flora. It gradually became apparent that the greatest impact on the incidence of life-threatening infection was not the environmental protection, but the suppression of the gastrointestinal flora, which promoted the development of infections due to Gram negative bacilli.

The choice of agents suitable for use in a prophylactic regimen depends on the organisms that are most likely to cause infection, the prevailing flora and their resistant patterns in the area where prophylaxis is to be applied; as well as the potential costs

and likely effects that may result from this method of antibiotic usage. The development of superinfection, whether from therapeutic or prophylactic use of an antibiotic, amounts to failure; this complication has frequently been noted to follow the administration of penicillin, streptomycin, methicillin, tetracycline, ampicillin and chloramphenicol [12]. The species causing superinfection are most commonly the endogenous *Enterobacteriaceae*, *Pseudomonaceae* or fungi.

The phenomenon of colonisation resistance was noted initially in patients undergoing treatment for haematological malignancy [244], where it was observed that the use of broad spectrum antibiotics was more likely to result in the problem of superinfection. The normal bacterial flora colonising the gastrointestinal tract, which is largely anaerobic, is easily eliminated by the use of such broad spectrum drugs and its protective effect which has been shown to prevent the overgrowth of other more potentially pathogenic aerobic bacteria and yeasts, is thus lost. The anaerobic flora of the digestive tract, particularly the Gram positive anaerobic flora, plays a major role in the ecological, flora-associated colonisation resistance by colonising mucus and the mucosa. The anaerobic flora in the lumen is thought to be largely derived from the flora associated with the mucosa. The primary composition of the indigenous flora is thought to be dependent on diet [245].

As discussed previously, the indigenous flora is thought to hinder colonisation by foreign bacteria, by blocking receptor sites. Nutrition for the enteral flora is obtained from the host, and mucus is thought to be of specific nutritional value to these organisms [244]; the indigenous flora may also possess specific enzymes for the digestion of nutrients of host origin which non-indigenous flora lack. Significant differences in the anaerobic colonising flora between individuals have been found, and these interindividual differences may determine the degree of colonisation resistance by that individual.

Le Frock et al [7] demonstrated that the aerobic faecal flora also undergoes changes during hospitalisation, even without the administration of antibiotics, radiation or surgery: on admission the most common aerobic bacteria were noted to be *Escherichia coli*, but this was gradually replaced by *Klebsiella*, *Proteus* and *Enterobacter spp.* Wells et al [19] demonstrated that the aerobic and facultative bacteria also have a role in colonisation resistance, and assist both in preventing gastrointestinal colonisation by potential pathogens, and in confining such pathogens to the lumen of the intestine.

van der Waaij [244] further demonstrated that there were marked differences in the colonising flora of normal human volunteers and in patients with acute leukaemia. He suggested that the leukaemics might have a "lower quality" of indigenous flora thus predisposing to colonisation by potential pathogens. Attempts at enhancing colonisation resistance have been attempted by the implantation of anaerobic bacteria by oral inoculation, however, such attempts have not been successful. The other technique directed at preserving colonisation resistance and maintaining or improving the anaerobic indigenous flora is selective decontamination of the digestive tract (SDD); however, while the potentially pathogenic aerobic Gram negative bacilli and yeasts may be largely eliminated by SDD, Gram positive infections still continue to occur, because they share sensitivity patterns with the indigenous flora that determines colonisation resistance.

Gorbach et al [18] has demonstrated that agents which do not inhibit the anaerobic species, only minimally decreased its proportion of the intestinal flora in normal volunteers, but they were unable to confirm that colonisation resistance was directly related to this anaerobic component. It has also not been convincingly demonstrated that agents which exert effects on both aerobic and anaerobic species actually promote the overgrowth of drug-resistant species. The phenomenon of colonisation resistance has remained somewhat controversial because it is argued that, if its relevance were absolute, the selection of resistant microorganisms should not occur [246] with the use of

a single agent, such as cotrimoxazole, designed to suppress the gut flora but preserve its anaerobic component. Clasener [12] suggests that colonisation resistance can be simply measured if it is assumed that its reduction leads to an increase in the concentration of aerobes in the faeces. Following the administration of antimicrobial agents, overgrowth of resistant organisms has been demonstrated in normal human volunteers receiving tetracycline, ampicillin, clindamycin, ceftriaxone, and moxalactam. Cotrimoxazole, however, was not found to cause overgrowth of resistant microorganisms except for occasional enterococcal overgrowth. Since 1977, successful infection prophylaxis in leukopaenia has been reported in placebo-controlled studies of oral cotrimoxazole, oral cotrimoxazole plus erythromycin, polymyxin E plus neomycin, and polymyxin E plus both neomycin and nalidixic acid.

7.11.1 The Selection of Agents for Antimicrobial Prophylaxis for Endogenous Infection

With careful selection of an antibiotic regimen, it is possible to eliminate the major potentially pathogenic microorganisms (*Enterobacteriaceae*, *Pseudomonaceae*, *Staphylococcus aureus* and *Candida* and other yeasts) in patients with an increased susceptibility to infection, without affecting colonisation resistance. Indeed, there is such a wide variety of agents available for the treatment of most infections, that it should be possible to select both prophylactic and therapeutic agents which do not affect colonisation resistance.

It is thought that the development of bacterial overgrowth, or the presence of high concentrations of potentially pathogenic microorganisms in the faeces, particularly if they are resistant, may be related to the development of subsequent infection. Failure of the prophylactic regimen is always easily explained by the presence of a gap in the spectrum of activity of the antimicrobial agents used, as microorganisms able to colonise the gastrointestinal tract will continue to do this in the face of prophylaxis, provided that they are not sensitive to the agents used. However, the number of

organisms colonising the gut should not increase exponentially if the limiting flora and colonisation resistance has been preserved.

1) Trimethoprim and sulphamethoxazole

The combination of trimethoprim-sulphamethoxazole was discovered to prevent infections due to *Pneumocystis carinii* in children, and the use of cotrimoxazole for the prevention of this infection in those who are at risk, and able to tolerate the drug, is well recognised. However, this antibiotic combination has also been used with considerable success in the prophylaxis of other infections; this is because the sulphonamides have not been observed to promote the overgrowth of potentially pathogenic microorganisms, although candidal colonisation of the gastrointestinal tract may occur. Cotrimoxazole should be used in combination with another antibiotic to prevent the selection of resistant bacteria, as colonisation with Gram negative organisms, while greatly reduced, is not eliminated. Some studies have noted that the Gram negative organisms that emerged were fully resistant to this agent; with the addition of polymyxin E however, this problem appears to be able to be overcome. One of the deficiencies of this drug is its lack of activity against *Pseudomonas aeruginosa*, and part of the rationale for combination therapy with polymyxin is to provide cover against this important nosocomial pathogen.

The risk of colonisation and infection by *Candida albicans* appears to be promoted by the use of cotrimoxazole, so that antifungal prophylaxis should be administered in conjunction with it. Amphotericin B has been found to be more effective than ketoconazole at preventing overgrowth by yeasts. The oral administration of topical antibiotic and antifungal preparations may be all that is required. The oral administration of cotrimoxazole in combination with such a preparation both decontaminates the gastrointestinal tract and provides systemic prophylaxis.

Cotrimoxazole has gained acceptance as an effective agent for long term prophylaxis against infection in leukopaenic patients. However allergic reactions and toxicity, usually due to the sulpha component, are not infrequent, and it has been reported that its use may prolong the neutropaenic period following the administration of cytotoxics 246.

2) The Cephalosporins

The cephalosporins are thought to be potentially damaging to colonisation resistance, as they exhibit activity against the anaerobic flora. Cefotaxime is an unusual beta-lactam antibiotic in that only 1% is excreted in the bile. Superinfections following its use are also thought to be uncommon. The effect of parenteral cefotaxime on the faecal flora has been extensively studied, however in both patients, and volunteers, and has demonstrated at least partial elimination of the *Enterobacteriaceae* without the emergence of resistant strains. For the above reasons cefotaxime is frequently selected as the parenteral agent of choice in regimens of selective decontamination for mechanically ventilated patients. It is administered as part of the initial therapy to achieve early elimination of potentially pathogenic flora.

3) The Polymyxins

Polymyxin B and E may be regarded as therapeutically equivalent. Resistance is reported to develop infrequently in originally susceptible bacterial species, and systemic toxicity following oral administration has not been reported, although parenteral administration commonly results in nausea and vomiting. Their oral administration has been demonstrated to achieve complete selective decontamination within a period of three days, compared with intervals as long as 7 to 9 days for nalidixic acid and cotrimoxazole. When used alone, a dose of 800mg daily is required because of marked inactivation of the drugs in the gastrointestinal tract; however, in combination therapy, the dose may be reduced to 400mg/day.

The polymyxins are effective against most Gram negative bacilli, except *Proteus spp.* to which they are intrinsically resistant, and for this reason they are most commonly used in combination with neomycin, tobramycin, nalidixic acid, cotrimoxazole or norfloxacin.

4) The Aminoglycosides

The use of oral neomycin has become established in preoperative bowel preparation for gastrointestinal surgery, often in combination with metronidazole; it has also been used for more prolonged periods to eliminate *Proteus spp* from the intestine of patients in hepatic coma. The drug is recognised to have a direct adverse effect on the intestinal mucosa, increasing gastrointestinal transit time. Its oral administration may lead to ototoxicity. With experimental use in mice, colonisation resistance has been shown to be affected, even at doses which fail to completely decontaminate the intestine.

In a study comparing the effects of the oral administration of aminoglycosides to achieve decontamination, only the use of tobramycin was not associated with a simultaneous disturbance in colonisation resistance. The disadvantage of tobramycin over neomycin is that the former is considerably more expensive. The combination of tobramycin and polymyxin appears to be satisfactory in achieving selective decontamination both in leukopaenic and mechanically ventilated patients, although its decontaminating spectrum, if used alone, is too narrow [12].

5) The Quinolones

Nalidixic acid, given as therapy for urinary tract infections, has been observed to promote the emergence of resistant strains of Gram negative bacilli in the faeces of up to 5% of all patients receiving this form of therapy. However, if combined with polymyxin alone, or polymyxin and neomycin, such resistance was not found to occur.

Side effects of therapy with the quinolones include manifestations of central nervous system toxicity, including seizures and intracranial hypertension have been reported in children, while other areas of potential toxicity such as crystalluria, cartilage damage and DNA damage have not yet been shown to be of clinical importance [247]. The newer generation of quinolones are generally thought to be safe and well tolerated, with a profile similar, or possibly even superior to that of other classes of antibiotics.

Norfloxacin and the other newer quinolones have been used in selective decontamination regimens both in leukopaenic and mechanically ventilated patients. Norfloxacin is particularly suited for enteral decontamination, as it is cheap and poorly absorbed from the intestine. These drugs do not affect colonisation resistance, are rapidly effective in suppressing the gut flora and have not been associated with the rapid development of resistance. They have much lower MICs and undergo much less inactivation in the faeces. While effective elimination of the *Enterobacteriaceae* from the gastrointestinal tract can be achieved with such agents without disturbing the anaerobic flora, resistant coagulase negative staphylococci and increased faecal concentrations of *Candida albicans* have been detected in some patients [246].

The quinolones have a superior spectrum of activity compared to cotrimoxazole, in that they are active against *Pseudomonas aeruginosa*, however, they lack activity against *Pneumocystis carinii*.

6) The Macrolides

The oral administration of either erythromycin or clindamycin has been found to eliminate the *Enterobacteriaceae* from the faeces of volunteers, without promoting the overgrowth of resistant organisms. In studies in mice, orally administered erythromycin did not affect colonisation resistance. In studies where the drug has been administered long term, for the prevention of acne or *Legionella pneumophila* infections, or in immunosuppressed renal transplant patients, there has not been

resistant organisms in the faecal flora [12]. The combination of erythromycin and cotrimoxazole has been used in leukopaenic patients, but the frequently experienced gastrointestinal intolerance associated with the use of this agent has limited its widespread use, as success depended on perfect compliance. Erythromycin is also noted for drug interactions.

7) Antifungal Agents

Neither nystatin nor amphotericin B has any antibacterial activity, and these agents therefore do not exert any effects on microbial colonisation resistance. The use of these agents requires that there should be a few hours of exposure to the site to be decontaminated for this to be achieved, and the use of an adhesive paste or lozenges is therefore preferable to an oral solution, when attempting to decontaminate the oropharynx. Amphotericin B is preferred to nystatin, because it shows a more favourable ratio between the dose given and faecal concentrations achieved, has lower MICs for *Candida* and is also more palatable.

Ketoconazole does exhibit antibacterial activity against a number of bacterial species, and might thus be expected to affect colonisation resistance; it is also sufficiently absorbed following oral administration to be able to achieve a systemic effect. In studies with leukopaenic patients it has been shown to be more successful at preventing fungal infections than the use of oral nystatin or amphotericin B, but following bone marrow transplantation this benefit was lost, presumably because of the poor gastrointestinal absorption.

In selecting an antibiotic for the treatment of an infection, the preservation of colonisation resistance as far as is possible should also be considered. Although it is difficult to find an alternative to the penicillins, some of the cephalosporins including cefotaxime, cefaclor, ceftazidime and cephradine would appear to have less effect on the anaerobic flora and may perhaps be substituted. It is thought that none of the

aminoglycosides, when administered intravenously has any effect on colonisation resistance. The quinolones are thought to be relatively safe, but should not be given to children. Metronidazole is thought to exert much less effect on colonisation resistance than clindamycin and is the drug of choice for anaerobic infections.

7.11.2 Selective Decontamination of the Digestive Tract

Unit acquired infection of all types increases with the duration of stay in the ICU, and may exceed 80% in those who remain in the unit for more than 5 days [156]. Once a cycle of induced suppression of host defences. sepsis and organ failure is established, conventional management has been recognised often to be inadequate, with the consequent high mortality associated with multiple system organ failure. While urinary tract infections, septicaemia and soft tissue infections are all common, it is the respiratory tract that accounts for the highest proportion of secondary infection, although there are many difficulties associated with its definition and diagnosis.

It is often difficult to distinguish between infections present on admission and those acquired within the unit, because infection may be subclinical, incubating or masked by other pathology. As previously discussed, it is customary to differentiate between primary infections, which are usually accepted as those occurring within the first 48 hours after admission, and which are considered to have been present or latent on admission (and thus often due to a different spectrum of organisms), and secondary infections, which manifest after 48 hours. These infections are of interest, because with optimal management, they are considered by many to be potentially preventable.

It was assumed that such infections were mainly exogenous, that is, acquired directly or indirectly from the other patients, the attending staff or the environment, and many of the techniques, which form an integral part of patient care, are designed to prevent such infections from developing. However, although the pathogenesis of infection in the ICU is both variable and complex, most unit infections are now thought be

endogenous, with the patient's own oropharynx, stomach and more distal gastrointestinal tract serving as the principal sources of infection. Such endogenous organisms are, however not the primary endogenous colonisers such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* which colonises the upper respiratory tract, *Staphylococcus aureus* and *Escherichia coli* which colonises the gut in healthy people in the community, but rather "secondary endogenous" organisms, or colonisers from the hospital bacteria. While a wide range of organisms may be involved in colonising and causing endogenous infection, certain groups of aerobic Gram negative bacilli (particularly *Escherichia coli*, *Klebsiella spp*, *Proteus spp*, *Enterobacter*, *Serratia spp* and *Pseudomonas species*, and less commonly *Acinetobacter spp*, although in some centres this is emerging as the most prominent, problematic organism) constitute the main problem. These organisms often show abnormal patterns of colonisation of the oropharynx and gastrointestinal tract, reflecting both the outgrowth of indigenous strains and colonisation with hospital strains of these organisms. Oropharyngeal colonisation with Gram negative bacilli is strongly associated with the subsequent development of respiratory tract infections, with more than 75% being preceded by oropharyngeal colonisation with the same organisms [4,248]. Wound, and urinary tract infections are also related to preceding gastrointestinal colonisation and the presence of indwelling catheters or instrumentation [4,5,30,156]. More than 50% of all patients admitted to the ICU are already colonised with the pathogen that subsequently causes their nosocomial infection [43]. While anaerobic organisms may be important in sepsis present on admission, they are seldom encountered as a cause of unit acquired infection.

Experience with granulocytopaenic patients [12,13] first demonstrated that this pattern of infection might respond to selective decontamination of the digestive tract, where non-absorbed antibiotics are used to eliminate, or greatly reduce, the numbers of aerobic Gram negative bacilli and yeasts in the gastrointestinal tract, thereby reducing the risk

of endogenous infection, while retaining the normal anaerobic flora; thus maintaining colonisation resistance against overgrowth with drug-resistant strains.

The first application of this technique to the ICU was in 1984 by Stoutenbeek and his group from Groningen in the Netherlands, [14,243] who described the use of a prophylactic regimen combining parenteral cefotaxime, and an enteral regimen of polymyxin E, tobramycin and amphotericin B, applied to the oropharynx and stomach. The enteral decontamination regimen was known as "selective decontamination", or SDD, while the addition of a parenteral agent gave the regimen the acronym of "SPEAR" for selective parenteral and enteral antisepsis regimen. The intestinal decontamination was applied for the duration of the patient's stay, while the cefotaxime, which has negligible effects on the anaerobic flora of the gastrointestinal tract, and is thus unlikely to hamper colonisation resistance, was given for the initial few days only. The cefotaxime was thus used as a supplement to the intestinal decontamination, at a stage before the full effect of intestinal and oropharyngeal decontamination was established, while it was still possible for subclinical infection acquired before, or at admission, to be incubating, and during which intubation and other invasive procedures were most likely to be performed. The use of the cefotaxime was independent of the usage of any other antibiotics, which might be indicated for the treatment of clinically or microbiologically diagnosed infection.

The results of the initial studies of selective decontamination (SDD) were most encouraging and showed dramatic reductions in the incidence of colonisation by aerobic Gram negative bacilli (AGNB) and yeasts, with an associated fall in the infection rate; some studies even reporting reductions in the mortality rate for selected groups of patients. If the incidence of secondary infection could be reduced, it followed that the costs entailed in the treatment of such infections (prolongation of ventilation, ICU stay, additional drugs, etc) would be avoided and the additional costs involved in the administration of prophylactic antibiotics, with the associated increase in

microbiological surveillance, would easily be justified as cost-saving. Of course, if the technique could be demonstrated to improve mortality in the ICU, its use would be justifiable at any price.

It was thought that by reducing the bacterial load in the gastrointestinal tract, and thus the transfer of endotoxin to the bloodstream [96], selective decontamination might be able to prevent the development of multiple organ system failure. If this mechanism held true, its effects on the mortality in the ICU could be remarkable. Polymyxin E which is used in many of the decontamination regimens, is recognised to bind to endotoxin, and might be partly responsible for this effect, which has not yet been convincingly proven.

The studies of selective decontamination have been performed on different ICU populations, using a variety of techniques both in terms of medication and study design. While the initial studies were flawed by small patient populations, historical control groups, and post-hoc patient stratification, the results were so promising that there has been a flurry of studies from numerous ICUs, particularly in Europe. These studies have looked at various types of ICUs and high risk sub-populations, in an attempt to establish where and whether this technique really has a role, and to assess the benefits to the patient in terms of morbidity, mortality and cost.

Although the decontamination regimens were primarily designed to have an effect on endogenous infections, some centres [229] also reported a beneficial secondary effect on the bacterial flora of the ICU, with a consequent reduction in the incidence of exogenous infection. Still other centres [3,249,250] have reported success in using the technique to eradicate multiply-resistant organisms from the ICU.

There has been continued concern however, that there is enormous potential for such a technique to exert selective pressures promoting antibiotic resistance, thereby promoting the emergence and overgrowth of organisms resistant to the antibiotics used.

There have, to date, been no reports in the literature on the microbial flora and its sensitivity patterns following prolonged use of this technique; however, a large part of the costs involved in using selective decontamination are incurred in the microbiology laboratory, where extensive and ongoing surveillance samples and cultures are performed to monitor the effects on the bacterial flora until the possible effects are fully known and understood.

The following is a review of the available literature of the trials to date on selective decontamination. While meta-analyses have reported many of these studies in terms of the methodology used, this review analyses the studies according to the populations studied.

1) Multiple Trauma

One of the areas where it has been suggested that conventional perioperative antimicrobial prophylaxis may cause more problems than it solves, is in patients with multiple trauma. There is concern that, apart from not being effective, it may induce the emergence of resistant bacterial strains, making the treatment of nosocomial infections, if and when they arise, more difficult. However, once a serious infection has developed in the patient who has sustained multiple trauma, multiple organ failure easily develops and the outcome, even with appropriate and adequate antibiotic therapy may often be fatal [180].

Selective decontamination which aims at selectively eliminating the Gram negative bacilli and maintaining the normal anaerobic flora, thus preserving the normal colonisation resistance to potentially pathogenic nosocomial bacteria, might thus be expected to circumvent the problems of antimicrobial prophylaxis, but nonetheless reduce the incidence of secondary infection in these patients. The studies of SDD which have shown the most positive results have indeed been in groups of patients admitted to the ICU because of multiple trauma; however, there are a number of methodological

problems with the most widely quoted studies, so that the results need to be interpreted with caution until more definitive studies become available.

In one of the earliest studies of selective decontamination in the ICU, STOUTENBEEK ET AL [14] assessed the effect of selective decontamination on colonisation and infection rates in multiple trauma patients. The study was not blinded, no placebo was used and the control group was historically gathered. The patients included in this study were all severely injured with Injury Severity Scores of approximately 34. 122 patients who stayed in the ICU for more than 5 days and required mechanical ventilation were investigated, including a control group of 59 patients who were retrospectively gathered and who had received no antibiotic prophylaxis. In these patients the infection rate was reported to be an astonishingly high 81%. They found that most infections in the control group were due to endogenous organisms and that, after two weeks in the ICU, more than 80% of patients were colonised. There were 63 patients who received SDD over a 12 month period, and in this group the infection rate was dramatically reduced to only 16%. The regimen used was topical Polymyxin E, Tobramycin, Amphotericin B, applied to the oropharyngeal cavity and enterally, and systemic cefotaxime which was continued until the patient was demonstrated to be free of potentially pathogenic microorganisms.

As part of the same study, the authors separately reported, as a prospective open study [243], the same two groups which they compared with two other regimens: a third group where enteral decontamination alone was performed in 17 patients, however here no difference in the infection rate compared with the control was demonstrated. In a fourth group of 25 patients, both intestinal and oropharyngeal decontamination were performed. In this fourth group they showed that while the incidence of secondary colonisation and infection with Gram negative bacilli was significantly reduced, early infections with Gram positive organisms were unaffected. It was only in those patients who received both systemic and enteral oropharyngeal and intestinal decontamination

that the incidence of early and late infections was significantly reduced. The definitions of microbial carriage states were carefully specified in this study, and similar definitions have since been employed by a number of other trialists : Colonisation was the presence of the same species of potentially pathogenic microorganism in an organ system for more than 3 days without signs of infection. Possibly more controversially, exogenous infection was defined as infection caused by potentially pathogenic microorganisms isolated from the site of infection, but without previous colonisation of the digestive tract; whereas endogenous infection was infection caused by microorganisms that had first colonised the digestive tract.

The definitions for site specific infection possibly account for the initially high infection rate, as they show a considerable microbiological weighting with minimal emphasis on the clinical presentation and status of the patients - and, in the absence of the patient when analysing an historical group of patients, such weighting might well have lead to an overdiagnosis of nosocomial infection. Respiratory tract infection was diagnosed on the basis of purulent sputum and dense growth in bacteriological cultures from the tracheal aspirate. The diagnosis of lower respiratory tract infection was made on physical and radiological signs of pulmonary infiltration, fever and leukocytosis. Unfortunately such a definition is rather too vague to be reliable. Urinary tract infection was diagnosed by culture of more than 100 000 organisms/ml from catheter specimen of urine. Wound infection was diagnosed on the basis of signs of inflammation, a purulent discharge from wounds and a positive Gram's stain, and culture. Septicaemias were recorded only if bacteriologically confirmed, but while specifying that to diagnose a *Staphylococcus epidermidis* bacteraemia, two positive blood cultures were required, again no further clinical parameters for any type of septicaemia were specified.

In the control group, 41% of patients were colonised by *Staphylococcus aureus* on admission, but this gradually disappeared during their ICU stay, while there was a

simultaneous increase in colonisation with Gram negative potentially pathogenic microorganisms. Early pneumonia (<48 hours) with *Staphylococcus aureus*, *Streptococcus pneumoniae* and/or *Haemophilus influenzae* was found to occur in 44% of these patients. Secondary colonisation of the oropharynx and trachea with Gram negative bacilli followed by pneumonia occurred in 20%, and the overall incidence of respiratory tract infections was 59%.

Only 24% of the group who received SDD were colonised by *Staphylococcus aureus* on admission, and the colonisation by all organisms was reported to decline during their ICU stay, with no secondary colonisation occurring. The high initial colonisation rates in both groups were explained by the rapid acquisition and colonisation by potentially pathogenic microorganisms following trauma, as a result of increased adherence, impaired oral defence mechanisms and a high exposure to the Gram negative organisms already colonising other patients in the unit, or in the food. The differences in the initial colonisation rates between the two groups were thought to be due to the fact that the initial enrollment specimens in the control group were taken the morning after admission, whereas those in the SDD group were taken immediately on admission.

The incidence of pneumonia during the ICU stay was 59% (20% were secondary infections) in the control group, of which 95% of the organisms were endogenous, while in the SDD group, the incidence was only 8%, and 57% of the organisms were endogenous. The incidence of other types of infection was also reduced. 32% of the control group developed urinary tract infections, 97% of which were due to endogenous organisms, but there was only one urinary tract infection which was not due to an endogenous organism in those who received SDD. Similarly, there was a 42% incidence of septicaemia in the control group of which 70% were due to endogenous organisms compared with only a 3% incidence in the SDD group in whom none of the episodes were due to endogenous organisms, specifically there were no

episodes of Gram negative septicaemia. The incidence of wound infections was 25% in the control group, 88% of which were endogenously acquired, compared with only 4% in the SDD group in whom 100% of the organisms were endogenous. Further interpretation of these figures is difficult, because the site specific infections are not reported as primary and secondary.

The effectiveness of the SDD regimen in eliminating Gram negative organisms from the gastrointestinal tract is extremely well demonstrated in this study, as is the increasing colonisation by these organisms in the control group, and the alterations that occur in the normal gastrointestinal flora during hospitalisation in the ICU. The initial samples [14] from the oropharynx in both groups showed a high level of colonisation by potentially pathogenic microorganisms (63% in the control and 41% in the SDD group), and while this persisted and increased in the patients in the control group (86% colonised by day 15 and 81% at day 21), by day 15 such organisms had been eliminated in those who received SDD, and such eradication continued at day 21. A similar pattern was seen in the samples taken from the rectum, although at both sites by day 21 there were only 6 patients in either limb of the study. While there are also tables provided which show a significantly lower number of potentially pathogenic microorganisms in isolates from the tracheal aspirate and urine, only the total numbers are provided, so that the effect with time of the decontamination regimen on these sites is not apparent. Later studies do not comment on the ability of selective decontamination to reduce the incidence of urinary tract infections, but concentrate almost exclusively on the prevention of nosocomial pneumonia.

The authors also found that with the implementation of SDD in their unit, a reduction in the contamination level of the ICU environment was achieved, without special cleansing procedures; this in itself was thought to have partly accounted for the dramatic reduction in the infection rate brought about by SDD. Importantly, the

emergence of resistance against the prophylactic topical and systemic antibiotics used for SDD, was not observed.

However, in spite of this dramatic reduction in the infection rate, the mortality is not commented upon in the initial study [14]. In the later report of the same study [243], 8% of the control group died in whom 59% had developed respiratory tract infections, 20% of which were nosocomial; 12% who had received intestinal decontamination alone, also with an overall incidence of 59% of respiratory tract infections, and an 18% incidence of secondary respiratory tract infections died; 4% who received oropharyngeal and intestinal decontamination died, and in these patients the overall incidence of respiratory tract infections was a similar 52%, but there were no secondary acquired infections; the mortality was 0% in those who received both enteral and parenteral decontamination, and these patients had only an 8% overall incidence of respiratory tract infections, with again no secondary infections.

Unfortunately, no attempt was made to address the problem of whether such deaths could be attributed to secondary infection. The low overall mortality, and the nonspecific diagnostic criteria used to diagnose lower respiratory tract infections, however, do cast doubt on the incidence and severity of the secondary infections in this study. The figures correlate poorly with other studies previously reported. It is difficult to accept that an infection rate of 81% can be associated with a mortality of only 8% in patients with an injury severity score of 34, further casting doubt on the diagnosis.

The costs of selective decontamination were not commented on in either of these papers, however in a further paper (Stoutenbeek C.P., et al A novel approach to antibiotic prophylaxis in multiple trauma patients. Actualites en anaesthesie reanimation, Librairie Aruette, Paris, 1986: 381-391) devoted to the same multiple trauma patients the authors justify the use of the technique thus: "more expenses have to be made for the oral non-absorbable antibiotics and the intensive bacteriological monitoring. The costs of systemic antibiotics are comparable with a conventional

antibiotic policy. The costs of SDD + bacteriological monitoring amounts ± 8% of the total ICU costs/patient. The savings are shortening of ICU stay, less need for isolation rooms, simplification of the care of the patients, less disposables, more survivors." Considering that the average costs of hospitalisation in an ICU as long ago as 1983, when this study was performed, were estimated by the same group [229] to be $ 8116 or $ 1365 per day or $ 22326 per survivor, whether such comments are indeed justified by the data provided, may be left to the reader to decide.

MIRANDA ET AL [229] reported, using the same patient data (although the figures are not presented), that the need for patient isolation because of severe infection was decreased by 90%, which they attributed to a 50% drop in the rate of nosocomial infection. Their practice was to isolate patients with persistent discharge of infected material, or those who were "resistant to treatment". As a result of being able to reduce the number of isolation rooms, the number of nurses, as well as the use of disposable equipment, which helped with cost-saving.

They found that the positive bacteriological samples taken from potentially contaminated sources in the ICU environment were reduced to 10% during the administration of SDD, compared with 100% previously. Of the organisms isolated, the Pseudomonaceae were the commonest in the ICU environment (60%), compared with the general ward, where the *Enterobacteriaceae* accounted for 92%. The surgical ward and, indeed the home environment, were found to be far more heavily contaminated than the ICU. They concluded from this that the routine hygienic precautions were not sufficient to remove contamination, and that the colonisation of a person, with normal colonisation resistance, had no correlation with the contamination of the environment. In the patient who has lost his normal colonisation resistance however, the contamination of the environment exerted a direct influence on the potential for colonisation with nosocomial bacterial flora.

With the use of SDD, there was an associated 12% increase in admission capacity to the ICU. The authors conclude by daring to suggest that architectural design and "special care facilities" will cease to be of high priority in infection control in the ICU as a result of SDD.

BOLAND, SADLER, STEWART ET AL from Charleston, West Virginia, reported a prospective double blind study of SPEAR in multiple trauma patients, using parenteral cefotaxime, or intravenous placebo for the first 72 hours, and oropharyngeal and enteral decontamination with polymyxin E, tobramycin, and nystatin, or placebo (poster ICC, Berlin 1991) to assess the efficacy of this technique in preventing ventilator associated pneumonia.

The diagnosis of ventilator-associated pneumonia was made by a positive sputum culture for bacteria, a temperature $> 38^{o}C$, a white cell count of more than 10 900/ml and a persistent infiltrate and/or a blood culture identical to the sputum culture. No further definitions were provided.

Patients who were considered to be likely to require ventilation for more than 5 days were selected on admission to the ICU and randomised; 70 patients were entered and 41 were evaluable (22 received placebo and 19 received SPEAR). The patients were fully comparable in terms of age, sex and APACHE II (20.6 SPEAR vs 16.3 control). No injury severity score was provided. The duration of ICU stay was significantly shorter in the placebo group (11 days vs 18.6). 10 (53%) patients who receive SPEAR developed ventilator-associated pneumonia, compared with 15 who received placebo (68%) and, in this subgroup, the patients were again fully comparable and the patients in the control group still showed a significantly shorter requirement for ICU care. The mortality rate in this study is not provided.

The organisms identified as causing respiratory tract infection were: *Staphylococcus aureus* (control 3, SPEAR 3), *Haemophilus influenzae* (control 3, SPEAR 1), and aerobic Gram negative bacilli (control 6, SPEAR 5).

While the number of patients in this study is unfortunately too small, the study design is the ideal way to assess any technique. The overall incidence of nosocomial pneumonia of 61% (although no time interval for its definition is specified) is sufficiently high for a significant reduction with the use of SPEAR to have been anticipated. The definitions and the effect on colonisation and resistance patterns presumably could not be provided in the abbreviated poster form. The fact that this study failed to achieve the desired result is explained as being due to a spectrum of organisms insensitive to the agents used in the decontamination regimen, and also to primary tracheal colonisation.

2) Multiple trauma with thoracic injury

Patients admitted with thoracic injuries requiring intensive care therapy for more than 5 days, with an injury severity score [251] of more than 25, were enrolled by VAN SAENE ET AL [252] in Groningen. 63 patients, who received an oral antibiotic programme of polymyxin E, tobramycin, and amphotericin B (administered to the oropharynx as a methylcellulose paste to the buccal mucosa, as an enteral solution down the nasogastric tube, to the vagina and to any gastrointestinal stomata), parenteral prophylaxis with cefotaxime for four days to eliminate potentially pathogenic colonising community-acquired bacteria, were reported. Colonised or infected wounds were treated with a local disinfecting solution which was also used to rinse out peritoneal, pleural or mediastinal cavities, where there was colonisation or infection.

They reported that the oropharynx was free of potentially pathogenic organisms within 3 days, the alimentary tract within 10 days and that "secondary colonisation was virtually prevented in all patients". Only 16% of the patients developed infections,

which were largely of the lower airways, compared with the previously observed 81% infection rate in the same unit, obtained by retrospective analysis [14].

The episodes of infection were all "primary endogenous infections" caused by organisms that the patients were carrying on admission to the ICU, half being community-acquired, the remainder *Enterobacteriaceae* or Pseudomonaceae. Cefotaxime cured all these infections easily, which is remarkable in view of the fact that 2 of the patients had *Staphylococcus epidermidis* septicaemias and three were reported to have lower airway infections due to *Staphylococcus aureus*. The resistance to the antibiotics used was reported to be low - less than 3% for polymxin E (including *Proteus spp*), less than 1% for tobramycin, and less than 4% for cefotaxime; since the implementation of the oral decontamination regimen, no outbreaks of multi-resistant organisms had been encountered.

While these results are most encouraging, there are several problems with the interpretation of this study, because it is uncontrolled and unblinded. The definitions of infection were not specified, which makes interpretation difficult, particularly when comparing results with a retrospectively calculated rate of infection of 81%, which would seem to be inordinately high. No time limits, for the study or the gathering of data for antibiotic resistance profiles, are specified, so that it is difficult to assess whether antibiotic resistance might still have developed.

3) The Surgical ICU

KERVER ET AL [253] from Utrecht, reported a prospective randomised study of 96 patients admitted to their surgical ICU, who required mechanical ventilation and hospitalisation, within the ICU, for more than 5 days. Approximately 25% were trauma patients, 25% non-elective abdominal surgery, the remainder being admitted following vascular, thoracic and elective abdominal surgery. The patients were randomly allocated to a control or study group who received oropharyngeal and enteral

decontamination with polymyxin E, tobramycin and amphotericin B, as well as parenteral prophylaxis in the form of cefotaxime for 5 days. This regimen was discontinued as soon as the cultures of the oropharynx and trachea revealed no microorganisms. The two groups were fully comparable in terms of age, sex distribution, and APACHE II score (15.1 control versus 14.6); however, the average duration of stay in the control group was not significantly prolonged at 20.1 versus 14.6 days. This study again found that colonisation of the oropharynx, respiratory and digestive tracts was reduced by the use of this regimen, while colonisation by Gram negative bacilli, which started at 30% in both groups increased throughout the duration of stay in those in the control group (51% at day 7 in the control versus 2% in the study patients). There were 107 infections in the 47 patients in the control group compared with 42 in the 49 in the study group and infections due to Gram negative bacilli were significantly reduced in the study group. The mortality due to secondary infection was significantly less in the study group.

The criteria used for diagnosis of infection included a number of features of multiple organ dysfunction, of which 3 were required for the diagnosis; however, the localising signs for the site of infection were not clearly specified for the respiratory tract where lower respiratory tract infection was diagnosed from "clinical and x-ray findings of pulmonary infiltration".

The incidence of secondary infection in this study was extremely high: 81% in the control group compared with 39% in the study group. The incidence of secondary lower respiratory tract infections was significantly lower in the study group where only 6 infections occurred in comparison with 40 in the 47 controls. A significant reduction in infection was also encountered with catheter related infections, and intra-abdominal infections; however, the incidence of urinary tract infections, phlebitis and wound infections was similar in both groups. Bacteraemias were significantly reduced in the

study patients, and occurred in 30% of the study patients compared with 57% of the control group.

The spectrum of pathogens causing the infections differed significantly between the two groups: 40 infections (37%) in the control group were due to 75 isolates of Gram negative bacteria, compared with only 6 infections caused by 8 isolates in the study group. The organisms most commonly isolated were *Pseudomonas spp* (17 vs 3), *Enterobacter* (11 vs 1), *Escherichia coli* (9 vs 0), *Klebsiella spp* (9 vs 1) and *Acinetobacter spp* and *Haemophilus influenzae* which caused 1 infection each in the study group.

There were 45 infections (42%) due to Gram positive infections in the control group compared with 28 (67%) in the study group, *Staphylococcus epidermidis* being the most common Gram positive organism in both groups. The effect of the decontamination regimen on the possible emergence of multiply resistant bacteria was not studied.

The number of antibiotic units administered parenterally to the control patients was 1407 compared with 1352 in the study patients, but whether this included the prophylactic cefotaxime is not specified. 40 of the 47 patients in the control group were treated with parenteral antibiotics on admission to the ICU as part of a short prophylactic or therapeutic regimen, although the number of patients infected on admission was not significantly higher in the control group (51% versus 69% in the study group). There was "no statistically significant difference in the use of parenteral antibiotics on admission" - a fact which is not surprising considering that part of the SDD regimen was the use of a parenteral agent for 5 days following admission. The effect on the colonisation rate by this extensive usage of antibiotics at admission is uncertain, however, the authors had previously demonstrated to their satisfaction that colonisation with *Pseudomonaceae* and *Enterobacteriaceae* could not be prevented by

parenteral antibiotics, and they use this fact to ascribe all benefit in the reduction in colonisation in the SDD group to the topical, enteral, decontamination regimen.

The overall mortality in the control group was 32% and in the study group 28.5%. Without specifying the means used to decide how death was attributed to secondary infection, the authors ascribed 8 of the 15 deaths in the control group to secondary infection, compared with only 2 of the 14 in the study group.

This study satisfies criticisms levelled against other studies in that the control patients were concurrent. The reduction in colonisation of the gastrointestinal tract and trachea is impressive and, although in an unblinded study there is always the potential for bias in the interpretation of results, the more than 50% reduction in the incidence of secondary infection, even with a non-specific definition of lower respiratory tract infection, is convincing. The incidence of secondary infection, even with the use of selective decontamination is still far too high and raises the question as to how stringently the diagnostic criteria were applied, or what the hygienic standards in this unit must be. An incidence of secondary infection of 39% after the successful introduction of a prophylactic regimen, in addition to perioperative antimicrobial prophylaxis, should surely be dealt with by the urgent development of an infection control team, and other techniques besides the use of still more antibiotics, to address the root cause of an extremely large problem.

The reduction in mortality due to secondary infection however, possibly needs to be defined more carefully, as this is one of the few studies which has reported this type of benefit from SDD, and the evidence for this is not convincing with the limited data provided.

Kerver et al [35] had previously published a prospective analysis of the incidence of colonisation and infection in 39 patients admitted to their surgical ICU. The incidence was similar to that in their study of selective decontamination, with 74% of the patients

developing secondary infection: 66.6% developed nosocomial pneumonia, 28.2% developed catheter-related bacteraemia, 17.9% wound infections. Again the infection rate in these patients is unlike any other studies reported where there was no underlying motive to demonstrate the efficacy of a new technique or drug (cf Donowitz et al [162] where the highest incidence of wound infection in any subgroup of surgical patients in the ICU was 9%). This enormous discrepancy in the incidence of secondary infection is neither addressed nor explained in either of their studies.

PUGIN ET AL [142] from Geneva, performed a randomised, placebo-controlled, double blind study of oropharyngeal decontamination without systemic prophylaxis, in their surgical ICU, to assess the efficacy of the regimen in preventing ventilator-associated pneumonia. 79 patients were randomised, but 27 were withdrawn because the duration of intubation was less than 48 hours. The regimen evaluated comprised oropharyngeal polymyxin B, neomycin and vancomycin, or placebo, which were administered 6 times daily to the oropharynx in 52 evaluable patients. The patients were assessed as being at high risk of acquiring ventilator associated pneumonia because of their requirement for prolonged ventilation; the average duration of ventilation was from 3 to 34 days (mean 10 days). Patients who had received organ transplantation were excluded from the study.

They demonstrated a significant reduction in the incidence of tracheobronchial colonisation by Gram negative bacteria and *Staphylococcus aureus*. The incidence of pneumonia was also significantly reduced (16% vs 78% $p < 0.0001$) in the first 12 days of ventilation. This was attributed to interruption of the "stomach to trachea" route of colonisation.

The definitions of pulmonary infection used in this study were still unsatisfactory, although more comprehensively reliable than many of the other studies reviewed. A scoring system was applied with a range from 0 - 12, ventilator associated pneumonia being diagnosed on a score of 7 or greater for 3 or more days. However, using this

scoring system it would still be possible to diagnose pneumonia, either without any septic focus, or without the lungs being the site of sepsis, in a colonised patient.

In patients not receiving intravenous antimicrobial prophylaxis, the incidence of ventilator-associated pneumonia was significantly higher in the placebo group (11 of 12 vs 2 of 11 patients, $p < 0.0017$). Aerobic Gram negative bacilli were isolated in 92% of the 25 cases of pneumonia and in 28% there were associated Gram positive cocci. The organisms causing "early" pneumonia differed from the late onset pneumonias, resembling more closely the organisms associated with community-acquired infections.

The 25 patients who received the decontamination, and the 27 placebo patients were fully comparable in terms of age, sex, APACHE II (15.8 vs 14.7), duration of ICU stay (12.8 days vs 14.7), days of study (11.8 vs 13.9), days of ventilation (9.6 vs 10.7), antacid therapy, and mortality (28% vs 26%). Two patients had to be withdrawn from the study because of heavy colonisation by yeasts, (one developed oral candidiasis, another candidaemia) but they both received placebo. There was no difference between the two groups in the number of patients receiving, and the duration of, antibiotic prophylaxis, although systemic antibiotics were prescribed less frequently in those who received the decontamination regimen.

15 identical strains of aerobic Gram negative bacilli were found first in the stomach and subsequently in the trachea, and 8 of these were later implicated in cases of pneumonia. Three strains of *Klebsiella spp* were first found in the trachea. The route of colonisation by *Staphylococcus aureus* was found to differ from that of aerobic Gram negative bacteria, in that colonisation of the trachea occurred as the primary event; colonisation of the stomach by this organism was not demonstrated at all. The route of colonisation of yeasts resembled that of the Gram negative bacilli, and the rate of colonisation was higher in those who received the active regimen. The rate of colonisation by yeasts was sufficiently high for the authors to recommend the inclusion of oral nystatin, in the future use of their regimen.

Parenteral antimicrobial prophylaxis was not routinely used in this study and in both groups only 56% received specific IV antibiotics. The incidence of early-onset pneumonia was decreased by the active oropharyngeal decontamination regimen alone.

The authors felt that cefotaxime, which has been the most commonly utilised antibiotic in decontamination regimens, was not suitable for routine use, because different antibiotics were indicated for different conditions, and the spectrum of activity against Gram positive and anaerobic organisms with this agent is limited. They also felt that the use of a parenteral agent had not been convincingly proven to be an effective component in decontamination regimens, and also that the optimal period for such prophylaxis had not been established. A strict antibiotic policy which reduced the total use of parenteral antibiotics to a minimum was advocated as the best way of preventing superinfections due to resistant strains. No new antibiotic resistance or cross-infections between patients of the study population, or other ICU patients were detected for the duration of the study, which was only conducted over a seven and a half month period.

The causes of death were similar, with 7 patients dying in each group: 3 active and 5 control patients from sepsis and multiple organ failure, 2 active and 1 control from ARDS and multiple organ failure, 1 in each group from cerebral failure and one patient in the active group from cardiac failure. While the mortality for patients with similar severity of illness in the ICU is generally estimated to be between 30 and 40%, the mortality rates in this study were similar for both groups at 28%. The numbers of patients in this study are too small for a significant reduction to have been expected, as the authors estimated that 376 patients would have been required in each limb to have an 80% chance of seeing a 10% reduction.

This study is unfortunately too small, and was conducted over too short a period, to provide conclusive results on the benefits and disadvantages of selective decontamination. Although the reduction in colonisation and ventilator-associated pneumonia is extremely impressive, an incidence of 78% in those who received the

control regimen is surprisingly high, particularly when compared with the incidence of secondary infection previously reported from this centre in Daschner's meta-analyis of nosocomial infection in Europe [9]. It is nonetheless interesting to note that such benefit could be achieved without decontaminating all patients in the ICU simultaneously, which is so vigorously advocated by Ledingham, van Saene and Kerver.

HARTENAUER ET AL [254] performed a prospective, consecutive, non-randomised, cross-over controlled study in two surgical ICUs in their hospital in Munster, Germany. The methodology of this study was extremely complex; patients in each unit who were expected to require intubation for $\geq$ 3 days and to remain in the ICU for $\geq$ 5 days were included. In this way 200 patients were enrolled. The study was deliberately designed to prevent a carry-over effect from altering the entire microbial flora, and thus masking the effect of the decontamination regimen. In the first unit, 50 suitable patients received the decontamination regimen during the first 6 months, while a further 61 received a control paste and suspension over the subsequent 6 months to ensure identical nursing care procedures. In the second unit, there were 49 patients who comprised the control group in the first 6 months, followed by 40 patients who were given the decontamination regimen over the ensuing 6 months. All patients were given cefotaxime for the first 4 days of their hospital stay. The oropharyngeal and enteral decontamination regimen comprised a paste and suspension of polymyxin E, tobramycin and amphotericin B. All patients in this study received stress ulcer prophylaxis with cimetidine and pirenzipine; patients with head injuries received triamcinolone.

Colonisation with Gram negative bacilli was significantly reduced with the SDD; aerobic Gram negative bacilli accounted for 18.9% of the surveillance strains isolated in the test group, compared with 35.6% in the control group. The differences between the two groups were especially pronounced for tracheobronchial and oropharyngeal samples, and in the period from day 4 to day 14.

The definitions of infection were clinically based. Bronchopulmonary infection was diagnosed by the finding of a new infiltrate on the chest radiograph, purulent tracheobronchial secretions, and one of the following: positive physical signs, hyper or hypothermia, leukocytosis or leukopaenia, and a decrease in arterial partial oxygen pressure. Such a definition could once again be criticised for excluding bronchial infections which would not be evident on the radiograph, and for being too broad so that non-infective conditions could be mis-diagnosed as infection. No attempt was made to distinguish between primary and secondary infections in this study, which makes interpretation and extrapolation of the data more difficult.

The patients in the control and test limbs were comparable in terms of age, sex, duration of stay, duration of mechanical ventilation and severity of illness scores.

The incidence of lower respiratory tract infections was significantly ($p < .001$) reduced from 45% to 10% in both units, with 46 episodes due to 65 organisms occurring in the control group compared with only 10 episodes due to 10 organisms in the test group. No episodes of bronchopulmonary infection in the test group were caused by aerobic Gram negative bacilli, compared with 75% in the control group. The pathogens responsible for the episodes of bronchopulmonary infection in the test group were: *Staphylococcus aureus* (3), coagulase negative staphylococci (2), *Legionella pneumophila* (4) and *Candida albicans* (1), this patient was colonised by *Candida* in the oropharynx, trachea and gastrointestinal tract before admission to the study, had repeated postoperative haemorrhages and died of multiple organ failure).

The incidence of urinary tract infections was reduced in the study patients from 16.4% to 10% in the one unit, and significantly from 35% to 8.2% in the other. The incidence of infections caused by Gram negative bacilli was greatly reduced in the test patients. The incidence of septicaemias, wound infections and catheter related infections did not differ between the two groups, and there were three cases of *Candida albicans*

septicaemia in the test group which were considered to be failures of the decontamination regimen.

There was no significant difference in mortality between the two groups (47.5% control vs 38% test, and 42.5% vs 30.6%). There were apparently fewer patients suffering from bronchopulmonary infections in the test group at the time of death, but, considering the small number of respiratory infections diagnosed, this must have been the case for the entire duration of ICU admission. The mortality rate is high in this study, APACHE II scores are not provided, but the acute physiology scores and ISS values are extremely high (APS 9-10, and ISS 39). The authors raise the question as to whether infection really is a contributor to mortality.

Surveillance samples were monitored for the development of antibiotic resistance, particularly aerobic Gram negative bacterial resistance to polymyxin E and tobramycin. Specimens taken on admission and 1 week later showed similar sensitivity patterns and for the one year period of the trial, no emergence of resistance of aerobic Gram negative bacilli to polymyxin or tobramycin was detected. Resistance-pattern analysis for oxacillin, cefotaxime and tobramycin was used to investigate whether the number of multi-resistant coagulase negative staphylococci increased with the prophylactic regimen. 24.3% were found to be resistant to all three antibiotics, and a bacteria-related comparison between test and control groups showed significantly ($p<0.001$) greater numbers of resistant coagulase negative staphylococci in the test group, although when copy strains (isolates from the same patient with the same sensitivity profile on different occasions) were eliminated from the analysis, the distribution of coagulase negative, resistant staphylococci was equal in all groups, and there was no overall increase.

AITCHISON, VAN DEN ENDE, VAN RENSBURG AND OPPERMAN from the University of Natal, reported their experience with SPEAR in a surgical ICU (poster, ICC, Berlin, 1991). This was a prospective, consecutive study in which 50 control patients who met

enrollment criteria of endotracheal intubation for more than 4 days and duration of ICU stay of > 5 days were conventionally managed, the following 50 patients were treated with a regimen of oropharyngeal and enteral decontamination using tobramycin, polymyxin E and amphotericin B, and systemic cefotaxime for the first 4 days following admission.

The patients in both limbs were fully comparable in terms of age, sex, number of patients with organ system failure (48 in each group), the number admitted following trauma (30 in each group), the ISS was 30.4 in the SPEAR group compared with 25.4 in the control, the APACHE II score was 19 in both groups.

Pneumonia was defined as the clinical manifestation of sepsis with purulent sputum, containing pus cells and a new radiological infiltrate.

Microbiological surveillance samples showed initially high rates of colonisation (60-70%) with AGNB in both groups, which declined in the trachea and stomach in those who received SDD, although the rectal colonisation remained unaltered.

The overall incidence of pneumonia was statistically reduced in the patients who received SPEAR: 30% vs 66%. The incidence of pneumonia occurring after 4 days was 24.4% in the SPEAR group, compared with a significantly higher 65% in the control group, although the incidence of pneumonia occurring after 21 days was a similar 30% in both groups. While aerobic Gram negative bacilli were implicated in 96% of pneumonias occurring in the control group, only 53% of episodes in the SPEAR group were due to these organisms; however, the incidence of both colonisation and infection due to oxacillin-resistant *Staphylococcus aureus* increased in the patients who receive SPEAR, and 53% of pneumonias in this group were caused by this organism compared with only 13.6% in the control group. The incidence of vascular catheter related sepsis was also reduced in the SPEAR group: 6% vs 22%. There was no effect on duration of stay or mortality, even with subgroup analysis (48% SPEAR vs 52% control).

The definitions and the use of a historical control group make the interpretation of this study difficult. It is noteworthy that in spite of the use of this regimen, there was no effect on mortality. The high incidence of infection in both groups was clearly reduced by the use of SPEAR, which seems to have had an influence on colonisation patterns. The rapid emergence of resistant staphylococci with the use of SPEAR is of concern, but unfortunately no further data on its possible effect on the resistance patterns of other organisms is provided.

CERRA ET AL [255] reported a prospective double-blind, placebo controlled study of selective decontamination using enteral norfloxacin and nystatin in forty-six patients in their surgical ICU in Minnesota, to assess whether this technique was able to reduce the incidence of nosocomial infection and produce an associated reduction in the incidecne of adult respiratory distress syndrome. Criteria for inclusion in the study were that the regimen should be initiated within 48 hours of ICU admission, that the patient should have an anticipated duration of ICU stay of more than 5 days, and that the patients should be hypermetabolic, but without evidence of progressive multiple organ failure. The active and placebo groups were fully comparable for age, sex, liver and renal function indices on admission; their durations of ICU admission were also similar (18 $\pm$ 3 days in the active vs 20 $\pm$ 4 days in the placebo group).

Broad definitions of nosocomial infection were used, however, the double blind nature of the study would have eliminated potential bias in the diagnosis of infection. There were 22 infections in 12 of the 25 patients in the active group compared with 42 infections ($p = 0.0002$) in 15 of the 21 patients in the placebo group. There was a reduction in the incidence of both nosocomial pneumonias (14 vs 23 $p = 0.025$) and bacteraemias (5 vs 12 $p = 0.025$) in the patients who received the active regimen, for all classes of microorganisms; however, the distribution of nosocomial organism types and infections were similar in both groups (8 in the active vs 16 placebo Gram positive infections, 8 vs 13 Gram negative infections and 6 vs 13 fungal infections).

The authors comment that there was no emergence of any resistant organisms detected during the study, but the exact duration over which the study was conducted is not specified, so that the potential for such drug-resistance to emerge or be detected is uncertain. The results of surveillance cultures were not provided other than stool cultures which did show some reduction in aerobic Gram negtive bacillary load, although no effect on *Candida spp* was demonstrated.

The 47% reduction in the incidence of nosocomial infection was not accompanied by a reduction in mortality, nor was there a significant reduction in the incidence of multiple organ failure or ARDS. The APACHE II score and other indices of severity of illness were not provided, making extrapolation to other studies difficult.

Unfortunately, the small number of patients in this study, the excessively high incidence of secondary infection and the use of a less standard regimen make the interpretation of these results difficult.

4) Special High Risk Groups

a) Liver Transplantation

Gram negative and Candidal infections have been noted to occur in up to 50% of patients undergoing liver transplantation. The source of such infections is thought to relate most frequently to the flora colonising the gastrointestinal tract. The use of selective decontamination, which has been shown to reduce the incidence of secondary infection in patients with multiple trauma, cirrhosis, and leukaemia by eliminating this potential reservoir of pathogens, might well also be expected to be of benefit in this group of patients.

WIESNER [256], while acknowledging the flaws in their trial, reported the satisfactory experience of his group at the Mayo Clinic with this technique in an uncontrolled, unblinded study, in which 145 patients undergoing orthotopic liver transplantation were

enrolled. The selective decontamination regimen used included polymyxin E, gentamicin and nystatin, in a suspension that was administered four times a day. This regimen was commenced three days before the liver transplant, and on the day of the transplant systemic prophylactic antibiotic therapy including cefotaxime and tobramycin were given for 48 hours. Postoperatively, the enteral decontamination was continued and oropharyngeal decontamination was also performed while the patient required mechanical ventilation.

Wiesner reported in this study that the incidence of Gram negative bacterial and Candidal infections encountered early after liver transplantation was very low, with only 42 major infections occurring in 37 patients; Gram negative organisms were only cultured from five of these patients. There was only one patient who developed systemic Candidiasis. The infections included 26 primary bacteraemias, 10 bacteraemias associated with another infectious site, 10 intra-abdominal abscesses, 5 hepatic abscesses, 5 cases of peritonitis, 5 episodes of pneumonia, and 1 episode of meningitis. Five deaths were associated with sepsis, three of which were bacterial, but only one was Gram negative, and two deaths were due to fungal sepsis. Because the SDD regimen does not cover Gram positive infections to any great extent, infection with Staphylococcus coagulase negative strains and *Streptococcus* group D strains emerged as important pathogens; however, without quoting other sources, the author seems satisfied that the incidence was similar to that of other studies in this group of patients, where SDD is not used.

b) Acute Hepatic Failure

Several features of acute liver failure and its management can account for the high incidence of infection associated with this condition, including impaired cell-mediated and humoral immunity. Bacterial and fungal infections, in particular, are common complications of acute hepatic failure, and contribute significantly to morbidity and mortality. In recent studies [257,258], bacterial infection was reported in 80% of patients

and 32% of these had concurrent fungal infections. Infection contributes to early mortality and late infection is responsible for death in up to 20%, so that much of the great effort and cost invested in the successful early treatment of these patients, is negated by the complication of late infections.

WILLIAMS and his group from King's College Hospital, London, (unpublished data: First European Consensus Conference of Intensive Care Medicine, December 1991) conducted a prospective, open controlled randomised study to evaluate the efficacy of selective parenteral and enteral decontamination (SPEAR) in the prophylaxis of secondary infections in 84 patients admitted with acute liver failure to their liver centre from November 1990 to May 1991.

All patients admitted with liver failure, with greater than grade II coma and staying in the unit for more than two days were included, although patients already receiving antibiotics on admission were excluded. The regimen comprised: Cefuroxime 1.5g 8 hourly, IV for 5 days, and a suspension of Polymyxin E, Tobramycin and Amphotericin B applied four times a day to the oropharynx in a paste, and nasogastrically. All patients also had Mupirocin 2% ointment applied to the anterior nares four times a day to eradicate carriage by *Staphylococcus aureus*, and Clotrimazole 10% vaginal cream was applied on admission to all female patients. Patients were allocated to one of two groups on admission: an infected group who were randomised to receive SPEAR (group 1), or IV antibiotics alone (group 2); or a non-infected group who were randomised to receive SPEAR (group 3) or no antibiotic until clinically indicated (group 4).

Of the 84 patients, 23 reached a coma grade III, and 61 a coma grade IV. The acute liver failure was due to paracetamol in 57 patients, virus related in 19 and due to other causes in 8. Renal failure developed in 42%. There were 43 deaths (51%), and 49% of these were related to sepsis. Although death due to sepsis was less frequent in those

who received SPEAR (7 deaths) than in those who did not (14 deaths), the difference did not achieve statistical significance.

In the infected group: 17 patients in Group 1, and 17 patients in Group II, there was no difference in the number of episodes of infection that occurred, 15 in each group. However, in the non-infected group, there was a significant difference in the number of infection episodes: 13 in the 23 patients in Group III and 28 in the 27 patients in Group IV ($p<0.004$), including a significant difference between early (<3 days) and late infections (late >4 days): none in Group III and 9 in Group IV. There were no bacteraemias in Group III and five in Group IV which was also statistically significant; chest infections occurred in 2 patients in Group III and 10 in Group IV, which was also significant. There was a significant difference in the incidence of fungal infections in the groups receiving SPEAR compared with the other groups. Emergence of drug resistance during the trial period was not observed.

The study would thus seem to provide convincing evidence of the efficacy of the regimen in reducing the incidence of secondary infection in this high risk population. However, when the numbers in the various groups are broken down, the size of the study becomes so small, that it loses much of its significance. Furthermore, the evidence would suggest that apart from the impact on fungal infections, cefuroxime is probably as efficacious as the entire SPEAR regimen.

c) Oesophageal Resection for Carcinoma

TETTEROO ET AL [259-261] prospectively randomised 181 patients, undergoing elective thoracic surgery for resection of carcinoma of the oesophagus, into those who received conventional therapy with perioperative antibiotic prophylaxis alone, and those who were treated, in addition, with selective decontamination (using a similar regimen to van Saene applied to the oropharynx, stomach and parenterally). The rate of infection prior to the trial, in a retrospectively selected cohort of patients without distant

metastases (using perioperative antimicrobial prophylaxis with cefamandole and metronidazole), was found to be: 21% for pneumonia, 5% for urinary tract infections, 7% for septicaemias, with a mortality of 5%.

67 patients were excluded, either because oesophageal resection was not performed or because of non-compliance with the regimen; eventually 114 patients were included in the study. The selective decontamination was commenced on the day of hospital admission and continued until day 10. Once again no definitions for site specific infection are provided; however, the authors felt able to report both a significant reduction in colonisation by aerobic Gram negative bacilli and the number of secondary (acquired >48 hours after admission) postoperative respiratory infections due to these organisms, in those who received SDD (51 infections in 32/56 controls versus 18 infections in 12/56 in the test group). This benefit was only sustained in those who remained in the ICU for less than four days.

The organisms causing the infections were largely endogenous in both groups (83% test group, 73% controls). In the control group 54% of infections were due to aerobic Gram negative bacilli (*Pseudomonas spp*, *Proteus spp*, *Klebsiella spp*, *Enterobacter spp*, *Acinetobacter spp*, *Citrobacter spp* and *Escherichia coli*), 41% were Gram positive cocci (*Staphylococcus aureus*, *epidermidis*, and *Enterococcus*), 5% being due to Gram negative diplococci (*Neisseria spp* and *Branhamella spp*). In the test patients, aerobic Gram negative bacilli accounted for only 15% of infections and the Gram positive cocci 85%. Following discontinuation of the SDD regimen, there were a further 12 infections in 4 patients in the test group, including 3 respiratory tract infections, and half of these infections were Gram negative or mixed.

In the 26 patients who stayed in the ICU for more than 4 days, the reduction in infectious complications and the number of respiratory infections in those receiving SDD was not significant. The number of urinary tract infections was similar in both groups, which they attributed to instrumentation of the urinary tract. There was no

difference in duration of ICU stay in those who received conventional therapy versus those who received SDD, and the mortality was also unaffected.

While this study again showed benefit in the reduction of predominantly respiratory tract infections with the use of SDD, there are again limitations with the interpretation: the study was not blinded, the definitions of infection were not carefully specified and the benefit was only for a circumscribed period of four days in the ICU. As most studies on nosocomial infection in the ICU only assess the prevention of infections that occurred after 3 to 5 days, because infections prior to that may have been already incubating and SDD regimens may not yet have fully taken effect, the benefits shown in this study really only amount to a more effective perioperative antibiotic prophylactic regimen.

d) Multiple Organ Failure: Combined Acute Renal and Respiratory Failure

McClelland et al [262] assessed the efficacy of selective decontamination in 15 patients with severe combined acute renal and respiratory failure, who required both mechanical ventilation and renal replacement therapy for at least 5 days. They compared the efficacy of a standard decontamination regimen using polymyxin E, tobramycin, and amphotericin B and systemic cefotaxime, with a control group of patients gathered retrospectively from the preceding 12 months with approximately matched severity of illness scores. The average APACHE II score in the SDD group was 21 $\pm$ 6 while in the control group it was 16 $\pm$ 5, with similar sepsis scores of 14 and 15. While 83% of the control population developed definable infections, the incidence was only 33% in the SDD group, which was just statistically significant; the incidence of respiratory tract infections was reduced most with only 1 patient in the SDD group developing an infection at this site, compared with five in the control group. The incidence of urinary tract infections was lower in the SDD group (13% vs 50%), although this did not achieve statistical significance. The incidence of wound infections, bacteraemias and other types of infection was identical in both groups.

The organisms causing the infections were different, with Gram negative bacteria and fungi again causing significantly more infections in the control group. They found that yeasts were the commonest organisms to be isolated in both groups. Coagulase negative staphylococci appeared more frequently in the patients treated with SDD, colonising 40% of patients at some time, compared with 25% of the controls. These organisms were observed to colonise the respiratory tract in four patients and the abdominal wounds of two others receiving SDD. The authors rightly comment on the concern that this arouses in a group at high risk of staphylococcal septicaemia, because of the use of IV dialysis cannulas and intra-cardiac catheters.

In spite of the reduction in infection with the use of SDD, the mortality in the two groups was virtually identical: 42% in the control versus 40% in the SDD group. The authors nevertheless felt that, irrespective of which group the patients belonged to, the mortality was causally related to infection: 73% of the patients with definite infections died, compared with 42% of those who had no infections. This was not of statistical significance.

There are a number of problems with the interpretation of this study. Firstly, the number of patients studied is too small, as there were only 7 of 15 patients with infection in the SDD group, compared with 17 infections in only 12 patients in the control group. The use of a historical control group and the unblinded, uncontrolled nature of the study further detract from these results. The definitions of infection provided are extremely inadequate (respiratory infection: purulent tracheal aspirate with a dense growth on bacteriological culture), so that the reported reduction in infections is, in fact, uninterpretable. The authors reference their definitions to papers by Stoutenbeek et al, but unfortunately the definitions used there were also unsatisfactory.

e) Patients with Burns

MACKIE, VAN HERTUM, SCHUMBERG ET AL from the Netherlands reported their experience with selective decontamination in patients with burns (poster presented at the ICC, Berlin, 1991). 31 consecutive patients with > 30% body surface area burns or inhalational burns were treated with intravenous cefotaxime for the initial 4 days and SDD, using oral tobramycin, amphotericin B and polymyxin E, as well as a paste which was applied to the buccal cavity in those with inhalational burns. These patients were compared with a historical control group of 33 patients with similar severity of burns, who had been treated conventionally. Patients who were admitted more than 24 hours after the burns, or who died within 24 hours of the burns, were excluded from both groups. All patients were treated in single bed isolation areas with strict barrier nursing.

Both groups were comparable in terms of age, sex, mean percent of body surface area of burn (control:43.9, SDD: 45.6), mean percent full-thickness burn (control:23.5, SDD:20.7), and inhalational injury (control:14, SDD:10).

The definition of respiratory tract infection was: physical signs on auscultation, concurrent fever >38.5 C, purulent sputum, new infiltrate on chest x-ray, and positive sputum culture. Colonisation was defined as the identification of potentially pathogenic microorganisms from any bacteriological culture.

The authors reported a marked reduction in colonisation by Gram negative bacilli in the SDD patients. *Pseudomonas aeruginosa* was virtually eradicated from gastric, faecal and urine cultures and the *Enterobacteriaceae* were virtually eliminated by the second week. There was however an increase in gastric colonisation with *Staphylococcus aureus* and yeasts. The colonisation of the wounds by Gram negative bacilli was also reduced, although the wounds of 9 of the 31 patients treated with SDD became colonised by *Pseudomonas aeruginosa*.

The incidence of infections was lower in the SDD treated patients: respiratory tract infections occurred in 6.5% compared with 27.3%; septicaemias in 3.2% vs 24.2%. Although the data was not provided, the reduction in respiratory infections was particularly marked in the patients with inhalational injury. The authors comment that they were impressed by the general well-being of the patients who received SDD. The use of antibiotic therapy was less with 48.4% requiring intravenous antibiotics in addition to SDD, compared with 78.8% in the control group. While the duration in ICU and the duration in hospital were identical in both groups, the mortality was significantly lower in the SDD group: 3.2% vs 21.2%.

While the reports on the effects of selective decontamination in this study on a specific high risk subgroup are most encouraging, they must be interpreted with a certain amount of caution, because of the small size of the study population, the use of an historical control group, and the inadequate definitions of colonisation and infection. The significant difference in mortality between the two groups is striking and further study in burns patients with such a technique is clearly warranted, although the emergence of Staphylococcal infections and colonisation which may be promoted by such a regimen, might possibly suggest that alternative agents might be better suited to a population such as this.

f) The Immunocompromised Patient

GUIOT ET AL [13] from Leiden, Holland, in 1981 reported a study of "selective antimicrobial modulation of human microbial flora". This study was performed in 39 granulocytopaenic patients (< 100 granulocytes/ml, associated with bone marrow failure), admitted to the isolation ward of their hospital for more than 7 days, because of their high risk of infection. 14 patients also with bone marrow failure, who were admitted to the hospital, but could not be accommodated in special isolation areas, and received only conventional therapy, were used as a control group.

Therapy for the underlying haematological disorders included: vincristine, doxorubicin and cytarabine in 15 patients as remission-induction therapy for acute myeloid leukaemia, and 11 patients underwent bone marrow transplantation for acute myeloid leukaemia, acute lymphocytic leukaemia or severe aplastic anaemia. 13 patients with aplastic anaemia were treated with anti-thymocyte globulin. In the control group, there were 11 patients treated with the same remission induction regimen for acute myeloid leukaemia, and 3 patients with aplastic anaemia who received androgens or corticosteroids.

The decontamination regimen used consisted of: a nasopharyngeal spray of gentamicin used 4 times daily, an ointment of amphotericin B, neomycin, and polymyxin B applied to the oropharynx, and used as a toothpaste, an enteral solution of neomycin, amphotericin B, polymyxin B and nalidixic acid given 4 times daily. The skin was washed with either povidone-iodine soap or water containing chlorhexidine on alternate days and the prepuce or vulvo-vaginal area was treated with a cetyl-based cream containing the same compounds used for oropharyngeal decontamination. If there was macroscopically persistent *Candida albicans* in the mouth, a gentian violet solution was used. Persistent potential skin pathogens were treated with silver sulfadiazine.

In 15 patients the complete regimen was not followed for short periods, because of nausea during chemotherapy or suspected hypersensitivity to the nalidixic acid.

The first 6 patients who were given the decontamination regimen were nursed in strict protective isolation with sterile food in laminar down-flow isolators, while the isolation measures in the subsequent 13 patients were down-graded gradually and in the last 20 patients, the patients were allowed to leave their isolation areas for short periods, to eat food with a low bacterial level and to have limited contact with non-sterilised dry and clean articles. The control patients were not nursed with laminar flow and received normal hospital food.

In both groups of patients, antibiotic therapy was not instituted until "infection was seriously suspected or proven". The definitions of site specific infections were not specified.

7 of the patients admitted to the treatment group, were admitted to the hospital with minor infections (clinical infection of skin or mucosae without deep extension), of whom 2 died of septicaemia unrelated to the site of admission infection. 5 patients were admitted with major infections (pneumonia or pyelonephritis) and two died before therapy had been started. The hospital acquired infections included 6 localised oral infections due to anaerobic flora, and 6 major acquired infections of which 5 started as skin infections and one patient died from a combination of infection and bleeding. The decontamination regimen was not completely successful in the patients who were infected on admission, and there appeared to be a good correlation between patients who remained persistently colonised by potentially pathogenic aerobic Gram negative bacilli and those who developed major infections.

In the control population, the patients were older, but their mean duration of granulocytopaenia was shorter. There was no difference in the number of minor infections, while the incidence of major infections was substantially higher (78% vs 36%) in the control group, if patients with acute myeloid leukaemia were compared. More fatal infections occurred (35% vs 19%) and it was thought that the number of days of fever due to underlying infection was higher.

This study was performed before selective decontamination had been introduced to the ICU, and at a stage when the diagnosis of pneumonia was less refined. The small number of patients, the nature of the underlying diseases and associated therapy, the poor choice of a control group (we are not told why it was elected not to treat these patients as aggressively as those who were isolated) all make this study unsuitable to draw adequate conclusions of the efficacy of an extremely elaborate technique of decontamination.

5) The General (Medical/Respiratory) Intensive Care Unit

LEDINGHAM ET AL [263] reported a study of selective decontamination (using a standard oropharyngeal and enteral regimen of polymxin E, tobramycin and amphotericin E), with systemic cefotaxime, in 324 patients. He used an historical control group of 161 patients and a test group of 163 patients in an unspecialised medico-surgical ICU. The diagnostic categories of the patients were : ± 38% post-surgical, 25% medical, 14% trauma, 7% drug overdose, 2% shock and 14% sepsis. The two groups were comparable in terms of demographic features, diagnostic categories and severity of illness.

Definitions of infection in this study were based on a scoring system. For all categories, two temperature spikes of greater than 38.5°C, a white cell count of more than 12 000 or less than 4 000 cells/ml, which scored one point each, were used; in addition criteria, from the infected system were required. For a respiratory infection, additional criteria were purulent sputum, a new pulmonary infiltrate on chest radiograph, an increase in the inspired oxygen fraction of 15% to maintain oxygenation; in order to make a diagnosis of respiratory tract infection, three criteria out of the potential five just enumerated were required.

The results of microbiological surveillance samples all showed a similar pattern, with aerobic Gram negative bacilli being isolated from gastric aspirate, oropharynx, tracheal aspirate in 8-25% of patients on admission. This proportion increased in the control group until the third or fourth day and then remained stable at 30-45%; however, in the SDD group, the values decreased and stabilised by day four at a value of less than 10%. The surveillance samples of rectal swabs also showed a marked reduction in the SDD, but not in the control group, although 20% of the SDD group remained positive at day ten. In both groups less than 5% of urine samples yielded significant growth of Gram negative bacilli. Coliform bacilli were the most common group of aerobic Gram negative bacilli to be isolated (80-90%) in both groups, except tracheal aspirates in the

SDD group, where *Pseudomonas spp* comprised 31% of the 42 isolates. The isolation of yeasts also decreased during the initial four days in the SDD group, but changed little with time in the control group. No increase in the incidence of drug resistance to the agents used for the regimen was encountered during the use of SDD. 14% of all tested clinical isolates of aerobic Gram negative bacilli, *Serratia spp* and *Acinetobacter spp* were resistant to cefotaxime (excluding *Pseudomonas species* which was regarded as always resistant); 15% of isolates were resistant to polymyxin E (mostly *Proteus spp*) and 3% (all *Serratia spp*) were resistant to tobramycin.

The incidence of secondary infections in the SDD group was 40% of that in the control group, with 24% of the control group being classified as infected compared with 10% of the SDD group. The number of episodes of infection was 37 in the control group and 13 in the SDD group, with 73% and 77% respectively being bacteriologically confirmed. The reduction in infection with SDD applied to all categories of infection excepting intra-abdominal (where there was only one episode), but was most striking for respiratory tract infection, where there was a six-fold reduction. Aerobic Gram negative bacilli accounted for 45% of the isolates in respiratory tract infections in the control group, compared with only 17% of all isolates from infected sites in the SDD group. While there was no evidence of primary infection predisposing to secondary infection in the SDD group, in the control group those who were infected on admission had a lower incidence of secondary infection, possibly because they received adequate antibiotics.

The overall mortality in the two groups was almost identical; however, when the subgroups were analysed separately, a statistically significant reduction in the mortality for multiple trauma patients was seen, although the number of patients in either limb was small (6 deaths out of 23 trauma admissions in the control group, compared with 0 deaths in 18 admissions during SDD). There was also a reduction in the mortality for

patients with a duration of stay in excess of 7 days (12 /35 in the controls versus 5/39) and mid-range APACHE II scores (18/31 versus 12/40).

The authors acknowledge the difficulties associated with attempting to interpret a prospective study using consecutive control and study groups, but argue that concurrent controls might have presented still greater difficulty, because the regimens might in themselves affect the bacterial ecology of the unit. The marked difference in the results of surveillance samples would also have made blinding, if the clinicians had been permitted access to these results, impossible. Nonetheless, an unblinded study with post-hoc stratification to detect at-risk groups who benefit, is not the ideal way to assess the efficacy of a novel therapeutic regimen. The Lancet, which carried the original article, also subsequently published an extensive correspondence on the subject (June 18,1988 pages 1388-1390) which included similar criticisms of the analysis.

The authors explained that their results differed from other studies in the overall incidence of infections, because they chose to separate primary and secondary infection. Part of the problem in evaluating this study and many others is that, although differentiating between primary and secondary infections (secondary being defined here as developing > 48 hours after admission), the duration of stay before the infection occurred is not sufficiently carefully specified. While it is probable that infections occurring after 48 hours might have been due to nosocomial pathogens, a cut-off for evaluating the incidence after the SDD regimen had taken effect - in this study after 4 days - might have provided more convincing evidence that the SDD regimen was responsible for this. Indeed, when interpreting the data on mortality, they point out that many patients died within the initial three days of admission, and therefore SDD cannot be considered to have been a factor.

UNERTL ET AL [264] in 1987 reported their experience with a topical regimen of decontamination applied to the nose, oropharynx and stomach in longterm ventilated patients in their general ICU in Munich, Germany. They conducted a randomised,

controlled trial over 7 months in 39 patients : 20 untreated patients were used as a control population and 19 patients formed the treatment group who received polymyxin B, gentamicin and amphotericin B, administered 6 hourly in a saline solution into the nose, oropharynx and enterally. Patients were included if they were intubated within 24 hours of the onset of acute disease or surgery, were expected to be ventilated for more than 6 days, were not infected, receiving systemic antibiotics, did not have ARDS, myelosuppression or leukopaenia which might have obscured the diagnosis of pneumonia. The maximum period of observation was 14 days following intubation or discharge from the ICU, whichever occurred first.

The patients were comparable in terms of age, sex, underlying disease, severity of illness determined by the simplified acute physiology score (mean of 12 in the control vs 13 in the SDD group), duration of treatment in the ICU (23 days in the control vs 18 days), period of ventilation (11 days in the control vs 16 in the SDD patients), and diagnostic categories on admission. Central nervous system disease was common in both groups: there were 10 in each admitted with neurological disease, and 13 in the control and 14 in the SDD group had Glasgow coma scales of <7. 6 patients in the control group died and in 5 the primary cause of death was related to neurological dysfunction, although at the time of death 3 patients were diagnosed as having pneumonia. In the treatment group there were 5 deaths, and 4 of these were also due to brain damage, but no patients had respiratory infections present either at or before the time of death. As a result of the high proportion of patients with cerebral damage, 17 patients in the control and 15 in the treatment group were treated with steroids.

Their choice of agents for the decontamination regimen was made because the predominating colonising organism in ventilated patients in the unit had previously been found to be *Pseudomonas aeruginosa*, which was sensitive to at least one of the two agents by disc-susceptibility testing: gentamicin covering at least 90% of

Staphylococcus aureus and the *Enterobacteriaceae* and 80% of the *Pseudomonas aeruginosa* isolates.

The definition of pneumonia was a new "definite" infiltrate on the chest X-ray, together with increasing amounts of purulent tracheobronchial secretions, containing > 30 000 granulocytes / microlitre and at least two further features: new febrile spikes > 38.5^{o}C, blood leukocyte count > 12 000/ml or < 4 000/ml, decrease of PaO2 requiring an increase of the FiO2 of at least 0.15 to maintain oxygen tension. The infiltrate was considered to be definite if two independent radiologists, unaware of the treatment group confirmed the infiltrate which did not reverse after physiotherapy. "Febrile purulent tracheobronchitis" was defined by the emergence of purulent tracheobronchial secretions containing > 30 000 granulocytes/microlitre, together with clinical signs of infection (new febrile spikes >38.5^{o}C) and these patients were also treated with antibiotics. The presence of a pathogen was used to only to define colonisation, but not to distinguish between colonisation and infection.

Colonisation of the oropharynx by potential respiratory pathogens was observed in 95% of the controls and 32% of the treated patients, which was a significant difference. *Enterobacteriaceae* and/or *Pseudomonas aeruginosa* were detected in 85% of the control and 16% of the treated patients. The colonisation patterns for the control patients showed an increase during hospitalisation, but declined in the treatment group. Similar patterns of colonisation were detected in the tracheobronchial system.

14 (70%) of the control patients developed respiratory infections including 9 pneumonias, but only 4 (21%) of the treatment group developed respiratory infections, including only one episode of pneumonia during the 14 day observation period. The respiratory infections in the treatment group were all preceded by colonisation of the airway, and in 87% there was also preceding oropharyngeal colonisation. The infections in the treatment group were all due to gentamicin-resistant Gram positive cocci or yeasts, and Gram negative rods were absent; however, in the control patients,

while Gram negative bacilli predominated in 72% of the isolates, the most common pathogen was *Staphylococcus aureus*.

Antibiotic therapy was required in 14 (65%) of the controls and 6 (30%) of the SDD group which was statistically significant. There was one adverse reaction to the prophylactic regimen in the form of moderate diarrhoea, which occurred in approximately one third of patients. Pathogens resistant to the agents used in the prophylactic regimen occurred in 4 patients in both groups. No comment is made on the time relationship of these isolates to the duration of use of the decontamination regimen in the unit, or their relationship to each other.

The small number of highly selected patients and unblinded nature of the study prevent conclusions being drawn from it. It is nonetheless of interest, because patients with neurological disease have not been reported in other studies [263,265] to be a group that stand to benefit from the use of selective decontamination, but the authors clearly found benefit in this study.

VAN UFFELEN ET AL [266] reported the results of a prospective analysis of patients requiring longterm admission (>10 days of mechanical ventilation) to their general ICU in Groningen, Holland who received the same prophylactic regimen as that administered to patients in their ICU in the previously reported studies (Stoutenbeek and van Saene) [14,243,252], namely oral and enteral polymyxin E, amphotericin B, tobramycin and parenteral cefotaxime which, in this study, was administered until the oropharyngeal cultures ceased to grow *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Branhamella catarrhalis*. This group presumably formed part of the initial study of selective decontamination reported from Groningen, as these patients were enrolled in 1983, however, the data was reported separately in 1987, and not as a subanalysis.

27 patients, 6 of whom were admitted with primary infections, were evaluable (7 trauma patients, 6 post abdominal surgery, 5 with neurological disease, 3 with chronic obstructive lung disease, 2 with adult respiratory distress syndrome and four others with Weil's disease, subarachnoid haemorrhage, tetanus and leukaemia). The mean duration of ICU stay in these patients was 30 days.

60% of patients remained free of bacterial colonisation in the oropharynx and trachea throughout their ICU stay, while in those who were colonised on admission, the aerobic Gram negative bacilli were eliminated from the oropharynx within 3 days, and the lower airways were also subsequently cleared. The rectal surveillance swabs showed clearing of AGNB within 7 days in 82%, although in the remaining patients, colonisation persisted throughout their ICU stays.

All the primary infections were cleared by the parenteral cefotaxime, and during the one year study period, no nosocomial pneumonias were identified, although the definitions of infection are not specified in this paper.

The study was reported as a pilot study of selective decontamination in this at-risk population group. As such, the numbers are too small for conclusions to be derived from it; nevertheless it is interesting to note that these authors found this technique of value in a population subgroup not demonstrated to benefit in other studies, such as the multicentre study reported by Gastinne et al [265].

In another paper [248] reporting their experience with 27 patients from the same unit, van Uffelen et al demonstrated a correlation between the type and load of flora colonising the oropharynx and the tracheal flora: once a bacterial species had been isolated from the oropharynx in high concentrations, the identical organism was isolated in more than 50% of patients from the trachea. 6 patients were reported to have acquired respiratory tract infections involving organisms from the oropharynx.

In this study, colonisation was defined as the appearance of any bacterial species in tracheal cultures, in the absence of purulent secretions or clinical evidence of infection. Bronchitis was defined as the presence of purulent secretions, but without clinical and radiological evidence of pneumonitis. A diagnosis of pneumonitis was made only when "unequivocal clinical or radiographic evidence of pulmonary parenchymal involvement was present."

Once again the definitions and numbers of patients studied are inadequate, although the evidence confirms that of other authors who have demonstrated the importance of colonisation of the oropharynx and stomach in the pathogenesis of nosocomial lower respiratory tract infection. It was this study of 27 patients that instigated the much larger and more widely publicised studies on selective decontamination by the group at Groningen.

In 1989, ULRICH ET AL [267] from the Hague in the Netherlands, studied the use of selective decontamination in a prospective randomised study, in a general ICU admitting a wide variety of diagnostic categories of patients, including general medical, surgical, neurological and neurosurgical patients, using a cheaper, modified regimen with norfloxacin, polymyxin E and amphotericin B as oropharyngeal and enteral agents, with systemic trimethoprim which was continued "until potentially pathogenic microorganisms could no longer be isolated from the oropharynx, respiratory or digestive tracts". If colonisation of the lower respiratory tract occurred in spite of the selective decontamination, antimicrobial treatment was started even in the absence of clinical evidence of infection. Control patients received peri-operative antibiotic prophylaxis and other antibiotics only when clinically indicated, and preferably with bacteriological substantiation. There was no minimum time limit for the duration of intubation or mechanical ventilation specified for evaluability in this study, however, the patients were required to have remained in the ICU for more than 5 days. 48 patients were randomised to receive the SDD regimen and 52 were controls.

There were differences in definitions compared with other studies: all organisms isolated after the immediate admission specimens, being regarded as ICU acquired. Lower respiratory tract infection was defined by the presence of clinical and radiological signs of pulmonary infiltration, with fever and leukocytosis, and a dense growth on culture of sputum or tracheal aspirate.

The two groups of patients were comparable in terms of sex, age, diagnostic categories and severity of illness, although there was a tendency for the patients who received SDD to have a more prolonged course in the ICU (16.9 days vs 13.4), and duration of ventilation (10.7 vs 7.8 days). The mean simplified acute physiology score was slightly higher in the control group (12.4 vs 11.5) and 6 control patients vs only 3 who received SDD required haemodialysis. Antibiotic usage was slightly greater in the control group (mean antibiotic units 11.1 vs 10.6), and the patients in this group were also slightly younger (60 years vs 64.3).

There was a significant reduction in oropharyngeal colonisation with the use of the SDD: both groups started off with 40% positive isolates for aerobic Gram negative bacilli, but after 7 days this had increased to 85% in the control patients which persisted at this level, compared with only a 3% incidence in the SDD group which declined to 0%. Gram positive organisms (predominantly *Streptococcus faecalis* and *Staphylococcus epidermidis*) were isolated from approximately 60% of both groups at admission, and this level was maintained in the SDD group, but rose to 80% in the control patients. Gram negative bacteria were isolated from the trachea in 24% of the control and 41% of the treatment group, but after 7 days, 67% of the control group compared with only 26% of the treatment group were colonised. The same phenomenon of increasing colonisation by Gram positive cocci was observed in the trachea in both groups.

The resistance patterns of the surveillance cultures were analysed, and resistance to the antibiotics in the decontamination regimen was not noticeably more marked in the

treatment than in the control patients. There are unfortunately no details provided on the sensitivity profiles over the study period, and no comment is made as to whether the patterns of antibiotic resistance changed during the trial, as a result of the extensive and topical usage of antibiotics.

40 patients in the control group (77%) developed 112 episodes of infection compared with 25 patients (52%) in the treatment group with 51 acquired infections. The incidence of Gram positive infections was similar in both groups (44 episodes in the control vs 41 in the treatment group). The incidence of Gram negative infections of the respiratory tract (6% vs 44%), urinary tract (4% vs 27%) and catheter-related sepsis (0% vs 15%) was significantly lower in the SDD group. The number of infections due to *Candida albicans* was also significantly lower in the SDD patients. There were three patients in the treatment group who developed respiratory tract infections due to *Pseudomonas aeruginosa*, apparently following successful initial decontamination. The authors invoke adherence mechanisms to explain colonisation of the trachea by-passing the usual initial stage of oropharyngeal colonisation, but suggest that decontamination of the patients' tracheostomy sites (all three had tracheostomies for prolonged ventilation) might have prevented these infections.

Both the overall mortality (54% vs 31%) and the "mortality attributable to sepsis" (15% vs 0%) were significantly lower in the decontaminated patients; however, no criteria as to how the cause of mortality was determined are specified.

The use of parenteral antibiotics did not differ significantly between the two groups, but the cost of bacteriological monitoring was noted to be higher in the control patients. The use of SDD did not shorten the duration of ICU stay, reduce duration of ventilation or antibiotic usage in this study, so cost benefit was not demonstrated. The different and cheaper agents in this study were felt to have been satisfactory substitutes for the conventional SDD regimen, although concern is expressed that the very low serum levels achieved with topical decontamination using an absorbable drug such as

norfloxacin might promote drug resistance. There were also three episodes of Gram positive infections which might have been prevented by cefotaxime and which were resistant to trimethoprim.

This study is one of a select few which was able to report an improvement in mortality with the use of selective decontamination. Reservations about this study however do exist, as the patient numbers were small, the criteria for diagnosing infection were not sufficiently specific, the study was not blinded and the criteria for diagnosing a reduction in sepsis-related deaths are not provided.

GODARD ET AL [268] reported in 1990 a double blind study of selective decontamination in their ICU in Lyon, France which admits all categories of patients. Only enteral decontamination was performed using tobramycin and polymyxin E; amphotericin B was administered to all patients. All patients admitted to the ICU during the trial period were enrolled, but there were 15 withdrawals (10 had received previous decontamination, 5 were not eligible because of gastro-oesophageal surgery) leaving 181 evaluable patients, 97 of whom received decontamination (there were 4 withdrawals in this group because of inadequate drug administration or treatment withdrawal) and 84 received placebo.

The trial design was complex: the ICU is divided into two individually run subunits, and in the first 3 months of the study all patients in the one subunit received placebo, and all patients in the other subunit the active regimen; this was followed by a two month break during which no decontamination was performed, and then a further 3 month period in which the treatment regimens in the two units were reversed. The rationale for this format was to avoid the carry-over effect causing misleading benefit in the placebo patients, or detracting from the benefit experienced by the decontamination in those who received the trial medication.

The two groups were fully comparable in terms of age, sex, diagnostic category and simplified acute physiology score (mean of 14.2 in the study group and 13.5 in the placebo patients). The patients did not require to be intubated at all for inclusion in the study, but there were similar numbers of ventilated and non-ventilated patients in both limbs of the study. The duration of intubation, ICU stay and the antibiotic requirements in the two groups were also similar.

The definition of primary infection, was an infection acquired within 48 hours of admission; all subsequent infections were regarded as ICU-acquired. The criteria for the diagnosis of pneumonia were: new or progressive infiltrate on the chest radiograph, purulent sputum, fever $>38^{o}C$, leukocytosis > 10 000/ml. Protected specimen brush samples were taken on all patients who fulfilled the above criteria, and the diagnosis was retained if the brush specimen yielded > 1 000 cfu/ml of a bacteria, or if a microorganism was cultured simultaneously from pleural effusion or blood culture and bronchial aspirate.

The incidence of primary infections was similar in both groups: 56% in the decontaminated patients compared with 58% in the placebo patients. Patients who underwent contaminated surgery or who were hospitalised after trauma all received intravenous antimicrobial prophylaxis.

"ICU-acquired infections" appeared significantly later and recurred less frequently in the decontaminated patients, although there was no statistical difference in the frequency of infections between the two groups. No infections occurred in patients who stayed less than 8 days in the ICU in either group. All infections were reduced in the treatment group, but a statistically significant effect was only noted with pneumonia; there were no bacteriologically confirmed cases of pneumonia which occurred in the decontaminated group, compared with 8 cases in the placebo patients (due to *Pseudomonas aeruginosa* in 5, *Haemophilus spp*, *Proteus spp* and *Staphylococcus aureus* one each). Urinary tract infections in patients with indwelling catheters were the

most frequent site of acquired infection, and in both groups such infections were due to Gram negative bacilli and Gram positive cocci, and occurred in the third week of ICU stay.

Among those who died, 6 untreated versus only one decontaminated patient, acquired at least one infection during their ICU stay. A similar difference was noted for the development of septic shock. There was a significant reduction in the number of ICU acquired infections due to Gram negative bacteria in the treatment group. In both groups, 15% of Gram negative bacteria from surveillance cultures of rectal swabs were tobramycin resistant. No surveillance screening for colonisation of oropharyngeal, tracheal, gastrointestinal or urinary flora was performed.

25% of the patients in both limbs stayed in the ICU for less than 48 hours; 55% - 60% remained for more than one week.

12 patients (12%) died in the decontamination group compared with 15 (18%) in the placebo group; thus, overall there was no significant reduction in mortality with this technique. With post hoc stratification, benefit from the decontamination was shown in those who stayed in the ICU for more than 7 days, or those with a mid-range SAPS. Interestingly, unlike other studies which suggested especial benefit for trauma patients from the use of SDD, no such benefit was demonstrated in this study where 41 patients received SDD, and a further 33 placebo; 34% of the SDD patients compared with 55% of the placebo developed infection in this subgroup.

There was no effect with the regimen on duration of ICU stay (although there was a non-significant trend with the mean in the decontaminated patients being 11 days vs 13 in the placebo patients). The authors estimated that a one day reduction in ICU stay would have been sufficient to have paid for the intestinal decontamination for 50 days.

The double blind nature of the study, and the differences in definitions, which were stricter than in many of the other trials, both combined to reduce the incidence of

pneumonia in the placebo limb to a mere 15%, and the incidence of other infections was also much lower. Part of the problem when attempting to compare this study with others is that not all patients were intubated, which in itself might have caused a considerable reduction in the infection rate. The efficacy of the decontamination regimen is suggested by the reduction in Gram negative infections, but surveillance cultures would have been reassuring to confirm the efficacy of enteral decontamination alone. The study was possibly too short in duration, for resistance profiles to have been studied, but in the longterm, such information should be presented. It is interesting to note that this is yet another study where in spite of a significant reduction in the incidence of pneumonia, no effect on mortality, nor duration of hospital and ICU stay were demonstrated.

GASTINNE ET AL in 1992 [265] reported a multi-centre randomised, controlled trial of selective decontamination from France, which was designed to assess the efficacy of the regimen in improving survival, both in the ICU, and at 60 days after randomisation. 445 patients in 15 intensive care units were given placebo (225) or tobramycin, polymyxin E and amphotericin paste (220) to the oropharynx and an enteral suspension. No parenteral prophylaxis was used, but 72% of the patients were receiving systemic antibiotics at the time of randomisation in any event. Enrollment criteria included mechanical ventilation for >48 hours, but the patient should not have been intubated more than 48 hours before randomisation. Patients with drug overdoses, neutropaenia (< 500 polymorphs/ml), or a simplified acute physiology score of more than 24 were excluded. The sample size of 600 patients was calculated to allow the detection of a 25% reduction in mortality among the treated patients, assuming a mortality of 40% in the placebo group.

Respiratory tract infections were classified as primary if they occurred within the first 48 hours of admission, and thereafter as secondary and ICU acquired. Pneumonia was defined as all of the following: purulent tracheal aspirate, fever (>38.5^{o}C), peripheral

leukocytosis (> 10 000/ml), associated with a new and persistent infiltrate on the chest radiograph. Fibreoptic bronchoscopy with specimens obtained by brushing was recommended but not mandatory, and bacteriological documentation was not required, as it was thought that the topical antibiotics might interfere with the accuracy of cultures. Tracheobronchitis was defined by the presence of clinical signs, but the absence of a pulmonary infiltrate on the chest radiograph.

The two groups were comparable in terms of the number and types of underlying diseases and diagnostic categories on admission; however, the simplified acute physiological score was higher in those randomised to receive SDD, there were also more males in this group, and there were more patients with more than one organ system failure on admission.

Primary pneumonia occurred in 14 patients (9 in the placebo group compared with 5 in the SDD group). Pneumonia developed in 13% in the ICU within 30 days of enrollment (33 in the placebo group and 26 in the SDD group), although pneumonia due to Gram negative bacilli was significantly reduced in the SDD patients. There was a trend toward an increase in the rate of staphylococcal pneumonia in those who received the active regimen (60% of patients with pneumonia in the treatment group had pneumonia due to this organism).

There was no difference in the duration of ventilation, or mean duration of ICU admission between the two groups.

170 of the 445 patients died in hospital, 88 in the SDD group and 82 in the placebo group; 142 of these deaths occurred in the ICU. The overall mortality rate in the ICU was 32% (34% in those who received SDD, compared with 30% in the placebo group), and the mortality rate at 60 days was similar. The 15-day and 30-day survival rates were 80% in the placebo group vs 76% in the treatment group and 74% vs 66% respectively. The estimated risk of death was 1.14 times higher in the treatment group.

The costs of the antibiotics in the SDD group were 2.2 times higher than in the placebo patients. The daily cost of the SDD was $ 66.50 per patient and the mean total charge per patient was $ 694 $\pm$ 544. There was no difference in the mean total charge for systemic antibiotics during the stay in the ICU between the two groups; although the mean charge per patient for the antibiotics used to treat all episodes of respiratory tract infections was higher in the placebo group, this difference was not significant.

The incidence of secondary pneumonia was low in this study (13% in the placebo group). The diagnostic criteria were more clearly specified and much stricter than in many of the other studies, so it is difficult to compare the results between the centres. The double-blind nature of the study may also have helped to ensure a more reliable diagnosis.

The population in this study may partly explain the discrepancy in the results with the use of SDD: 10% were admitted after emergency surgery, 25% with pneumonia, and a further 25% were immunocompromised by chronic renal failure, HIV, or carcinoma. A high proportion were unconscious or had more than one organ system failure at admission, and almost half had a simplified acute physiology score of more than 13. 67 patients (15%) were admitted following trauma which was documented to be a statistically significant adverse prognostic factor; however, in their discussion the authors comment that multiple trauma may be a subgroup that may stand to benefit from the use of SDD. Unfortunately no subgroup analysis is provided.

While this study has overcome many of the drawbacks of previous studies in terms of methodology - it is double-blind, controlled, prospective and the numbers are sufficiently large; there are nonetheless a few problems with it: being a multicentre study, there is not the uniformity of practice, nursing etc which are encountered in a single centre study, and the contributions to mortality, and the infection rate from the various units are not specified. The other major criticism which could be levelled at this study is the complete absence of microbiological data: there is no mention of

surveillance samples, so that there is in fact no evidence that the patients were adequately decontaminated. No comment is made about the other patients in the unit who might possibly have caused cross-infection if they were overtly septic; the infection rate before the trial is not commented upon and the possibility of a carry-over effect from the decontaminated patients to the others which might have negated some of the benefit of the SDD is not mentioned.

AERDTS ET AL [269] in 1990 reported a prospective, randomised three-limbed study of selective decontamination, in combination with initial cefotaxime, performed in an ICU in Nijmegen, Holland. There were two control groups, each with a different antibiotic policy to be used in the event of infection, thereby to determine the possible influence of antibiotics which affect colonisation resistance on the colonisation and infection rate.

All patients who were expected to require mechanical ventilation for at least 5 days were included in the study, regardless of their underlying condition. After stratification, using the APACHE II score, the patients were allocated to one of the three treatment groups. In control group A, no antibiotic prophylaxis was provided, and only antibiotics, which were known to affect colonisation resistance were used, (ampicillin, piperacillin, gentamicin and lincomycin being the preferred drugs); therapy being instituted on clinical evidence of infection. In control group B, patients also received antibiotics only if clinically indicated, however only antibiotics known to have no effect on colonisation resistance were used (cefotaxime, or cefuroxime in combination with gentamicin, and metronidazole if anaerobic infection was suspected). In group C, SDD using systemic prophylaxis with cefotaxime for the first 5 days, and oral and enteral decontamination with polymyxin E, norfloxacin and amphotericin B were given to all patients from admission until extubation; further infections were treated as in group B. This slightly different regimen from the more conventional polymyxin E, tobramycin and amphotericin B was used, because norfloxacin is not only cheaper than tobramycin, but also theoretically safer, and the spectrum across

which tobramycin causes decontamination is narrower. Polymyxin E was used to increase the spectrum of activity against Pseudomonaceae against which norfloxacin was less active.

All infections that were not present on admission but developed after this, were regarded as nosocomial. Lower respiratory tract infection was defined as : positive culture of the tracheal aspirate and a Gram stain showing many leukocytes, as well as the causative organism. In addition, two of the following three criteria had to be met: purulent appearance of the tracheal aspirate, peripheral leukocytosis > 12 000/ml or fever > 38^0C.

88 patients were randomised on admission, but 24 were excluded because of premature discontinuation of ventilation. 56 patients thus were evaluable : A 18, B 21, C 17. The three groups were comparable in terms of age, sex, duration of intubation (25 days vs 22 days vs 16 days), duration of ICU stay (30 days vs 25 days vs 23 days), and APACHE II score (mean 22.6, 23.4, 20.5) respectively.

In patients in groups A and B, oropharyngeal colonisation with *Haemophilus influenzae* decreased during ICU stay, while in group C colonisation with this organism was eliminated, similarly *Staphylococcus aureus* colonisation of the oropharynx was eliminated in the patients in group C; yeasts were almost completely eliminated in this group, but colonisation with these organisms did not increase in any group with antibiotic therapy.

Colonisation of the lower respiratory tract was present in 53% of patients admitted without infection in groups A and B, and in 64% in group C. Gram positive cocci were the predominant organisms isolated. Lower respiratory tract colonisation was eliminated in all patients in group C by 5 days, but in 7 patients in the other 2 groups, colonisation later gave rise to infection.

Colonisation of the stomach with Gram negative bacilli was shown in 50% of patients in group A on admission, compared with 19% in group B and 29% in group C. These figures increased for groups A and B, but these organisms were virtually eliminated from the patients in group C. The number of patients colonised by Gram positive cocci and yeasts increased from 15% on admission in the control groups to over 30%, but again colonisation with these organisms was virtually eradicated in group C. Although it took longer for rectal colonisation patterns to change, a similar phenomenon was also demonstrated.

78% of the patients in group A acquired lower respiratory tract infections, compared with 62% in group B and only one patient (6%) in group C. Almost all infections in the control groups were considered to be endogenous in origin, but the only infection in group C was thought to have been due to cross-infection. No details are provided of other sites of infection.

94% of the patients in group A and 100% in group B were treated with systemic antibiotics, compared with only 65% in group C. No emergence of resistance to cefotaxime was noted in this study, and no comment on the emergence of resistance to norfloxacin is made.

The slightly different and arguably insufficient criteria to diagnose lower respiratory tract infection, the small number of patients in each limb and the unblinded nature of the study all make its interpretation difficult. There was nonetheless both a decrease in colonisation and lower respiratory tract infections in group C, associated with a small reduction in duration of stay, and duration of ventilation in these patients; although the APACHE II score in this limb was also the lowest. The small numbers make the unchanged mortality rate uninterpretable.

It is interesting to note that, despite attempts to preserve normal colonisation resistance, the incidence of infections in group B was unaltered and colonisation with Gram

negative bacilli increased. This would suggest that it is not the use of antibiotics, that alter colonisation resistance, which influence the bacterial colonisation patterns in the critically ill.

PALOMAR, BARCENILLA, ALVAREZ ET AL from Barcelona, compared the efficacy of preventing nosocomial pneumonia with the use of sucralfate in combination with parenteral decontamination using cefotaxime, with conventional decontamination, versus no prophylaxis. (Prevention of nosocomial pneumonia in ventilated patients using selective decontamination of the digestive tract, cefotaxime and sucralfate, Poster, ICC Berlin, 1991) They reported a prospective, randomised, multicentre (10 hospitals) study of the two prophylactic regimens in the prevention of respiratory infections in ventilated patients admitted to the ICU. There was one control limb who received only antacids or H-2 blockers by nasogastric tube; a second group received selective oropharyngeal and enteral decontamination using polymyxin E, tobramycin and amphotericin B, plus parenteral cefotaxime for the first 4 days of ICU stay. In the third group, patients received cefotaxime and sucralfate for the period of intubation.

87 patients were evaluable, 31 received antacids and no prophylaxis, 26 SDD, and 30 sucralfate and cefotaxime. The patients were comparable in terms of age, sex distribution and APACHE II scores (17.4, 15.6, 17.2 respectively). The duration of ventilation in the three groups was similar (7.2, 10 and 9.4 respectively). Although the types of ICUs are not specified, the overwhelming majority of patients studied would appear to have been neurological, with only small representations of patients with primarily respiratory or other diseases.

The diagnosis of nosocomial pneumonia was made using quantitative cultures obtained by bronchoalveolar lavage or protected specimen brush in half of the cases, but the definition of pneumonia was not specified further and patients were reported as having a high probability of having developed nosocomial pneumonia, which in an open study is possibly a dangerous way of introducing bias.

The overall incidence of secondary infection was reduced, by the introduction of some form of prophylaxis, although this did not achieve statistical significance. The infection rate in the control group was 80.6%, compared with 60% in those who received sucralfate and cefotaxime and 38.5% in the patients who received SDD.

The incidence of nosocomial pneumonia was significantly reduced in the two groups who received some form of prophylaxis, compared with the control group (19.2% SDD, 26.7% in those who received cefotaxime and sucralfate, 58.1% in the control group). The nosocomial pneumonias that occurred in the groups who received prophylaxis developed later than those in the patients who received no prophylactic therapy. Staphylococci were the major cause of nosocomial pneumonias in all three groups; Gram negative organisms were the predominant cause of all nosocomial infections in the control group, while they were still more frequent pathogens than Gram positive infections in the sucralfate and cefotaxime group; however, in the SDD group, the vast majority of all nosocomially acquired infections were due to Gram positive organisms.

The authors attributed the high incidence of staphylococcal infections encountered to the fact that "this organism is the most frequently encountered coloniser of patients with neurological disease", that there is a high prevalence of staphylococci in the ICUs studied (whether multiply resistant or otherwise and whether this incidence of infection is higher than previously is not mentioned), lastly that the staphylococci are not sensitive to the agents used in the decontamination regimen.

No mention is made of the effect of either form of prophylactic regimen on the resistance patterns, nor is any data provided to demonstrate the efficacy of the decontamination regimens in reducing colonisation with Gram negative and other pathogens. That this was achieved is nonetheless suggested by the differing spectrum of organisms causing infections in these two groups.

There was however no difference in mortality between the three groups, except with a subanalysis of the trauma patients, in whom the mortality appeared significantly lower in those who received the conventional SDD regimen.

This study is once again flawed by its multicentred, open design, the small number of patients enrolled and the complexity of regimens evaluated, as well as the poor diagnostic criteria used. No data is provided as to whether any of the units studied were known to have problems with staphylococci prior to the study, or whether this was exacerbated by the introduction of SDD. The extremely high baseline infection rate of over 80% is not satisfactorily explained, nor is there any data provided as to whether all the infections emanated from one centre. It is thus difficult to be certain as to whether the high incidence of infection and its reduction in the two prophylactic groups was purely due to the fact that these two groups received more careful nursing than those in the control group.

The use of selective decontamination to improve an infection rate of over 80%, when the problem is predominantly due to staphylococci, which are well recognised to be spread both endogenously and exogenously, must be questioned. The appropriateness of the agents selected, in view of the recognised sensitivity patterns of the staphylococci, is questionable. The effect this regimen might have had on the incidence and resistance patterns of both the staphylococci and other pathogens should surely have been of sufficient import for the data to have been provided.

JACOBS, FOWERAKER AND ROBERTS (Effectiveness of SDD and cefotaxime in an ICU with a policy encouraging low gastric pH. Poster, ICC, Berlin, 1991). Jacobs et al reported the results of a study of selective decontamination plus cefotaxime in a randomised controlled trial using oropharyngeal and enteral decontamination with polymyxin E, amphotericin B, and tobramycin in their ICU (no category of ICU-type specified). Enrollment criteria for this study included an assessment of a ventilatory requirement exceeding 3 days.

79 patients were enrolled, 36 received SDD and there were 43 in the control group. The two groups were comparable for sex, age, mean APACHE II score (17 in the SDD group compared with 18 in the control), duration of ICU stay (10 days in both groups), the use of steroids, H-2 antagonists, and mortality (39% vs 53%). The diagnostic categories on admission included sepsis (19% vs 14), neurosurgery (58% vs 47%)and low cardiac output states (17% vs 40%) which were fairly equally distributed between the groups.

The authors emphasise, what is often regarded as fairly standard ICU practice, that, in both groups, an attempt to maintain a low gastric pH was made by: the avoidance of H-2 blockers, antacids, steroids; the administration of dopamine and sucralfate to prevent stress ulceration, and the use of intermittent enteral feeding. (How many patients received sucralfate is not specified, nor is there any mention of the very real concern that this drug may bind to enterally administered agents for decontamination, and thereby inactivate them [64]). This study differs from other reported studies of SDD, however, in that daily measurements of gastric pH were made at midday, which was the end of the fasting period in the enterally fed patients.

The diagnostic criteria for nosocomial pneumonia in this study included: alveolar infiltrates on more than two chest X-rays (the time interval is not specified), a rectal temperature of more than 38.4^{o}C, moderate or copious purulent tracheal aspirate, a leukocyte count of more than 13 000/ml, and a heavy growth of organisms from tracheal aspirates before starting antibiotic therapy.

Colonisation by the same organism of the oropharynx, trachea and stomach was prevented in those who received SDD, and this was significantly different from those in the control group; but the patients who were colonised at three sites in the control group were also observed to have an elevated gastric pH. The incidence of nosocomial pneumonia, in spite of the very non-specific diagnostic criteria in this study, was low: 0 patients who received SDD and only 4 patients (10%) in the control population. The

controls were shown to have an elevated gastric pH, and were colonised by aerobic Gram negative bacilli. 14% of the patients who received SDD and 16% in the control group developed nosocomial bacteraemias, and this was associated with an elevated gastric pH in all the control patients who developed bacteraemia. The mortality was not significantly different: 39% in the SDD group and 53% in the control group; the duration of ICU stay was similar in both groups of patients.

The authors conclude by recommending routine gastric pH monitoring for ventilated patients, and suggest that if a low gastric pH cannot be maintained, selective decontamination should be instituted. This is a clearly inappropriate suggestion, as most studies would suggest that the benefit from SDD is derived by the early prevention of colonisation rather than awaiting for problems to arise. The possible beneficial effect of sucralfate on the control population, and its potential for inactivating the drugs and thus preventing decontamination in the SDD group, is not addressed in this study.

No data is provided on the colonisation or resistance patterns or the microbial pathogens encountered during this study. As with so many of the other studies, the population studied is once again too small and the unblinded character, with rather loose definitions of infection prevents the data from significantly adding to the evidence either for or against SDD.

BLAIR, WEBB, LOWRY, ARMSTRONG ET AL (Use of selective decontamination of the digestive tract (SDD) in an intensive care unit (ICU); an open prospective randomised concurrent controlled trial. Poster ICC, Berlin, 1991) from Belfast, reported a study of selective decontamination in which 331 patients were enrolled over an 18 month period in a regional ICU. The patients were stratified within 6 hours of admission into four groups according to their APACHE II score, and randomised to the control group or to receive a regimen of SDD comprising: oropharyngeal and enteral polymyxin E, tobramycin and amphotericin B, and parenteral cefotaxime for the first 4 days. There was no requirement for a minimum duration of ventilation or ICU stay.

161 patients were enrolled into the SDD group and there were 170 controls. The groups were comparable in terms of age, sex, episodes of primary infection, admission diagnosis, APACHE II score and sepsis score on admission.

No definitions of infection or colonisation were provided. Colonisation of the trachea with aerobic Gram negative bacilli and yeasts was significantly reduced in the patients who received SDD, compared with the control group; there was a less marked effect on colonisation of the gastric aspirate, and no difference in colonisation of the rectum was noted. Rapid colonisation of all sites by coagulase negative staphylococci was observed in the patients who received SDD, especially of the stomach and trachea.

Resistance to cefotaxime did not emerge during the study, but there was a trend towards tobramycin resistance developing in the patients who received SDD. Aminoglycoside resistant coagulase negative staphylococci appeared earlier in all sites of the SDD patients, and overall 79% of isolates from such patients were tobramycin resistant compared with their later appearance in 60% of isolates from the controls.

The number of patients with secondary infections was significantly reduced in the SDD group, where 21 infections occurred in 126 patients (16.7%) compared with 40 infections in the 130 controls (30.8%). Respiratory tract infections were also significantly reduced (10% in those who received SDD compared with 29% in the controls). The organisms causing infection in the two groups differed in that while there were very few infections attributed to aerobic Gram negative bacilli in the patients who received SDD, there were similar numbers of infections in both groups due to Gram positive organisms and yeasts.

There was no difference in either duration of stay in the ICU nor mortality between the two groups, although there was a trend towards a reduction in mortality in the patients with mid-range and very high APACHE II scores.

The authors concluded that while they were able to demonstrate a reduction in the incidence of infection, morbidity and mortality were unaffected and the implementation of SDD would require rigourous infection control, particularly in view of the potential emergence of coagulase negative staphylococci.

The patient population in this study is considerably larger, but there are certain flaws inherent to this study: the study is not blinded, the ICU population is not defined further than by a scoring system assessment, there are no definitions of infection provided and there is no cut-off time to distinguish between primary and secondary infections, nor is there any attempt to study the at-risk population who remained for sufficiently long in the ICU to develop nosocomial infection (which might have reduced the effective population size considerably). The efficacy of the technique of selective decontamination in reducing respiratory infections (and at other sites, although no further details are provided) is however well demonstrated, although once again it is remarkable to note the lack of effect on morbidity and mortality.

FINCH, TOMLINSON, HOLLIDAY ET AL (Use of selective decontamination of the digestive tract (SDD) plus systemic cefotaxime in the prevention of secondary sepsis in a medical/surgical intensive care unit. Poster, ICC, Berlin, 1991) reported a study of 44 evaluable patients admitted to an open randomised trial of selective decontamination in their general ICU in Nottingham. In this study, randomisation was delayed for 60 - 72 hours after admission to the ICU. The control patients were managed conventionally while those randomised to receive SDD were given parenteral cefotaxime for the initial 4 days and gentamicin, amphotericin B and polymyxin E were applied to the oropharynx and enterally for the duration of ICU admission.

The patients in both groups were comparable in terms of sex, age, admission diagnoses, the number of primary infections, and the simplified acute physiology scores.

No definitions of infection or colonisation were provided. Colonisation of the respiratory and upper gastrointestinal tract by aerobic Gram negative bacilli and yeasts was significantly reduced in the patients who received SDD, although this effect was less marked and not statistically significant in the lower gastrointestinal tract. Colonisation by Gram positive organisms initially decreased in both groups, but in the patients who received SDD these organisms tended to persist and even increased in number with time. Resistance to the agents used in the SDD regimen was detected in 7 patients.

The incidence of secondary infection was reduced in the patients who received SDD (7 infections, or 35%, vs 12 infections, or 50%, in the control group), and their antibiotic requirements were also less. The duration of ICU stay was reduced, although this was not significant: 10 days vs 16 days in the controls. The mortality in both groups was high 65% in the patients who received SDD vs 42% in the controls, but this difference did not achieve statistical significance.

This study is again marred by the small numbers, the absence of definitions of infection, and its unblinded design. Once again, the efficacy of SDD in reducing colonisation and infection is demonstrated, but little further benefit seems to have accrued from the use of the regimen in this study.

COCKERILL ET AL [270] from the Mayo Clinic reported a randomised controlled, but unblinded study, of selective decontamination using intravenous cefotaxime for the initial 72 hours, and oral and enteral gentamicin, polymyxin and nystatin for the duration of ICU stay, in their surgical and medical ICUs, over a three year period. 150 patients who were thought likely to remain in the ICU for more than 3 days were randomised to the active and control groups, which each comprised 75 patients; patients who were infected or had received antibiotics within the 24 hours prior to randomisation were excluded. The aim of their study was to assess the efficacy of the regimen in preventing nosocomial infection.

Pneumonia was defined clinically and by laboratory evidence of infection localised to the lung. A new and progressive pulmonary infiltrate compatible with pneumonia, with purulent secretions, isolation of a potential pathogen, and fever, leukocytosis or both, were required. In two patients the diagnosis was not made until autopsy. Tracheobronchitis was defined as the presence of increased purulent endotracheal secretions requiring frequent suctioning and the presence of a potential pathogen. If pathogens were isolated without criteria for pneumonia or tracheobronchitis being met, colonisation was recorded. A 90% concurrence was achieved between two investigators, the one blinded, in the diagnosis of pneumonia. Bacteriuria was defined as colonisation of the urinary tract, unless the presence of fever, flank pain and leukocyte casts suggested pyelonephritis, or in patients without a urinary catheter, if dysuria and frequency with pyuria and bacteriuria suggested cystitis. The other definitions were fairly standard.

The patient characteristics of the two groups were similar in terms of age, sex, the use of antacid therapy, and primary diagnoses. The severity of illness scores were also similar with a mean APACHE II of 18.3 vs 18.6 , ISS mean of 24 vs 24.8 respectively in the controls compared with the active group. 10 patients withdrew from the treatment group because of distaste for the oral paste, or diarrhoea, but these patients were nonetheless included in the analysis. 36% of the controls and 35% of the test patients remained in the ICU for less than 4 days. The total duration of hospital and ICU stay did not differ significantly between the two groups; however, the median duration of intubation was significantly shorter in the decontaminated patients (3 vs 5 days $p=0.022$). 89% of the controls and only 80% of the decontaminated patient group were intubated at some stage of their ICU stay.

Potential pathogens were reported to have been eliminated form the oropharynx of 67% of the test patients, and from the rectum in 55%, although the time interval is not specified; the authors report that in those in which decontamination was not achieved,

the majority of patients had left the ICU within 4 days. Colonisation of the respiratory and urinary tracts was more frequent in controls than in the decontaminated patients (42 vs 27 episodes $p=0.01$). Decontamination was reported to have had little effect on Gram positive cocci, but its effect on the incidence of these organisms as pathogens or the emergence of resistance were not commented upon. The antimicrobial resistance patterns of Gram negative bacilli in this institution are reported be low, but the resistance of isolates to gentamicin or third-generation cephalosporins was 11% in controls vs 16% in the test patients.

The control group were reported to be more likely to have fever while in the ICU, and such episodes were also more prolonged than in the test patients. A significant decrease in the number of days that parenteral antibiotics were administered when compared with the decontaminated patients was noted (9 days vs 4 days, $p<0.0001$), only when the cefotaxime required by the protocol was excluded.

The incidence of infectious episodes was significantly reduced in the decontaminated patients (12 episodes among 10 patients vs 36 episodes among 19 patients in the controls). This difference was noted to be especially marked for infections caused by the Gram negative bacilli: 3 episodes vs 23 ($p<0.002$), and 0 bacteraemias compared with 10 ($p= 0.004$). The incidence of pneumonia was 5.3% in the controls vs 4% in the test patients, while the incidence of tracheobronchitis was 10.7% vs 1.3%. There were no episodes of urinary tract infection documented during the study period.

16 of the 75 controls and 11 of the test patients died during their total period of hospitalisation. In 6 controls and 2 test patients, the patients either died with, or because of, infection. The calculated cost of SDD was $212 per patient. The authors suggest that, although they were not able to achieve statistically significant reductions in morbidity and mortality, the reduction in infections with the potential cost-saving that this, and the trend towards reduced morbidity and mortality, illustrate the benefit of the application of this technique in selected long-term patients in the ICU.

The authors have conducted a prolonged study (3 years) of selective decontamination using satisfactory definitions of infection, although the definition for tracheobronchitis is extremely non-specific. However, there are nevertheless difficulties with the interpretation of their results. 35% of the patients did not remain in the ICU for as long as 4 days, and it has been well demonstrated that the enteral decontamination may take at least as long as this to achieve its goals of upper gastrointestinal decontamination. The effects that are being reported may thus largely be the result of the parenteral cefotaxime, but this is not addressed. When their statistics are applied to the much smaller number of patients remaining after 4 days, the same conclusions might not be applicable. The inclusion of non-intubated patients in this study, still further reduces the evaluable population, as these patients are recognised not to develop respiratory infections. The disparity in the number of patients requiring intubation and ventilation is also not adequately addressed, as this in itself would have biased the control group to a higher incidence of nosocomial respiratory tract infections. The exclusion of infected patients in this study, unfortunately also makes its comparison with other where this was a prerequisite for inclusion, studies difficult.

WINTER ET AL [271] reported a controlled trial of selective decontamination of the digestive tract performed in 91 patients in their general ICU in Bristol, whom they compared with 84 historical and 92 contemporaneous controls. The regimen consisted of topical polymyxin E, tobramycin and amphotericin B administered for the duration of ICU stay and parenteral ceftazidime administered for the initial three days only. Patients were enrolled if they were assessed as being likely to require ICU admission for more than 48 hours; patients in the two control groups were comparable with the study patients in terms of age, sex, admitting diagnosis, median APACHE II (13 in the SDD patients, which was statistically higher than that in the historical controls), median ISS (25 in the SDD group), and median initial sepsis score (5 in the SDD group).

The criteria for diagnosing infection required two temperature spikes $>38.5^{o}C$ within a 24 hour period, and a white cell count >12 or $< 4 \times 10^{9}$ /L. In addition, for the diagnosis of pneumonia, a positive bronchoalveolar lavage was regarded as essential, as well as the presence of two of the following: purulent sputum, new infiltrates on the chest radiograph or an increase of 0.15 in FiO_2 to maintain equivalent oxygenation. Other definitions were fairly standard; no further attempt was made to differentiate between bronchial and parenchymal lung infection.

18% of the SDD patients were primarily infected on admission to the ICU compared with 20% of the historical controls and 30% of the contemporaneous controls, which was significantly different; although the authors comment that there was no evidence that primary infection predisposed to the development of secondary infection. The incidence of secondary infection was significantly lower in the patients who received SDD (3% vs 32% in the historical and 35% in the contemporaneous control groups, $p < 0.01$), although there was no difference in the timing of infections. The rate of colonisation with potential pathogens, particularly Gram negative bacilli, was significantly reduced at throat, gastric and rectal sites in the patients who received SDD, although there was no reduction of Gram negative bacteria in tracheal aspirates. *Pseudomonas aeruginosa* was the most frequently isolated pathogen, and the only pathogen identified as a cause of secondary infection in patients who received SDD. Significantly more ($p < 0.01$) *Acinetobacter spp* isolates were recovered from rectal, throat and tracheal specimens of the patients in the contemporaneous control group, than from the other two groups. No patients developed infection or received antibiotics for possible infection caused by resistant bacteria, however. The antibiotic usage for all three groups was similar, although therapy with systemic amphotericin B was only used in the contemporaneous control group for two patients with aspergillus infection.

The average duration of ICU stay was shorter in the patients who received SDD (6.38 vs 7.3 in the historical and 7.97 days in the contemporaneous controls), but this did not

achieve significance. 64% of the SDD group survived to leave hospital, compared with 60% of the historical and 56% of the contemporanous controls. There was no significant difference in overall mortality. The authors found that, when all patients were considered together, they were able to show a clear association between the incidence of infection and adverse outcome: 56% of patients with primary infection died, compared with 35% without this problem; there was also an association between secondary infection and mortality (58% vs 37%).

The authors concluded that SDD provided an effective method for reducing the incidence of secondary infections, particularly in the subgroups of trauma patients, vascular surgery and long-stay patients. The technique was expensive in terms of drug costs, nursing time and microbiological surveillance. Although their results could not be interpreted as showing that SDD predisposed to secondary infection or colonisation by resistant bacteria, there was concern that the increased colonisation by *Acinetobacter spp* might be an indication of an alteration in the bacterial flora of the ICU as a result of the technique, reinforcing the importance of ongoing microbiological surveillance.

This study incorporated sufficient patient numbers to provide useful information on the value of SDD, although the absence of blinding is unfortunate. The diagnostic criteria for infection differed from other studies, but incorporated a number of clinical parameters. It is of concern that the levels of antibiotics in the bronchial secretions achieved even with the topical agents in SDD, may be sufficient to have treated, rather than prevented, early secondary infections [272]. A further criticism might be that the duration of ICU stay and intubation were not sufficiently clearly specified or used to allow the SDD to have taken effect. The mean duration of stay was only 6 days, at which stay the benefit of SDD is just becoming apparent, while the benefit of the parenteral agent may have reduced the incidence of early infections in these patients and thus contributed to the favourable results.

6) Intestinal Decontamination to control nosocomial multi-resistant Gram negative bacilli

BRUN-BUISSON ET AL [250] reported a study in 1989, performed in the medical ICU of their hospital in Paris, to assess the efficacy of intestinal decontamination in controlling an outbreak of intestinal colonisation and infection with multi-resistant *Enterobacteriaceae*, and to examine the effects of the regimen on endemic nosocomial infection rates.

A 10-week prospective study was performed to assess the incidence and then an 8-week randomised, open trial of intestinal decontamination using consecutive and randomised controls followed. The study was conducted over two successive periods because of the possibility of a cross-over effect on nosocomial infections from the group given intestinal decontamination to the concurrent control group. The intestinal decontamination regimen consisted of neomycin, polymyxin E, and nalidixic acid, but no oropharyngeal nor parenteral prophylaxis were used, as these were thought to be of less clearly proven benefit and might have promoted the development of further organisms being resistant to the regimen used. All tracheally intubated patients received oropharyngeal disinfection with a povidone-iodine solution at least 3 times a day.

Nosocomial infection was defined as any infection that was diagnosed during the ICU stay or within 48 hours of discharge. Pneumonia was defined as the occurrence of fever ($>38^{o}C$), peripheral leukocytosis ($>$ 10 000/ml), purulent sputum or tracheal aspirate associated with a new and persistent infiltrate on the chest radiograph, and the culture of at least 10^9 colony forming units/l from a protected wedged catheter sample of bronchial secretions. The growth of at least 10^9 colony forming units/l and purulent sputum, with no definite or new infiltrate was diagnosed as tracheobronchitis.

Colonisation of the digestive tract with multi-resistant organisms was assessed in all patients by sequential rectal swab cultures, both during the study period and the month after the prophylaxis trial.

Patients who stayed in the ICU for less than 48 hours were excluded from the study. 124 patients (63% of all admissions) were enrolled in the initial 10-week control period. 143 patients were admitted during the 8-week study period and, after exclusions because of low severity of illness score, or neutropaenia, 123 patients were included, of whom 68 were assigned to the control group and 65 to the decontamination regimen. The groups were demographically entirely comparable.

On admission, a multi-resistant strain was detected on the rectal swab of two patients from the first study period, none from the control group and one from a decontaminated patient. More than 2 weeks elapsed between admission and first detection of multi-resistant *Klebsiella pneumoniae* or other *Enterobacteriaceae* in rectal swab specimens of patients acquiring colonisation by such organisms during their stay in the ICU. Multi-resistant strains were isolated from 19.6% of patients, at a mean of 16 days after admission during the initial study period, 10% of patients in the control group and only 2% (1 patient) in the decontamination group. None of the patients admitted in the month following the trial, was colonised by multi-resistant *Enterobacteriaceae*.

The overgrowth of at least one of the species possibly resistant to the intestinal decontamination regimen, was detected at least once in the stool specimens of 32% of the control patients and 58% of the decontaminated study patients, in whom overgrowth of Gram positive cocci was significantly more frequent when compared with the control group. The rectal concentration of *Pseudomonas spp* did not differ between these two groups. The strains of *Enterobacteriaceae* (mostly *Klebsiella pneumoniae*) involved in the outbreak studied were remarkable by the presence of

transferable resistance to both third-generation cephalosporins and to most aminoglycosides, including amikacin.

The digestive tract of the patients in the ICU was recognised to be an important reservoir of the epidemic strains, and an incidence of 20% in intestinal colonisation was documented during the initial period of monitoring, although about half of the colonised patients remained asymptomatic carriers only. In all the patients who developed infection due to these organisms, colonisation with the multi-resistant organism preceded detection of the organism clinically by about 10 days.

Most of the multi-resistant isolates were the same strain of *Klebsiella pneumoniae*, which suggested a major role for cross infection in addition to plasmid transfer; however, environmental studies failed to isolate the common source and, although hand transmission by the staff was considered the most likely method of transmission, and control measures were attempted, these were not successful until the attempt at eradication, using intestinal decontamination. The cross-over effect of the prophylactic regimen from the decontaminated patients to the control patients was anticipated by the investigators, and was well demonstrated by the reduced intestinal colonisation by resistant organisms in the control patients, compared with those in the initial study period.

While the authors do not advocate intestinal decontamination as a substitute for recognised hygienic precautions in the prevention of infection, such as hand-washing, the isolation of infected patients, and a restricted antibiotic policy; there may be a role for a method such as this in controlling an outbreak of a multi-resistant organism, which at least circumvents the closure of an ICU, which is already a limited resource in any hospital.

There was an incidence of secondary infection of 30.3% over the entire study period, and no significant difference was noted in the incidence of infections, or the

distribution of the organisms causing nosocomial infections, between the three groups. *Pseudomonas spp* infections tended, however, to be more common in the decontaminated patients than in the controls, whereas *Enterobacteriaceae* infections were more common in the controls than in the study patients. The duration between admission and infection was similar in all groups at 10 $\pm$ 4.5 days.

The authors acknowledge that the size of their study may have been too small to detect a significant reduction in the incidence of secondary infection; however, if the results of other studies were reliable enough to be able to be extrapolated to their unit, a reduction in infection should have been seen. They suggest that the primarily medical population of their unit might have been a population group unlikely to benefit from selective decontamination, compared with the multiple trauma and postoperative patients where most benefit has been reported.

The overall mortality rate in the ICU was 20% in the patients in the initial study period, 24% in the control patients and 22% in the patients who received intestinal decontamination. It was thought that nosocomial infection contributed to death in similar proportions of each group (9%, 10%, 8.5% respectively), although the criteria for this were not specified.

The authors conclude that while there may be a role for selective decontamination to be used for a limited period to control an outbreak of a resistant organism, they were unable to demonstrate any benefit from this technique in the prevention of endemic nosocomial infection, and that such use may not only not be cost-effective, but also potentially hazardous, because further bacterial resistance is likely to emerge.

7) The Paediatric ICU

ZOBEL ET AL [273] reported a study of selective decontamination performed in a paediatric ICU population who all required intubation, ventilation and ICU therapy for at least 4 days in their hospital in Graz, Austria. Patients were randomly assigned to

receive decontamination with oral and enteral polymyxin E, gentamicin and amphotericin B and parenteral cefotaxime, while the control group received perioperative prophylaxis and conventional therapy as indicated.

The definition of a respiratory tract infection was the presence of purulent sputum with a positive culture and new pulmonary infiltrates on the chest radiograph, in association with pyrexia ($>38.5^{0}C$), and a white cell count $>14\ 000/ml$ or $<3\ 000/ml$.

The patients in both groups were comparable in terms of age, sex, body weight, severity of illness and therapeutic and monitoring expense. There was no significant difference between the groups in terms of duration of ICU stay, ventilation, nor systemic antibiotic therapy.

The colonisation patterns resembled the other studies in that colonisation in both groups was similar on admission (24% in the treatment group, compared with 20% in the control); colonisation with Gram negative organisms gradually disappeared in the decontaminated patients, whereas in the control group colonisation with organisms such as *Pseudomonas aeruginosa* and *Klebsiella spp* increased from 10% to 52%. In both groups the colonisation of the respiratory tract by Gram positive organisms increased, but Gram negative bacteria and yeasts were not found in the respiratory tract of the treatment group. Urinary tract colonisation was minimal in both groups. There was no development of resistance to the drugs used for decontamination during the trial.

36% (10 patients) in the control group developed secondary infections (6 respiratory tract infections due to endogenous Gram negative organisms, 2 catheter related staphylococcal infections and one fungal and one staphylococcal septicaemia), compared with only 8% (2 patients) in the treatment group, and both these infections were due to *Staphylococcus aureus* (one tracheobronchitis and one catheter related infection). In all patients with respiratory infections, the infections were preceded by colonisation of the oropharynx. There were five deaths, 3 in the treatment group and 2

in the controls, all apparently because of multiple organ failure with low cardiac output states; however, without specifying how this was determined, "no patients died from uncontrolled infection".

While this study again showed convincing eradication of colonisation by endogenous Gram negative organisms, with a lower incidence of infection due to such organisms in the decontaminated patients, the incidence of staphylococcal infections would appear to have been high in this unit. Whether this phenomenon was related to the SDD regimen used, which might promote the emergence of staphylococcus as a pathogen was not addressed. The microbiological data presented in this paper is limited.

Once again, the unblinded nature of the study, the small numbers of patients, and differences in definitions prevent the conclusions from being definitive.

8) The effect of selective decontamination on antibiotic resistance profiles

There is much concern that the use of topical antibiotics may promote the emergence of resistance, particularly the widespread use of topical antibiotics in a prophylactic capacity. Much of the uncertainty over the role of selective decontamination has stemmed from the potential adverse effects that this regimen might exert on the ICU microbial flora, and routine microbiological surveillance has been recognised to be a sine qua non since the regimen was first instituted by Stoutenbeek et al [274]. Nevertheless, most reported studies of SDD have failed to demonstrate a significant adverse effect on the aetiology and resistance patterns of the pathogens encountered following the use of SDD; the caveat being that in most cases the technique had possibly not been applied for sufficiently long for major effects to have become apparent; in some cases, they also have not been adequately looked for.

That SDD must have some major effects on the bacterial flora would appear to be likely from the success that Brun-Buisson et al reported [249] with its use to eradicate multiply-resistant Gram negative bacilli from their ICU.

STOUTENBEEK ET AL [14,275] reported the effect of selective decontamination on the emergence of resistant bacteria, using data from 164 multiple trauma patients studied in their ICU over a 30 month period in their ICU. They found no increase in the percentage of patients with acquired drug-resistant Gram negative bacilli: 4% of the strains of the 374 isolates were resistant to tobramycin; all strains, except for the 12% of isolates which were *Proteus spp*, were sensitive to polymyxin E; *Escherichia coli*, *Klebsiella spp*, and *Proteus spp* were invariably sensitive to cefotaxime. However, a "considerable" percentage of *Pseudomonas spp*, *Acinetobacter spp*, *Enterobacter cloacae* and *Citrobacter spp* were found to be cefotaxime resistant. 96% of the flora present on admission were sensitive to cefotaxime, and the majority of cefotaxime-resistant Gram negative organisms were considered to have been acquired within the hospital.

35% of patients acquired one or more different strains during their stay in the ICU, which were mostly isolated from the rectal swabs. The Gram negative organisms most frequently acquired included: *Pseudomonas spp*, *Enterobacter spp*, *Acinetobacter spp*, and *Proteus spp*. Forty percent of these isolates were cefotaxime resistant, although none was resistant to the combination of antibiotics used in the enteral regimen. The majority of acquired organisms were isolated only once, but in 21% secondary colonisation, usually of the rectum, followed, and in 66% of these cases, the organisms were subsequently eliminated by the enteral antibiotics. 10% of the gastrointestinal colonisation was with cefotaxime-resistant Gram negative organisms, but colonisation of the lower respiratory tract, urinary tract or wounds with cefotaxime-resistant Gram negative organisms was only found in 2%. There was no increase in the incidence of cefotaxime-resistant strains, and the majority of organisms identified which were resistant to cefotaxime, were initially isolated in low concentration from the gastrointestinal tract, suggesting that they may already have been present from admission. There were eight strains of Gram negative bacilli which had previously been sensitive to cefotaxime which developed resistance, which the authors ascribed to the

presence of sub-inhibitory concentrations of cefotaxime in the faeces. These organisms were not resistant to the enteral antibiotics, however, and the "majority" were eliminated before clinical problems arose.

Aminoglycoside resistance was not common in this study, which the authors explain by the fact that gentamicin and vancomycin are inactivated in the faeces, whereas the tobramycin, which they used instead, is not. The synergistic effect of the agents used in the enteral regimen and the preservation of the anaerobic flora were also invoked to explain this discrepancy. Resistance to polymyxin E did not occur during the study, other than in *Proteus spp* which is recognised to be intrinsically resistant to this antibiotic.

The infections with resistant organisms included three wound infections with cefotaxime-resistant Gram negative bacilli (*Enterobacter* cloacae, *Pseudomonas aeruginosa* and *Acinetobacter spp*), and one respiratory tract infection with *Acinetobacter spp*. There were no secondary Gram negative urinary tract infections; however, before the addition of cefotaxime to the regimen, there were three cases of Gram negative septicaemia (*Escherichia coli*, *Proteus mirabilis* and *Acinetobacter calcoaceticus*).

This study is one of a very few which have reported in detail the effects of selective decontamination on the resistance patterns of the microbial flora. Unfortunately the regimen used was not uniform over the time period during which the study was conducted and cefotaxime was not routinely used for the whole period, so that the ultimate impact on resistance to this agent may have been underestimated. While the effect on colonisation of the gastrointestinal tract by Gram negative organisms is extremely dramatic with the use of SDD, the authors do not address the other important issue of the potential adverse effects the regimen may have on the Gram positive flora, particularly the staphylococci.

ARMSTRONG ET AL [276] reported the effect of selective decontamination on the resistance patterns of Pseudomonads during their 18 month study of SDD in 331 patients. Pseudomonads were isolated from 27% of the patients who received SDD and 30% of controls. The respiratory tracts of 8% and 9% of patients, respectively, were colonised by Pseudomonads on admission, and although this incidence increased in both groups, there was a trend for this to be curtailed in the patients receiving SDD. There was a reduction in the incidence of clinical infections with this organism, despite the fact that the authors reported that the SDD patients appeared to act as a reservoir for persistent strains. The epidemiology of *Pseudomonas aeruginosa* did however appear to be influenced by the use of SDD, as the introduction of an aminoglycoside-resistant strain to the ICU seemed to become more easily established, possibly due to the altered colonisation resistance of the patients and the tobramycin resistance of the organism. The question as to whether the frequency of infections due to *Pseudomonas spp* was actually increased due to the persistent reservoir that the SDD patients served to maintain is raised. Unfortunately the incidence of infections caused by this organism prior to the study is not presented, but this study does raise important issues which have not been adequately dealt with in other reports and for which the answers are at present, not available.

Limited reports on the effect of SDD on the Gram positive organisms are available, although several studies have suggested that the use of the regimen is associated with an increase in colonisation and possibly infection by these organisms [256,273], Finch et al, Palomar et al .

NAU ET AL [277] reported that, following the introduction of SDD (parenteral cefuroxime for the initial 3-5 days, and enteral polymyxin E, amphotericin B and gentamicin) to their unit for the management of intubated neurological patients, there was an alarming increase in the incidence of cefuroxime and gentamicin resistant staphylococci, with a concomitant increase in gentamicin resistance amongst the Pseudomonaceae. There was

an increase in methicillin-resistant staphylococci, and the gentamicin resistance was associated with amikacin resistance. They suggest that SDD is hazardous in selecting and inducing antimicrobial resistance, and abandoned the technique.

KONRAD ET AL [278] reported similar findings in their study, where there was an increase in colonisation and infection caused by DNase negative staphylococci, an increase in methicillin- , cefotaxime- and tobramycin- resistant staphylococci, and cefotaxime-resistant *Enterobacteriaceae* and *Pseudomonads* in the patients receiving SDD.

9) The antibiotic levels achieved in the bronchial tree and serum during SDD.

GASTINNE ET AL [272] reported a study in which they aimed to determine whether there were detectable levels of antibiotics in the bronchial secretions and serum of patients receiving SDD. Tobramycin and amphotericin B levels were determined every 3 days in the serum, tracheal aspirates, and distal bronchial secretions of 15 patients who received SDD and mechanical ventilation for more than 10 days. They showed that 82% of tracheal aspirates contained detectable levels of tobramycin, although the levels fluctuated widely, and that tobramycin levels were detectable in the serum of 50% of the specimens, as well as the distal bronchial secretions, particularly in those patients with renal impairment. The tobramycin level was frequently found to be above or near the MIC of common bacterial pathogens, and the MICs of the majority of pathogens that could be cultured were higher than corresponding drug levels.

The authors point out that the presence of bactericidal antimicrobial concentrations within the bronchial secretions may prevent the development of nosocomial respiratory tract infections, by eliminating pre-existing colonisation in situ, rather than by merely exerting an effect on the gastrointestinal tract. Their findings are also of importance, because the definitions of respiratory tract infection used in many of the studies of SDD hinge on microbiological criteria, (both proximal culture of tracheal aspirate or the number of colony forming units obtained on culture of protected specimen brush samples), and thus may not be valid. Finally the nephrotoxic effects of persistent

samples), and thus may not be valid. Finally the nephrotoxic effects of persistent aminoglycoside administration need to be considered when this regimen is used for prolonged periods, if enterally administered tobramycin is able to achieve significant serum levels.

10) Summary of Trials

In the light of the above, selective decontamination has been demonstrated to have effects which include an unequivocal reduction in colonisation by Gram negative bacteria colonising the oropharynx and stomach, with a more variable effect on colonisation patterns of the lower gastrointestinal tract. The effect on yeasts is also more unpredictable. Many of the studies have reported a high incidence of infections due to Gram positive cocci, although none has reported outbreaks of resistant organisms with the use of this technique, albeit over limited periods, to date. All the studies have reported a reduction in respiratory tract infections, with a more variable effect on urinary tract and catheter related infections.

Almost all the studies have indicated that, in spite of the reduction in infection, there was no associated benefit on morbidity and mortality. The costs of this technique are not insignificant, hence the attempts at developing regimens using cheaper agents with similar efficacy.

The primary aim presumably, when embarking on the routine use of SDD, is to reduce morbidity and mortality through a reduction in secondary infections, but the majority of studies mentioned above have failed to do this conclusively through faults in study design including the use of different diagnostic criteria, many of which are too non-specific to be considered reliable, or repeatable. The small patient numbers, uncontrolled, or unblinded studies, and post hoc stratification in an attempt to show benefit have prevented this technique from being able to be unreservedly accepted as a new and routine part of intensive care patient management.

As a result of the still questionable evidence on the benefit of selective decontamination, meta-analyses using the available evidence have been performed, as it is well recognised that to prove that any technique has a beneficial effect on mortality, requires vast numbers of enrolled patients. By combining the data of the published studies, it has been hoped that more conclusive results might be obtained.

VANDENBROUCKE-GRAULS ET AL [279] published a meta-analysis of the effect of selective decontamination of the digestive tract on the incidence of respiratory tract infections and mortality in the intensive care unit in 1991. They evaluated 1489 patients who had been incorporated into 11 studies between January 1984 and December 1990, according to whether the study design used an historical control group of untreated patients or a randomised control.

All the studies which were used in this meta-analysis have been reviewed above and include the publications by Stoutenbeek, Ledingham, Brun-Buisson, Hartenauer, Kerver, Ulrich, Tetteroo, Aerdts, Unertl and Mc Clelland, except for that of Konrad (published in German). As was mentioned when reviewing these papers, the studies are not homogeneous as some (Stoutenbeek, Ledingham, Konrad, Hartenauer, McClelland, Aerdts, Tetteroo) used initial parenteral prophylaxis with cefotaxime.

The authors warn that the results of this meta-analysis need to be interpreted with caution, as the studies analysed all used the selective decontamination for different indications, in different patient groups and with different prophylactic regimens; they also point out that there may be unsuccessful studies which had not been analysed because they had not been published. They blame poor diagnostic criteria on the striking difference of the effect of this regimen on the incidence of infection and mortality.

Selective decontamination in this meta-analysis was shown to have a significant effect on the frequency of respiratory tract infections, but its effect on mortality, however,

was not clearly shown. There was a 10% reduction in mortality in the historical control groups, with a confidence interval so wide that it ranged from a 33% reduction to a 25% increase in mortality. Among the randomised and alternate trials, there was about a 33% reduction in mortality, with the confidence interval ranging from a 50% decrease to a 10% increase. The studies of Stoutenbeek, using an historical control, and Ulrich, were largely responsible for this benefit; when these studies were removed from the meta-analysis, no benefit was found. The role of cefotaxime in these studies was not conclusively demonstrated. There was no difference in mortality in the studies in which parenteral antibiotic prophylaxis with this agent was provided, and those in which it was not given.

LIBERATI AND BRAZZI from Milan (Meta-analysis of randomised controlled trials on the effect of Selective Decontamination of the Digestive Tract. SDD Trialists Group, submitted for publication) performed a meta-analysis of 22 randomised controlled studies published/unpublished since 1984. Altogether 4073 patients were analysed, of whom 2011 received active therapy and 2062 no treatment or placebo; in this group there were 1083 deaths. The endpoints of this study were pulmonary infections and overall mortality. Despite the wide heterogeneity of the trials analysed, this study once again confirmed that SDD significantly reduces pulmonary infections; however, the overall mortality was only marginally affected.

According to their analysis, the pooled odds ratio for pulmonary infections was 0.38 (95% CI= 0.32-0.45), while that for mortality was 0.92 (95% CI= 0.79-1.06). A 19% statistically significant relative reduction in the odds of death emerged, however when trials with a systemic antibiotic were added to the enteral decontamination regimen (2381 patients and 599 deaths) there was an odds ratio = 0.81 (95% CI = 0.67-0.99). Using these estimates, 8 patients would need to be treated (range 7-9) to prevent one pulmonary infection and 27 patients (range 15-530) to prevent one death.

The authors emphasise that while this treatment has been shown to affect the incidence of pulmonary infections significantly, a properly conducted study with some 1500-2000 patients, and using mortality as an endpoint, would be the ideal to identify the clinical relevance and cost-effectiveness profile of selective decontamination, and to determine which patient-mix is most likely to benefit from this technique. Their analysis suggests that both topical and parenteral agents are required for the technique to be effective.

In general, the reviews of SDD have echoed doubts and caution rather than embracing the technique. van Dalen, as early as 1989 [280] cautioned that "if the costs and the risk of the emergence of resistance are accepted, as well as the uncertainty of diagnostic accuracy in respiratory tract infections, SDD may be effective in patients requiring mechanical ventilation for more than 5 days."

WEINSTEIN [281] reviewed the role of SDD following the reported successful eradication of a multiply-resistant *Klebsiella spp* strain with the use of this technique [250]. While acknowledging that the results were difficult to explain, and there was still a potential risk of resistant organisms emerging, his conclusions were fairly positive, pending the results of definitive studies. He suggested that the regimen might be used in selected high risk groups, or as an empiric measure where other approaches had failed.

REIDY ET AL [282,283] from Ledingham's unit in Glasgow also reviewed the role of SDD and concluded that it had a definite role in ICU management, although which patient groups were most likely to benefit was not yet apparent, with the available studies. There was a suggestion that trauma patients and other long-stay groups were most likely to show benefit, however. They commented that, in spite of the variations in trial design, there was a "remarkable" consistency in the reported results from many centres. SDD was clearly demonstrated to reduce the rate of colonisation by aerobic Gram negative bacilli of the upper GIT and airway, with an associated reduction in the infection rate by these organisms, particularly secondary respiratory tract infections. By comparing the efficacy of the regimens in decontaminating the oropharynx, the authors

concluded that this is an important component of SDD, but that the importance of gastric decontamination is less well established.

In the studies reviewed, no increase in antibiotic resistance by Gram negative organisms was detected, however, several centres did note an increased incidence of resistant Gram positive organisms, which resulted in infections in some centres. Cross-infection between contaminated and decontaminated patients, which was part of the rationale for the consecutive design of some studies, however, did not seem to be an important consideration, as there was no substantial difference in the infection rate between these and concurrent trials.

Reidy suggests that part of the reason for the failure of SDD to reduce mortality may be that the wrong group of patients was selected, because the number of patients recorded as dying from infectious causes is small; patients who are uninfected on admission and who are pre-selected as likely to require prolonged ventilation may also be at greater risk of brain death, or death from other underlying causes. The lack of evidence for a causal relationship between secondary infection and death is also cited as a potential explanation. Another potential mechanism which is invoked is that bowel endotoxin may be responsible for the development of multiple organ failure, and that the level of gastrointestinal decontamination achieved with SDD may not actually be sufficient to inhibit the endotoxin from still being formed and absorbed.

With his interest in the gastrointestinal origin of endotoxin and its potential role in the induction of multiple organ failure, DIETCH [284] posed the question as to whether SDD failed to improve survival, because it was directed only at the pathogen, and not at improving the resistance of the host to infection. Bacterial translocation requires the disruption of the ecological balance of the normal intestinal microflora with bacterial overgrowth, or impairment of the host immune defences, or either the physical or physiological disruption of the function of the mucosal barrier. He suggested that SDD could and would not alone be able to increase survival, because the studies had enrolled

mostly immunocompromised patients, with impaired intestinal barrier function, without addressing the underlying issues of preventing the mechanisms involved in bacterial translocation.

GORIS ET AL [192] studied the effects of SDD on survival and organ function in an experimental model of sepsis with multiple organ failure. Their study is the only reported experimental model of the effect of SDD, and their findings both coincide with and contradict the conclusions reached by Deitch. They showed that SDD effectively prevented bacterial translocation of *Enterobacteriaceae*, with an associated decrease in the early mortality. However, the late mortality was unaffected, and seemingly unrelated to bacterial translocation. They suggested that SDD would be unlikely to have a major influence on mortality in patients, because therapy is introduced at a later stage than in the experimental model, thereby losing the advantage in a reduced early mortality; as a result of ileus, trauma or peritonitis, the therapeutic effect of SDD would also be likely to be still further delayed. The authors suggest that multiple organ failure and sepsis which are the major causes of death in the ICU are the result of a severe generalised autoinflammatory reaction to massive stimuli such as trauma, in which activated macrophages, rather than bacteria or endotoxins, play the dominant role.

VAN SAENE ET AL [285] reviewed 16 controlled trials of selective decontamination that had been published prior to December 1990. They concluded that selective decontamination had generally been shown to reduce microbial carriage and acquired infections. They admitted that the benefit in terms of mortality had been less convincingly demonstrated, which they attributed to the fact that many of the patients in the studies had largely irreversible diseases and thus would have been unlikely to have shown significant benefit.

Van Saene et al [286] commented on the controversy surrounding SDD in a "critical evaluation of the clinical, bacteriological and epidemiological benefits"; the reviews

that had disputed the efficacy of the technique were hotly attacked, while any evidence in support of the regimen was eagerly grasped to argue in favour of this approach, which, they suggested should even be carried into the ward as part of prophylaxis for major surgery. The authors reviewed twenty studies available by 1991 and concluded, with no further evidence than has been provided in the previous chapters, that SDD was indicated for trauma patients, in certain elective surgical procedures including liver transplantation and oesophageal resection, and finally in the control of outbreaks of ICU infection.

FINK [287] commented that future trials of SDD should preselect subgroups at high risk for mortality related to secondary infection, as the causes of mortality in the ICU were mostly a result of the underlying disease process, only a very select few dying as a result of acquired infection. He criticised physicians in North America for being slow to adopt the technique because of the cost constraints of this extremely expensive regimen. He acknowledged that the risk of the emergence of antimicrobial resistance was yet another strong detractor from the use of SDD, and in particular the risk of the emergence of gentamicin resistant enterococci and overgrowth with coagulase negative staphylococci was of great concern. If SDD were really of value, the benefits, measured by cost and mortality, might have been expected to have already been more evident and clinicians might require less persuasion to adopt SDD, rather than still awaiting the results of bigger and better trials.

CRAVEN [288] provided one of the more recent editorials on the controversy over SDD. While commenting that almost all studies had shown a reduction in the incidence of respiratory tract infection, he cautioned that the diagnosis of nosocomial respiratory tract infection was difficult, and often unreliable; few studies had been able to show an improvement in mortality, morbidity as measured by duration of ICU stay or ventilation, or cost. While nosocomial infection increases mortality, he acknowledged that it was both difficult and controversial to segregate the mortality attributable to

infection. He felt that in view of the current lack of consensus on the role of SDD, the best regimen and the appropriate target population, the technique still needed to be regarded as experimental, and could not be recommended as a routine prophylactic strategy. In the interim, established infection prevention methods should continue to be carefully implemented.

Part of the rationale for the use of selective decontamination has been that this technique may reduce the colonisation of patients and thus make it easier to maintain an uncontaminated environment in the ICU [229]. This possible benefit would appear to be doubtful in view of the increasing evidence of the overgrowth of Gram positive bacteria associated with the use of SDD. Whether any study will ever be able to resolve convincingly the contribution that nosocomial infection plays in causing the death of an already critically ill patient is doubtful.

7.12 The Role of Selective Decontamination in the Prevention of Nosocomial Infection

Despite almost a decade since SDD was introduced to the practice of critical care medicine, its role is still not clearly established, and the indications for its use remain controversial. There are several reasons for this: the regimens used in many of the studies have varied, with some studies including both parenteral and enteral agents, while others have used only enteral agents; the controversy over the role of parenteral agents still not having been satisfactorily resolved. Even the agents used are not standardised. The ICU populations that have been studied have been different, allowing conclusions to be drawn as to subgroups that may potentially benefit from the technique. There is no uniformity in trial design and many of the studies have had inherent flaws such as post-hoc stratification and insufficient patient numbers, making any conclusions drawn suspect. The definitions of nosocomial infection are a further stumbling block in achieving consensus. There are as yet no standardised definitions for diagnosing nosocomial infection, and the diagnosis, particularly of nosocomial

pneumonia, is extremely difficult. The use of the protected specimen brush would appear to have superceded clinical definitions in many quarters, but what the microbiological cut-off should be in a patient who is receiving antibiotics is uncertain, particularly if the agents used in the SDD regimen are able to achieve therapeutic levels in the bronchial secretions and serum. In many of the studies, the distinction between colonisation and infection has not been adequately defined. While the majority of studies have shown a reduction in the incidence of nosocomial respiratory tract infections, the effects of SDD on morbidity and mortality remain less convincing. The data on the effect of SDD on the emergence of resistant micro-organisms remains controversial. While studies have not convincingly demonstrated an increase in the incidence of resistant aerobic Gram negative bacilli, there have been reports showing an increased incidence or persistence of *Pseudomonas aeruginosa*, and the adverse effects reported from several centres on organisms inherently insensitive to the agents in the regimen is of concern. Finally, the cost of the regimen is not insignificant, particularly when the drug costs, pharmacy and increased nursing time, as well as the considerable laboratory load imposed by the seemingly essential microbiological surveillance, are all taken into account.

Stoutenbeek showed a reduction in the incidence of nosocomial respiratory tract infections, urinary tract infections, bacteraemias and wound infections [14], in the initial studies of the regimen. Ledingham was able to show a reduction predominantly in the incidence of respiratory tract infections, but no reduction in the incidence of bacteraemia [263]. Kerver reported a reduction in the incidence of bacteraemias, intra-abdominal infections, as well as respiratory tract infections, but no effect on urinary tract infections [253]. Aerdts found that the incidence of respiratory tract infections was reduced, but was unable to confirm a reduction in the incidence of other types of nosocomial infection [269]; this was also the experience of Tetteroo [260]. The French studies [250,268] failed to find a significant reduction in the incidence of nosocomial infection. The majority of other studies have reported a reduction in the incidence of

secondary respiratory tract infections, but have either not commented upon, or have not detected a significant reduction in the incidence of other types of infection. The implied consensus being that SDD may have some role in the prevention of respiratory tract infection, but that its effect at other sites is far from clear.

In general, the reviews of SDD have echoed doubts and caution rather than embracing the technique. The conclusions at the first European Consensus Conference on SDD were that the use of this technique was able to reduce the incidence of nosocomial infection, particularly superinfection of the respiratory tract. However, there were no specific indications for its use, and there was no proven reduction of morbidity, duration of ICU stay, or mortality associated with its use; furthermore, there was no decrease in the costs of ICU therapy if this technique was employed. While acknowledging that the conclusions should not be considered definitive, the recently completed "Meta-analysis of randomised controlled trials on the effect of Selective Decontamination of the Digestive Tract" which has been submitted for publication, in which our study of SDD was included, showed a significant reduction in respiratory tract infections, and had a moderate effect on mortality.

CHAPTER 8. THE TREATMENT OF NOSOCOMIAL INFECTIONS IN THE ICU

8.1. The treatment of nosocomial pneumonia

The diagnosis of nosocomial pneumonia in the ventilated patient has been shown to be difficult, and requires a high index of suspicion. The importance of ongoing monitoring and surveillance of all parameters which may provide early indications of the development of infection at any site, cannot be over-emphasised, and is one of the mainstays of intensive care. The regular analysis of blood-gas, serum chemical and haematological parameters may provide early evidence of organ dysfunction, but microbiological surveillance cultures are the most valuable tool in providing ongoing information as to the prevailing bacterial flora, and thus serve as a useful guide in selecting the most appropriate empirical antibiotic therapy. This may then be modified, pending the culture results obtained by more specific diagnostic procedures, and thus avoiding delay at a critical phase. The importance of the Gram stain in guiding initial therapy should not be forgotten in guiding the selection of therapy. Numerous pus cells in association with a predominant organism, particularly if Gram positive, are likely to give an accurate guide to the type of antimicrobial therapy.

The spectrum of pathogens causing nosocomial infection in the ICU, depends to a certain extent on the individual hospital, the specific ICU and patient population that is being considered; however, the majority of such infections are due to aerobic Gram negative bacilli including the *Enterobacteriaceae*, particularly *E.coli* and *Klebsiella spp*, although *Pseudomonas spp* and *Acinetobacter spp* are also important, but may show more of a geographic variability. The staphylococci are also an important cause of nosocomial infection, and in patients who are immunocompromised or have received multiple courses of antibiotic therapy, the yeasts need to be considered.

The selection of antimicrobial agents for the therapy of nosocomial infections in the ICU, should follow the same principles as when choosing the most appropriate agent for therapy elsewhere. Once the patient has been hospitalised for more than 48 hours, the organism should be assumed to be hospital-acquired and the choice of antibiotic should take the resistance profiles and spectrum of pathogens into account. Because the patients are critically ill and there is no room for miscalculation, the tendency is to commence therapy with fairly broad spectrum drugs directed at the most likely causative organisms; once confirmatory evidence of the aetiological agent has been obtained, therapy can then be more specifically directed and unnecessary agents should be discontinued as soon as possible, to prevent the emergence of resistance [214]. It is however important, in view of the critically severe nature of the patients' illness, that there be a minimum of delay in the initiation of therapy, as it has been demonstrated, both in the treatment of pneumonias due to Gram negative organisms [289] and bacteraemias due to Gram negative organisms [290], that the achievement of early therapeutic aminoglycoside levels is a significant factor in determining outcome. While the measurement of aminoglycoside levels is a fairly simple and routine procedure, techniques are not as readily available for measuring the serum levels of other antimicrobials, but it would be fair to assume that a similar relationship must exist.

The choice of antimicrobial agent needs to be determined by the antibiotic policy laid down for the hospital and ICU. A close liaison between the teams of microbiologists and clinicians is helpful in formulating the most effective, early therapeutic strategies, in the often complex problems encountered in the ICU. The use of empirical antibiotic combinations such as beta-lactam agents in combination with aminoglycosides [291,292] are widely used, because of the synergy, improved bactericidal effect, which is thought to impact on outcome [292], as well as the broad spectrum of cover such a combination provides. It is also thought that combination therapy may help in the prevention of antibiotic resistance.

With the increasing prevalence of antimicrobial resistance, there is an ongoing search for new-lines of therapy, preferably containing new chemical entities which may bypass already established resistance mechanisms. The quinolones are a class of antibiotic that are currently being promoted, because of their pharmacokinetic and apparently good safety profile, wide spectrum of activity and relative novelty [247,293]. The recently developed agent imipenem/cilastatin, combines a beta-lactam and cilastatin (an enzyme inhibitor that blocks the extensive renal metabolism of the drug) and has found a place in the ICU as a broad spectrum agent in the treatment of severe infections with minimal side-effects; it is particularly indicated for the treatment of nosocomial multi-resistant infections, but is expensive and needs to be kept as a last resort agent to preserve its therapeutic range of activity.

(i) The treatment of pneumonias due to Gram negative organisms with aerosolised antibiotics

Despite broad clinical experience with Gram negative pneumonia, there is no consensus about the optimal number of antibiotics for therapy, or the length of treatment. The response of nosocomial Gram negative pneumonia to appropriate antimicrobial therapy is recognised often to be poor; this has been attributed to poor penetration of the bronchial secretions by the aminoglycosides, even in the face of adequate serum levels, binding of these drugs within the bronchial tree, and a possible inhibitory effect of the low pH of purulent bronchial secretions.

While the endotracheal administration of antibiotics for the prophylaxis of nosocomial pneumonia remains controversial as a result of the above studies, others have attempted a similar form of therapy for the treatment of established severe Gram negative bronchopneumonia, rather than as prophylaxis. The appeal of this form of therapy lies in its ability to place the antibiotic at the site of infection, while still theoretically avoiding the problems of systemic toxicity.

Klastersky et al [294] reported a study, conducted over a two year period in a neurosurgical ICU in Brussels, to evaluate the efficacy of endotracheally administered aminoglycosides as prophylaxis, or therapy, for Gram negative nosocomially acquired infections in intubated patients.

Inclusion criteria for this study were the presence of a tracheostomy or endotracheal tube, a depressed level of consciousness and purulent sputum in which Gram negative bacilli were evident on smear, and which were cultured as the predominant organism; clinical and radiological signs of pulmonary parenchymal involvement, with fever and an increased white cell count, as well as a normal serum creatinine. The diagnosis of pneumonia further required the agreement of two separate observers. All patients received a minimum of four days of therapy, the mean in the active group being 7.3 days vs 6.9 days in the control.

The study was a double-blind design with endotracheal administration of sisomicin or placebo being performed three times a day. All patients also received intravenous sisomicin and carbenicillin. A "favourable" response to therapy was regarded as an improvement in the clinical and radiological signs of bronchopulmonary infection, with the patient surviving the episode or dying from an unrelated cause at least 72 hours after the completion of therapy. Eradication of the organisms from the sputum was not a prerequisite for considering the response to therapy as favourable.

There were 20 patients enrolled who received placebo and 18 who received sisomicin. The patients were comparable in terms of age, sex, and underlying disease.

Colonisation by potentially pathogenic bacteria in the trachea occurred in 5 patients receiving placebo and in 7 treated with sisomicin; in all instances bar one, the organism was sensitive to sisomicin. A new clinical pulmonary superinfection occurred in 3 patients receiving placebo and 4 treated with endotracheal sisomicin.

The levels of sisomicin in the serum and in bronchial secretions were measured in 17 patients in both groups; the aminoglycoside levels in the bronchial secretions of those receiving endotracheal placebo were considerably lower than the serum levels, and were not found to be bactericidal at one hour after administration. In those who received endotracheal and systemic therapy, however, both serum and bronchial levels were higher, and the bronchial levels were bactericidal. By measuring the levels of sisomicin late in the course of therapy in some patients, the authors established to their satisfaction, that accumulation had not occurred.

There was a favourable response to therapy in 45% of the patients who received placebo, and 77% of those who received endotracheally administered sisomicin; this difference was significant. There were similar numbers of infections due to *Pseudomonas aeruginosa* in both groups, 50% of those in the placebo group responded to endotracheal administration of placebo plus systemic therapy, while 75% showed a favourable response to endotracheal sisomicin.

The majority of deaths were attributed to noninfectious complications; 4 (20%) of those receiving placebo died from their underlying disease, while a further 4 were thought to have died as a result of infection. There were no deaths in those receiving sisomicin that were attributable to infection, although 5 (28%) patients died from their underlying disease, and 4 of these were documented to have had infections with *Pseudomonas aeruginosa*.

The emergence of sisomicin resistant organisms was not detected, and the therapy was well tolerated. Although the numbers were small, this study also seemingly demonstrated an improvement in mortality with this form of therapy. However, the authors warn that this form of treatment should only be reserved for patients with documented Gram negative bacterial pneumonia, with careful microbiological surveillance to detect the possible emergence of drug resistant organisms; it is even recommended that patients receiving this form of therapy should be isolated.

Brown et al [295] more recently reported a multi-centre, prospective, double-blind study to determine the efficacy and safety of endotracheal tobramycin in the treatment of Gram negative bacterial pneumonia. Patients were randomised to receive either tobramycin or placebo, administered endotracheally every 8 hours, as well as intravenous tobramycin and either cefazolin or piperacillin. 85 patients (45 in the study group and 40 in the placebo group) were enrolled, of whom 41 were fully evaluable.

Diagnostic criteria for Gram negative bacterial pneumonia included an infiltrate on the chest radiograph, predominance of Gram negative organisms on Gram's stain of the tracheal aspirate in association with a predominance of leukocytes over squamous cells, grossly purulent tracheobronchial secretions, fever $>38^{o}C$ on rectal measurement and/or a leukocyte count of more than 10 000/ml or less than 5 000/ml with a left shift.

Patients receiving endotracheal tobramycin were more likely to have a bacteriological cure, and the pathogen was more often eradicated by endotracheally administered drugs than by those administered intravenously. Pathogens were eliminated in 56% of patients who received endotracheal tobramycin, compared with only 25% of those who received placebo which was statistically significant. The antibiotic serum levels in the two groups were similar, but had to be modified to maintain peak and trough levels. There was no more frequent emergence of drug resistance in the active group than in those who received placebo. However, analysis of the entire group demonstrated that symptomatic improvement, adverse events (including a worsening of renal function, and unexplained supraventricular tachycardia) and either clinical response or failure, occurred in a similar number of patients in both groups; the mortality was also not significantly different.

The authors concluded that endotracheally administered antibiotics could be used as an adjunct to systemic antibiotic therapy in the treatment of pneumonia, with good tolerance and safety.

This study was performed over an 18 month period as a multicentre study yet only succeeded in enroling 41 fully evaluable patients; the impact of more widespread use of endotracheal tobramycin on antimicrobial resistance patterns within a single unit is not established and, in view of the evidence of antibiotic resistance patterns associated with other topical regimens, warrants further study. The small number of patients makes interpretation of this carefully conducted study difficult. It is difficult to envisage much role for an expensive adjunct to more conventional therapy, associated with an increased incidence of unexplained supraventricular tachycardia, where the results failed to demonstrate any clinical improvement or reduction in mortality.

(ii) Other modalities

The other modalities for the treatment of pneumonia in the ICU include supportive care in the form of specialised ventilatory techniques to ensure both adequate oxygen delivery and uptake, techniques such as positive airway pressure ventilation, physiotherapy and the use of bronchodilators.

The use of immunotherapy in the form of monoclonal antibody preparations directed against endotoxin, tumour necrosis factor, interleukin I and other cytokine mediators of the inflammatory cascade, although still in its infancy, appears to be showing promise in opening up a new therapeutic avenue, in the management of nosocomial infections and other causes of overwhelming sepsis, which lead to the development of organ dysfunction; thereby aiming to prevent the spiral into multiple organ dysfunction to septic shock and death. Although all extremely important and interesting, they are beyond the scope of this thesis.

8.2 The treatment of urinary tract infections

In general it is not recommended that asymptomatic bacteriuria should be treated. However, Krieger et al [76] demonstrated that bacteriuria due to *Serratia marcescens* was associated with a high incidence of bacteraemia, and thus in such cases, earlier

therapy is probably indicated. There are no trials available looking at the most appropriate management of such clinical situations.

With or without antimicrobial therapy, most cases of catheter-associated bacteriuria should disappear spontaneously on removal of the catheter. However, patients with catheter-associated bacteriuria are thought to have an increased incidence of post-catheterisation symptomatic urinary tract infections; thus the use of antimicrobial therapy in patients with bacteriuria who are about to have their catheters removed may be appropriate.

For the patient who develops symptoms and signs of bacteraemia, the physician needs to exclude other potential sources of sepsis, by culturing all potential sites, including the blood. If results of surveillance samples are available, these may be valuable in guiding initial empirical antibiotic therapy. The antibiotic selection needs to be based on the knowledge of the locally prevailing organisms and their sensitivity patterns. It would seem to be good practice to remove a potentially colonised and infected catheter, if infection or heavy colonisation are detected.

8.3 The treatment of vascular catheter-related sepsis

Despite careful attention to aseptic technique during the preparation and administration of intravenous solutions, the infusion and its apparatus are likely to continue to be needed to be considered as a potential source of sepsis, in the differential diagnosis of fever. There are no clinically distinguishing features to assist in the diagnosis, and a high degree of suspicion with a low threshold for the removal of all intravenous lines needs to be maintained to prevent the potentially serious sequelae that can follow catheter-related sepsis. The placement of the catheter for more than 48 hours, or the presence of phlebitis at the infusion site if noted, should both suggest that the intravenous line is a possible cause of infection - phlebitis is reported to be a feature in over half of all episodes of catheter-related septicaemias [80].

The most common organisms causing bacteraemias related to intravenous line infections are the Staphylococci, while Gram negative bacteria normally account for about one third of such cases [90,93]. Multiply resistant coagulase negative staphylococci are becoming increasingly common causative organisms of line sepsis, particularly in patients who have already received antibiotic therapy, and accounted for 44% of the organisms isolated in the study by Brun-Buisson et al [90], although they were less important in causing clinically significant infection. If it is suspected that the intravenous catheter is the source of sepsis and this organism is implicated, therapy with cloxacillin, fucidin, clindamycin or vancomycin should be commenced, and the catheter removed.

One of the most serious complications of intravenous therapy is the development of suppurative thrombophlebitis. Patients with burns are the most susceptible, and this complication is frequently the cause of death in such patients. The diagnosis may go entirely unsuspected antemortem, as local signs of inflammation are reported to be absent in up to 70% of cases, and the signs and symptoms may only manifest 2 to 10 days after the catheter has been removed [80]. The clinical suspicion of this complication requires immediate surgical intervention. Antibiotic therapy should be based on the Gram's stain of pus obtained from the vein, but if this does not show organisms, initial antibiotic therapy should be initially directed against methicillin-resistant staphylococci and Gram negative bacteria.

PART TWO

CHAPTER 9. ORIGINAL RESEARCH PROJECT

A DOUBLE BLIND, PLACEBO CONTROLLED EVALUATION OF THE EFFICACY AND SAFETY OF CEFOTAXIME PLUS SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT (SDD) AMONG CRITICALLY ILL PATIENTS IN AN INTENSIVE CARE ENVIRONMENT

Investigator

J.M.J. Hammond

Respiratory ICU

Department of Medicine

University of Cape Town and Groote Schuur Hospital

Co-investigators:

Professor P.D.Potgieter

Head of Respiratory ICU

Department of Anaesthetics

University of Cape Town and Groote Schuur Hospital

Professor A.A.Forder

Head of the Department of Medical Microbiology

University of Cape Town and Groote Schuur Hospital

Dr G.L.Saunders

Department of Medical Micobiology

University of Cape Town and Groote Schuur Hospital

This study was sponsored by Roussel Laboratories.

Introduction

This study protocol was developed in 1988, at which time many of the studies reviewed above had not yet been either performed or published. The study protocol which follows is the original protocol, which was used for the study which was performed from January 1989 to December 1990.

9.1 Protocol

Nosocomial infection is recognised to be a major cause of morbidity and mortality in patients requiring admission to the intensive unit. The overall incidence in our local respiratory ICU was reported to be 23.6% [148] and, as in other centres, the most important site of such infection is the lower respiratory tract.

The majority of nosocomial infections are thought to be due to endogenous organisms, resulting from the aspiration of the secretions from the oropharynx and gastrointestinal tract, which have become colonised by resistant organisms from the hospital environment. Both the severity of the patient's illness and the excessive use of antimicrobial agents, alter the normal anaerobic flora of the gastrointestinal tract which usually provides colonisation resistance against colonisation with other more potentially pathogenic bacteria. The use of antacids and H-2 antagonists, which are often routinely used to prevent stress ulceration, also alter the protective acid barrier of the stomach and may thereby promote colonisation of the stomach and oropharynx. Studies using sucralfate rather than antacids or H-2 antagonists have reportedly reduced nosocomial respiratory infections from 34% to 10.3% [55,62].

Recent studies using selective decontamination of the digestive tract (SDD) with preservation of the anaerobic flora, have shown marked reduction in gastrointestinal colonisation, where potentially pathogenic aerobic Gram negative bacteria are eliminated from the gastrointestinal tract with the use of non-absorbable antibiotics. The studies have been extended with inclusion of parenteral cefotaxime for the first 48 hours of treatment, and more recent studies have shown a significant reduction in the incidence of nosocomial infections. However, the overall mortality has remained unchanged, except in selected groups, such as trauma patients [243,263,296].

The above studies support the use of these regimens in the intensive care unit to reduce the incidence of nosocomial infections. However, recommendations that they should be widely accepted were criticised in correspondence in the Lancet (Noone, Bunney, Inglis, Lancet 1988; 18 June : 1388-1389). All these previous studies had used historical controls rather than concurrent controls, which might have influenced the results, as it is well recognised that infections frequently follow cyclical changes which may be unexplained. A number of confounding factors, including the lack of control of H-2 antagonists may also have influenced the results; if the gastric acidity is controlled

there may be no further reduction in the nosocomial infection rate, colonisation or mortality in selected groups. These previous studies have shown no influence on the duration of stay in intensive care, and varying effects on the mortality. Other centres such as the Royal Free Hospital in London have achieved equivalent results with other regimens illustrating the need for results to be interpreted in the light of the prevailing conditions where the study was carried out.

Similarly, this regimen, which is designed to prevent nosocomial infection, needs to be thoroughly evaluated in the environment where it will be used before becoming common practice, in order to ensure that it achieves its aims of reducing morbidity, mortality and the overall cost of intensive care. Furthermore, a revised study protocol using concurrent controls and avoiding earlier flaws in study design should eliminate the previous criticisms.

2. Objectives

The objective of this study is to determine the effectiveness of selective decontamination of the digestive tract in the prevention of secondary infections occurring after 48 hours of admission to the ICU, and within 48 hours of discharge from the ICU, in critically ill patients and to determine whether SDD is cost-effective in the management of seriously ill intensive care patients. This will be evaluated in terms of the incidence of morbidity and mortality, secondary infection and the additional costs incurred in the investigation and management of these secondary infections.

3. Design

This study is a double-blind placebo controlled comparative evaluation of the selective parenteral and enteral antisepsis regimen (SPEAR) in the prevention of acute secondary infections in critically ill patients in the ICU environment in the Groote Schuur Hospital, Cape Town. Patients will be entered to the trial on admission to the Unit.

4. Patient Selection

4.1 Patient Inclusion Criteria

4.1.1 Patients who are likely to be intubated for at least 48 hours and stay 5 days in the ICU should be included. The outcome in others excluded who meet entry criteria should be analysed separately.

4.1.2 Those who fail to meet the entry criteria, after randomisation, will be excluded from analysis.

4.2 Patient Exclusion Criteria

The following patients will **not** be enrolled:

4.2.1 Patients with a history of hypersensitivity to any of the investigational drugs, or a history of documented anaphylactic reactions to the penicillins.

The patient can be withdrawn if the clinician feels it to be in the patient's own interest.

5. Procedures

5.1 Dosage and Administration

Patients will be reviewed by a designated Critical Care staff member and allocated according to a randomised code list to either the test group or the control group.

The SDD and cefotaxime will be administered as follows:

a) SDD gel 5g (Amphotericin B 2%, Polymyxin E 2% and Tobramycin 2%) applied to the oral mucosa 6 hourly with a prefilled disposable syringe and spread evenly with a gloved finger, throughout the period of intubation and up to 48 hours after extubation. An identical placebo gel will be used in the placebo group.

b) SDD liquid 10 ml (Amphotericin B 500 mg, Polymyxin E 100 mg, Tobramycin 80 mg) delivered orally or per nasogastric tube 6 hourly. If a nasogastric tube is used, gastric suction will be discontinued one hour after each dose throughout the stay in the ICU.

c) Cefotaxime 1g intravenously 8 hourly administered on admission and continued for the full first 72 hours of the study. The dosage will be adjusted according to body weight in patients less than 50 kg: to 50 mg/kg body weight per day. All patients in the study (including the placebo group) will receive cefotaxime or a previously prescribed antibiotic as mentioned in (d).

d) Patients arriving in the ICU and already receiving an antibiotic (other than cefotaxime) will be kept on that antibiotic if the organism(s) involved show sensitivity.

Patients on prophylactic antibiotics following surgery or trauma patients on antibiotics other than cefotaxime, will be changed to cefotaxime treatment.

5.2 Concurrent Treatment

Non-antimicrobial drug therapy may be administered concurrently, but must be recorded on the case report form. Probenecid and antimicrobial therapy (other than cefotaxime and the SDD antimicrobials) will be documented on the case report form. H-2 antagonists will be used in patients with known ulcer disease and evidence of overt gastrointestinal bleeding, and in other high risk patients (burns, severe head injuries and liver failure). No other anti-ulcer preparations will be allowed.

If antimicrobial therapy other than cefotaxime is indicated by clinical or microbiological findings, the oral decontamination therapy may be continued at the discretion of the physician.

Inappropriate metronidazole should be discontinued and patients will remain on the trial, otherwise metronidazole may be continued.

Surgical procedures may be performed but must be documented on the case report form.

6. Evaluation Criteria

Objectives

1. To determine the incidence of secondary infections occurring 48 hours after admission to the ICU. Hospital and community acquired organisms will be evaluated separately.

2. To evaluate the effect of this regimen on the clinically significant isolates in the Unit. The resistance patterns of clinically significant isolates in the ICU from 12 months preceding the trial will be compared with the last 12 months of the study period.

3. To analyse mortality rates in:

* death of patients staying longer than 5 days in the ICU

* death of patients with an admission APACHE II score of <17 , 17 - 30 , >30.

4. To evaluate total cost involved of antibiotics used during patient's stay in the ICU relating to

* SDD regimen

* treatment of secondary infection

6.1 Clinical Criteria

A medical history will be taken and a complete physical examination will be performed on admission before SDD and cefotaxime therapy, to detect the clinical signs of any infection of the pulmonary system, the intravenous line, the urinary tract, soft tissue sepsis, or generalised septicaemia. (See Appendix for definitions). Evaluation of the severity of the illness according to the APACHE II score and organ failure will be calculated on admission. Injury severity scores will be calculated on admission in injured patients. During treatment, patients will be observed daily to evaluate their clinical status and to detect evidence of systemic or local infections. The physical examination will be repeated within 48 hours after the completion of therapy.

6.2 Laboratory Determinations

Routine laboratory evaluation (haematology, chemistry, bacteriology) should be carried out as usual.

6.3 Bacteriology

6.3.1 Screening

Aerobic bacterial cultures will be obtained from the oropharynx (properly taken swab), gastric aspirates (obtained via nasogastric tubes), rectum (faecally-soiled swab), urine, tracheal aspirates in intubated patients, and wounds (when present) on the day of admission, and twice weekly thereafter with specific identification of Enterococci, *Acinetobacter*, Pseudomonas, *Klebsiella spp*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and yeasts. Intravenous catheters will be cultured on removal. Colony counts for Gram positive and Gram negative bacteria and yeasts will be recorded. Cultures will be done twice weekly, on discontinuation of the study and 3 days after discharge from the Unit if the patient is still hospitalised.

6.3.2 Clinical

When an acute infection is suspected clinically appropriate additional cultures will be obtained for the isolation, identification and sensitivity testing of the causative pathogen(s). The source of the cultures must be recorded on the case report form. Where multiple cultures of the same site are taken, it must be so indicated.

All these results will be maintained on a daily updated log for screening cultures and clinical cultures.

6.4 Sensitivity Testing

Susceptibility testing of the pathogenic organism(s) to cefotaxime sodium will be determined by disc sensitivity using a 30 ug cefotaxime disc or by determination of the minimum inhibitory concentrations (MICs). As determined by the Kirby-Bauer method, organisms are susceptible to cefotaxime if the zone of inhibition is >20mm. Disc sensitivity findings of 15 to 19 mm (intermediate zone) indicate that the organisms may be susceptible if a higher dosage of cefotaxime is used. A disc sensitivity finding of <14mm indicates resistance to cefotaxime. The MIC breakpoints are sensitive at < 16ug/ml and resistant at >64 ug/ml. Susceptibility testing will only be performed on pathogenic isolates (Eg in blood or otherwise sterile body fluids) and surveillance culture isolates from wounds, tracheal aspirates and urines when colony counts of bacteria exceed 10^3 organisms/ml.

7. Adverse Experiences

Any adverse experience occurring during the study must be reported in the case report form. The investigator must state whether the cause of the adverse experience was related to the study drug, concurrent drug therapy, an underlying disease, a combination of these factors, or is unknown. Patients with an adverse experience will be carefully followed-up to determine the outcome. If a serious or alarming adverse

experience occurs which may be related to the study drug, therapy will be discontinued immediately and the patient will be treated accordingly.

8. Institutional Review Committee

In accordance with the Medicines Control Council of South Africa, the appropriate Ethical Committee must review this protocol.

The Ethics Committee of the University of Cape Town approved the protocol.

9. Informed Consent

This should be given by the patient or a family member where indicated, prior to entry to the study.

Prior to the commencement of the study, the protocol was altered to allow patients to be enrolled, if the attending physician who was not involved in the trial, agreed. At this stage, this technique was already an accepted form of prophylaxis, and none of the drugs used was experimental. This modification was accepted by the Ethical Review Committee.

10. Confidentiality

All personal information pertaining to patients during this study and in any subsequent reports will be kept confidential. Patients will be identified by their names, and by a patient number.

11. Statistical Evaluation

Statistical planning of the study involved the Department of Biostatistics at the Medical Research Council. It is planned to enrol 400 evaluable patients into the study, which should provide a sufficiently powerful model to show a statistical difference in mortality, as well as reductions in the incidence of infection and morbidity, based on

the current mortality and infection rate in the ICU and previously reported studies on SDD. With a confidence interval of 95% and power of 80%, a 50% reduction in the mortality rate of 25% should be demonstrated by enrolling 334 evaluable patients, while a 50% reduction in the infection rate from 23% should be able to be achieved with 370 patients.

Data is to be gathered using a DBase IV programme data-base, and the statistical analysis will be performed using Epi-Info Stat-Calc (U.S.Department of Health and Human Services/Public Health Service/Centres for Disease Control, Atlanta, USA), and Statgraphics and these statistics would be complemented by the assistance of the Department of Biostatistics (Dr Carl Lombard) at the Medical Research Council. Statistical methods will include exact Chi-square testing for comparison of patients with multiple infections, Chi-square 2x2 tables for comparing two binomial proportions, and Fisher's exact test for small sample sizes, with t-testing for continuous variables, and confidence intervals where appropriate.

Appendix

DEFINITIONS OF INFECTION

Endpoints for infection are defined as follows:

I. A significant organism is a pathogenic organism(s) isolated in association with the following clinical infections:

a) Septicaemia:

The clinical observation of all of the following:

1) a rise or fall in the temperature

2) a rise in the white cell count or a left shift in its morphology

3) evidence of organ dysfunction such as hypoxaemia, renal dysfunction, hepatic dysfunction, central nervous system dysfunction etc.

4) a positive blood culture.

b) Nosocomial Pneumonia:

A new radiological infiltrate on the chest X-ray occurring 48 hours after admission to the ICU with all of the following findings:

1) purulent sputum with more than 25 leukocytes and less than 10 squames per low power field

2) increased temperature $>38^{o}C$

3) increased white cell count $>10\ 000/ml$, an increasing white cell count ($>2\ 000/ml$) or a shift the morphology of the white cells

4) respiratory or nosocomial pathogen cultured from the tracheal aspirate

5) deterioration in gas exchange (PaO_2 decrease of more than 2kPa)

c) Bronchial infection was defined as all of the following:

1) purulent bronchial secretions with more than 25 leukocytes per low power field

2) increased temperature

3) increased white cell count ($>10\ 000/ml$) or left shift

4) respiratory or nosocomial pathogen cultured from secretions

5) no radiological changes.

Colonisation of the bronchial tree was defined as the culture of the same organism on 2 or more occasions without the signs of a systemic infection.

d) Urinary tract Infection

in the non-catheterised patient:

a urine culture yielding more than 100 000 colony forming units of aerobic bacteria, or fungi with dysuria and pyuria (> 10 white cells per high power field).

in the patient who had either been catheterised for more than 48 hours before collection of the specimen or who was catheterised during the 48 hours prior to the collection of the specimen:

bacteria in the urine
white cells in the urine
local or systemic signs of infection.

Colonisation of the urinary tract was defined as the culture of the same organism on 2 or more occasions without the signs of systemic infection.

e) Wound Infection: positive culture of aerobic or anaerobic bacteria, or fungi, in the presence of pus draining or aspirated from a wound.

f) Abscess, Phlegmon or other fluid collection: a positive culture of aerobic or anaerobic bacteria, or fungi, obtained from a localised tissue collection.

g) Sinusitis: clouding of a sinus on X-ray and clinical features of infection with isolation of bacteria (aerobic or anaerobic) or fungi from an aspirate of the sinus or a nasal discharge in the presence of white cells.

h) Enteritis : the isolation of enteric bacterial pathogens or Clostridium difficile toxin in the presence of diarrhoea or mucosal changes on proctoscopic examination.

i) Vascular catheter- related sepsis defined as all of the following:

1) an increased temperature ($>38^{o}C$)

2) an increased white cell count ($>10\ 000/ml$) or a left shift in the white cell morphology

3) defervescence of symptoms on the removal of the catheter

4) with or without a positive catheter tip culture or blood culture

5) with or without evidence of local inflammation.

Colonisation of an intravascular device was defined as a positive culture without signs of local or systemic infection.

9.2 : PRESENTATION OF RESULTS

9.2.1 Introduction

The aim of performing this double-blind randomised study of selective decontamination was to evaluate accurately the efficacy of this technique in reducing the incidence of nosocomial infection, its associated morbidity and mortality, as well as its cost-effectiveness and potential effects on the microbial flora. As outlined above, there have been numerous studies on selective decontamination, but the majority have not been blinded or have used historical control groups, with post hoc stratification to identify sub groups that might benefit from the use of this technique; the studies have also been too small to establish a conclusive role for this technique.

9.2.2 Patients and Methods

All patients admitted to the multi-disciplinary respiratory ICU who were considered to be at high risk of developing secondary infection, because of an expected duration of intubation of at least 48 hours, and an anticipated duration of stay of at least 5 days were included in this study. This assessment was made by the attending physician using guide-lines from previous analysis of admissions to this unit, which had showed that

patients with asthma, overdoses and those admitted electively postoperatively, were unlikely to meet these criteria. Data was also collected on patients who were not enrolled, but who subsequently fulfilled the enrollment criteria, in order to seek selection bias and provide an additional control group; this data was analysed separately.

Consent for enrollment to the trial was obtained from the patient, a close relative, or the responsible physician (who was not taking part in the study) if no-one else was available, as the study was not investigating a new drug, but designed to assess the efficacy of a regimen of drugs of established safety and efficacy. Only patients with a history of hypersensitivity to the study drugs, or of anaphylaxis to penicillin were excluded. The study was approved by the ethics committee of the University of Cape Town.

On admission, patients were randomised by computer-generated numbers to groups receiving placebo or the SDD regimen, and either regimen was commenced within 6 hours of admission. The regimen consisted of 2 ml methylcellulose gel containing amphotericin B 2%, tobramycin 2% and polymyxin E 2% applied to the oral mucosa every 6 hours with a gloved finger (or an indistinguishable placebo), and 10 ml of a solution of amphotericin B 500 mg, tobramycin 80 mg and polymyxin E 100 mg by mouth or nasogastric tube (or 10 ml of indistinguishable placebo solution). Nasogastric suction was discontinued for one hour after each dose of SDD.

Cefotaxime 1g 8 hourly was given intravenously to all patients for 72 hours; it was felt that the use of intravenous placebo instead of the active antibiotic might have necessitated the withdrawal of excessive numbers of patients to establish whether they were receiving the active medication. Patients already receiving an antibiotic for a pre-existing infection on admission to the ICU were continued on the antibiotic if the sensitivity patterns were appropriate, or if the patient appeared to be responding; otherwise, if appropriate, cefotaxime was substituted.

No use of anti-cytokine therapy was made for the duration of the study.

No routine prophylaxis against gastrointestinal bleeding was used. Ranitidine was used in patients with pre-existing ulcer disease or active gastrointestinal haemorrhage, and in those at high risk of gastrointestinal haemorrhage (from burns, liver failure or head injury). Sucralfate was not used for the duration of the study, because it is thought to bind to enteral medication and might thus have inactivated the drugs administered for decontamination,[64] and also because of its own antibacterial properties [59] which might have caused difficulty with the interpretation of results.

The respiratory ICU, in which the study was conducted, comprises two units with a total of 10 beds and admits patients with medical, surgical, obstetric and gynaecological diseases, including patients who have sustained multiple trauma, although patients with primary head injuries are admitted to the neurosurgical ICU.

Patients were fully examined on entry, an admission diagnosis was defined and the severity of illness was assessed according to the APACHE II [297], organ failure [298] and injury severity scoring systems [299]. Factors recognised as likely to affect the development of secondary infection [30,203], such as the presence of diabetes mellitus or other immunocompromising diseases, the presence of malnutrition, alcohol abuse, the use of steroid and other immunosuppressive therapy, and the use of antacids or H-2 antagonists were documented specifically.

In all intubated patients, nasogastric tubes were placed for the duration of ventilation. Patients were intubated via the nasal route unless there was a specific contraindication to this. In the majority of patients requiring intubation for more than 10 to 14 days, a tracheostomy was performed.

Routine investigations included daily chest radiography during ventilation, laboratory evaluation of haematology, serum and urine chemistry; other investigations were performed as necessary. Clinical microbiological surveillance studies were performed

twice weekly and more often if indicated. Daily clinical examinations including monitoring for evidence of secondary infections were performed, and a careful note was made of all complications that developed while in the ICU.

Specific note was taken of factors and their duration which might predispose to the development of secondary infection while in the ICU, including the level of consciousness, the degree of sedation and mobilisation, the presence of bulbar dysfunction, the presence of ileus, and the use of invasive therapeutic and monitoring devices, such as intubation, ventilation, plasma exchange, dialysis, nasogastric drainage, total parenteral nutrition, which might have been required as part of management. Follow-up of all patients was continued until discharge from hospital.

Nosocomial infection was diagnosed if signs developed more than 48 hours after admission to the ICU. The following definitions of infection were used:

Septicaemia was diagnosed as the clinical observation of all of the following with no obvious localising site of infection:

a positive blood culture

a rise or fall in temperature ($> 38^{o}C$ or $< 35.5^{o}C$)

a rise in white blood cell count ($> 10\ 000$/ml), or a left shift in its morphology

evidence of organ dysfunction. Criteria for organ dysfunction were defined as follows:

lung: PaO_2 < 8kPa on 40% oxygen, or respiratory rate < 5/minute or > 49/minute, or $PaCO_2$ > 6kPa, or $AaDO_2$ > 46 kPa, or dependent on ventilator for > 4 days.

kidney: urine output < 479ml/24 hours, or < 159ml/8 hours, or serum creatinine > 300 mmol/l, or serum urea > 20 mmol/l.

liver:liver enzymes more than twice normal or total bilirubin > 50 mmol/l.

central nervous system: unconscious with a Glasgow coma scale of < 6 without the use of sedatives for more than 24 hours

haematological: white cell count < 1 000/ml, or platelets 20 000/ml.

cardiovascular: mean blood pressure < 49 mm Hg, or pH < 7.24.

Nosocomial pneumonia was defined as a new infiltrate on the chest radiograph more than 48 hours after admission to the ICU, purulent bronchial secretions with many leukocytes, temperature above 38°C, white blood cell count > 10^{10}/l , increasing or showing a left shift, substantial numbers of organisms shown by Gram staining of the tracheal aspirate, with a pure growth cultured from the tracheal aspirate, and a deterioration in gas exchange of 2kPa or more.

Bronchial infection was defined by the presence of all the features of pneumonia, except the radiographic changes.

Urinary tract infection in patients who had been catheterised for at least 48 hours before collection of the specimen, was defined by the presence of local or systemic signs of infection, with culture of bacteria or yeasts, and the presence of more than 10^8 white cells per litre of urine.

Vascular-catheter related sepsis was defined as temperature above 38°C, white blood cell count above 10^{10}/l or left shift, with relief of signs on removal of the catheter; a positive catheter tip culture, blood culture, or the presence of local inflammation were not required for the diagnosis.

If a nosocomial infection was diagnosed, appropriate cultures were taken for isolation, identification and sensitivity testing of the causative organisms. All central venous catheters were cultured on removal. The results of diagnostic and clinical surveillance samples were available to the clinicians.

Aerobic cultures of oropharyngeal swabs, gastric aspirates, faecally soiled rectal swabs, urine, tracheal aspirates, wound swabs, or other secretions were taken on admission and then twice a week throughout the ICU stay; final specimens were taken 3 days after discharge from the ICU. To avoid carry-over of topical antibiotics from the SDD regimen, specimens were plated out, then placed in 10ml broth overnight to dilute any antibiotics present. Growth density was graded 1-5 by a semiquantitative method [243].

Enterococci, Acinetobacter spp, Pseudomonas spp, Klebsiella spp, Staphylococcus aureus, Staphylococcus epidermidis and yeasts were identified and antibiotic sensitivity patterns tested by standard disc-diffusion methods. *Enterobacteriaceae* were identified to species.

The clinical cause of death was characterised as unrelated, possibly related or definitely related to secondary infection; when possible these results were confirmed at autopsy.

The costs of SDD and the additional costs of investigation and treatment of any episodes of nosocomial infection were recorded.

Statistical analysis was done using the statistical programme "Statcalc" of Epi-Info (Version 5) (U.S.Department of Health and Human Sciences/Public Health Service/Centre for Disease Control U.S.A.); the "Statgraphics" programme and the Medical Research Council Department of Biostatistics (Dr Carl Lombard). Chi-square testing with 2x2 tables and 2x5 tables for categorical variables, Fisher's exact test for small sample sizes, contingency tables, Wilcoxon-rank, Student's t test for continuous variables and confidence intervals, were used where appropriate.

9.2.3 Results

Between January 1989 and December 1990, 719 patients were admitted to the Respiratory ICU, of whom 322 fulfilled the criteria for study entry on admission. 83 were subsequently withdrawn: 3 for protocol violations (1 patient refused to continue with the enteral medication, 1 patient was suspected to have a drug allergy to the enteral medication, but was later found to have received placebo, and 1 patient was treated with sucralfate), and the remaining 80 because their duration of ICU stay was too short. 28 of those excluded, none of whom developed infection, died within 5 days of admission. There were, in addition, 36 patients who were not initially included, but who were subsequently found to have satisfied the study criteria; their data was analysed separately.

The various groups were similar in terms of baseline characteristics (Table Seven).

Table Seven - Baseline Characteristics**

	SDD group n=114	Placebo group n=125	Withdrawn n=83	Suitable but not included n=36
Mean age	43.5 ± 15.5	43.5 ± 16.5	42.7 ± 16.3	46.3 ± 16.6
Male/female	67/47	69/56	47/36	14/22
Race				
Black	33	32	25	7
White	20	21	16	3
Mixed	61	72	42	26
APACHE II	13.9	14.0	16.9	14.8
SD	± 8.4	± 7.1	± 10.2	± 8.9
Organ	1.29	1.34	1.45	1.25
failure*	± 0.55	± 0.55	± 0.85	± 0.56
ISS	28.9	28.4	20.5	32.7
	± 14.0	± 13.5	± 11.5	± 11.9

**By Knaus' criteria* 298

± values are standard deviation

ISS: Injury Severity Score 299

*** No statistical difference between the active and control groups, or "suitable" group was found, using Chi square, Student's t and contingency tables where appropriate.*

The medical diagnoses and surgical categories of the patients are shown in Table Eight. The diagnoses are similar in all groups, other than the patients who were suitable,

where there were more asthmatics and other disease categories not normally thought likely to lead to prolonged ICU admission.

Table Eight: Diagnosis on Admission

	SDD 114	Placebo 125	Withdrawn 83	Suitable 36
Medical	59	77	53	20
Asthma	4	1	1	8
COAD	3	5	11	0
Pneumonia	12	24	7	3
ARDS	4	9	4	0
Other resp	9	6	9	0
Neurological	12	19	9	4
Cardiovascul	3	1	2	1
Poisoning	0	0	3	1
Other diseas*	12	12	7	1
Surgical	16	15	15	3
Cardiothorac	1	2	1	1
General surg	10	10	7	0
Obst & gynae	5	2	4	0
Orthopaedic	0	1	3	2
Trauma	39	33	15	13

Other diseases*	SDD	Placebo	Withdrawn	Suitable
Septicaemia	7	9	0	1
Connect Tis	2	1	2	0
Glomneph	2	0	1	0
Hypothermia	1	0	0	0
35% burns	0	1	0	0
Liver fail	0	1	2	0
Leukaemia	0	0	1	0
Septic abort	0	0	1	0

No significant difference between the 4 groups, using Chi square and contingency tables.

The prevalence of pre-existing disease and the incidence of other immunocompromising factors during ICU stay were similarly distributed between the SDD and placebo groups (Table Nine)

Table Nine: Underlying disease and Immunocompromising Factors

	SDD n=114	Placebo n=125	Withdrawn n=83	Suitable n=36
Cyclophos	1	1	1	0
Cytotoxic	0	0	1	0
Medrol	1	1	1	0
Pred >40mg	1	2	3	2
Pred <40mg	7	6	4	6
Total drugs	10	10	10	8
Carcinoma	5	2	5	0
Diabetes	8	10	7	5
Conn tiss dis	1	4	2	0
Malnutrition	11	10	6	2
Obese	11	19	9	6
Alcohol abuse	20	35	17	7
Peptic ulcer	6	7	5	2
Shocked on adm	16	11	10	3
Emerg surg	9	8	5	0
Infected on admission	59	76	30	26

(Cylophos =cyclophosphamide, cytotoxic = antineoplastic chemotherapy, pred = prednisone, conn tiss dis = connective tissue disease)
Malnutrition and obesity were judged clinically.
Alcohol abuse was defined as >4g alcohol/day: (>1 bottle wine/>4 tots/>5 beers/day).
Shocked on adm (admission) was defined as a systolic blood pressure for less than 70mm Hg for more than one hour.
Univariate statistical analysis of the factors potentially predisposing to infection was performed using Chi-square, Mantel-Haenszel, Phi Coefficient and contingency tables, but failed to demonstrate any difference between the active and placebo groups.

Other factors predisposing to nosocomial infection were also distributed with equal frequency between the active, placebo and suitable groups (Table Ten).

The neurological status was assessed according to the following schema:

1. Orientated: fully responsive and aware of surroundings
2. Confused: inappropriate response
3. Unconscious: not responding to verbal commands
4. Comatose: not purposeful response to pain (i.e. Glasgow coma scale < 6)

Table Ten: Factors Predisposing to Secondary Infection in the ICU*

	SDD n=114	Placebo n=125	Withdrawn n=83	Suitable n=36
Albumin <30mmol/l	77	83	34	17
Coma day 3	34	49	12	16
Coma 4	25	30	17	10
Bulbar dysfunct	9	5	1	0
Bedbound >5 days	81	96	6	30
Ulcer	27	33	15	3
Femoral line	11	9	1	3
Ileus >5 days	41	36	3	8
TPN	32	44	6	10
Enteral feed	96	117	46	31

** No statistical difference between the groups was demonstrated using Chi square.*
Coma day 3 was a neurological grade ≥ 3 for 3 days
Coma 4 was a neurological grade of 4 at any stage (Glasgow coma scale <6).
Bulbar dysfunction was documented according to whether the patient was able to swallow his secretions or required dental suction and/or a vocal aid added to the tracheostomy.
Bedbound > 5 days: Mobility of the patient was documented as to whether the patient was able to be mobilised to a chair within 5 days.
Ulcer therapy: denotes whether the patient required ranitidine for suspected or proven gastrointestinal bleeding.
Femoral line: denotes the presence of an intravenous femoral catheter for access, dialysis, plasma exchange etc. The risk of catheter-related sepsis is highest at this site.
Ileus > 5 days denotes patients who required prolonged nasogastric drainage for persistent ileus for more than 5 days.
TPN denotes patients who received total parenteral nutrition.
Enteral feed denotes patients who were enterally fed via the nasogastric tube.

The following table documents the ventilatory therapy (Table Eleven) and again shows that there were no differences between the two groups that might have favoured the one developing infection over the other.

Table Eleven: Ventilatory Therapy

	SDD n=114	**Placebo** n=125	**Withdrawn** n=83	**Suitable** n=36
IPPV(no)	9	6	10	6
CPPV(no)	105	119	71	30
Trache(no)	39	52	5	11
ETT(days)	7.6	8.0	2.3	7.5
	± 5.4	± 5.2	± 1.1	± 4.8
Trache(days)	22.1	17.7	29.0	18.8
	± 16.1	± 13.8	± 42.5	± 14.8

± = plus or minus standard deviation.

IPPV denotes intermittent positive pressure ventilation

CPPV denotes continuous positive pressure ventilation

Trache denotes tracheostomy

ETT denotes endotracheal tube

No statistical difference could be demonstrated between the active and placebo groups, using Chi-square and Student's t tests.

Numerous devices and life-support procedures are recognised to be significant predisposing factors associated with the development of nosocomial infection. Of these, haemodialysis, plasmapheresis, central lines, particularly for the administration of TPN and pulmonary artery catheters, are recognised to be important. The frequency of their use was equally distributed in both groups, as is indicated in Table Twelve. Enteral feeds were used in significantly more patients in the placebo group, may have a

protective effect on the intestinal mucosa, but may also contribute to infection by introducing exogenous organisms, increasing gastric pH and facilitating aspiration.

Table Twelve: Invasive Procedures used in the ICU*

	SDD n=114	Placebo n=125	Withdrawn n=83	Suitable n=36
Haemodialys	8	11	1	1
Plasmapheres	5	4	0	0
Chest drain	37	42	11	11
Art. line	56	76 p=0.09	32	12
Central line	88	107p=0.13	48	23
Periph line	114	125	83	36
P A cath	75	80	43	25
TPN	32	44 p=0.29	6	10
Enteral feed	96	117p=0.03	46	31

Haemodialys denotes haemodialysis.

Plasmapheres denotes plasmapheresis.

Art line denotes arterial line.

P.A.cath denotes pulmonary artery catheter.

** No statistical difference was demonstrated between the active and placebo groups using Chi square tests.*

There was no significant difference in the number of patients who developed secondary infections between the active and placebo groups using Chi-Square (p=0.1714), categorical variables 2x5 (p=0.1368), exact Chi-square test (p=0.0523); however, when the Wilcoxon-rank test was used, ranking the number of infections per patient, it was possible to show a statistical benefit in the active group (p=0.0465).

The incidence of all infections (other than abscesses) but including respiratory tract infections, did not differ significantly between the placebo and active groups. The types of infection are shown in Table Thirteen. There were very few secondary infections encountered in the withdrawn group, as a result of the short duration of stay in the majority. In the suitable group, the incidence of secondary infection resemble that of the placebo group, reflecting the absence of selection bias, in spite of these patients requiring more prolonged admission than had been anticipated.

Abscesses occurred significantly more frequently in the placebo group. The aetiological agents causing the abscesses in the placebo group were : *E.coli* 2, *S.aureus* 3, *Enterobacter spp* 1, *Candida albicans* 4; in the active group there was only one soft tissue infection due to *S.aureus*. These abscesses were mainly intra-abdominal and, because of the small numbers involved, the significance of this finding is questionable.

Table Thirteen: Types of Infection

	SDD n=114	Placebo n=125	Withdrawn n=83	Suitable n=36
Infections:				
Total no	44	64	5	16
No of patients*	31	44 p=0.17	2	11
(%)	(26)	(34)	(2)	(33)
Pneumonia	8	8	1	1
Bronchial	15	20	3	10
Sinusitis	2	0	0	0
Septicaemia	7	10	0	1
IV catheter	6	9	0	1
Urinary tract	3	5	0	3
Abscess*	1	10 p=0.057	0	2
Wound	2	2	0	0

** p values with Chi-square testing.*

Table Fourteen shows the total number of organisms causing infection in the various groups. There were fourteen infections which were caused by multiple pathogens.

There was a significantly higher incidence of Gram positive infections in the patients who received SDD (p=0.003, Chi-Square testing), whereas in the placebo group, the incidence of Gram negative infections, especially infections caused by the *Enterobacteriaceae*, was significantly increased (p=0.022 and p=0.034, respectively). The suitable group again is shown to mirror the placebo group.

Table Fourteen: Organisms causing Infection

	SDD	Placebo	Withdrawn	Suitable
Gram positive	27	22 p=0.003	0	4
S.aureus	15	9	0	3
S.epidermidis	11	7	0	1
Enterococcus	0	3	0	0
S. milleri	1	1	0	0
Other *strep*	0	2	0	0
Gram negative	16	42 p=0.022	4	14
Enterobacteria	4	19 p=0.034	0	7
E.coli	0	7	0	3
Klebsiella spp	2	5	0	2
Proteus spp	1	1	0	0
Enterobacter	1	6	0	2
Pseudomonas sp	2	5	2	0
Acinetobacter	10	15	2	6
H. influenzae	0	2	0	1
M.catarrhalis	0	1	0	0
Candida	1	5	0	0
Viruses	0	1	0	0
Other	1	1	0	2

Table Fifteen demonstrates the organisms causing bronchial infections. There were no infections due to the *Enterobacteriaceae* in the SDD group, however, the number of infections due to *S.aureus* and the non-fermenters was similar in both groups. There were no infections caused by *Streptococcus pneumoniae* in either group, presumably as a result of the 72 hours of cefotaxime, although such infections were not encountered in the "suitable but not included" group either.

Table Fifteen: Organisms causing bronchial infections

	SDD	Placebo	Withdrawn	Suitable
S.aureus	7	5	0	2
S.epidermidis	1	0	0	0
H. influenzae	0	1	0	1
M.catarrhalis	0	1	0	0
E.coli	0	1	0	0
Klebsiella spp	0	1	0	0
Pseudomonas sp	1	3	1	0
Enterobacter	0	2	0	1
Acinetobacter	6	7	2	6
Other	0	0	0	1

Table Sixteen illustrates the organisms causing nosocomial pneumonia. Although the incidence of pneumonia was similar in both SDD and placebo groups, a pattern of causative organisms similar to those causing the bronchial infections is again seen. It is interesting to note that in the group receiving SDD, *S.epidermidis*, an organism not usually associated with pneumonia was considered to be the infecting agent in four cases of respiratory tract infection. *Acinetobacter spp*, a non-fermenting Gram negative organism, endemic to our ICU was the most common pathogen in all groups, and appeared to be uninfluenced by this regimen of SDD.

Table Sixteen: Organisms causing pneumonia

	SDD	Placebo	Withdrawn	Suitable
S.aureus	3	1	0	0
S.epidermidis	3	0	0	0
H. influenzae	0	1	0	0
M.catarrhalis	0	1	0	0
Klebsiella spp	0	1	0	1
Pseudomonas sp	0	1	1	0
Enterobacter	0	0	0	1
Acinetobacter	2	3	0	0
Other	0	1	0	0

Table Seventeen shows the organisms causing septicaemia. While a pattern and spectrum of pathogens similar to other sites was seen in both groups, it is interesting to note that an episode of fungaemia did occur in a patient receiving SDD.

Table Seventeen: Organisms causing Septicaemia

	SDD	Placebo	Withdrawn	Suitable
S.aureus	2	2	0	0
S.epidermidis	1	2	0	0
E.coli	0	1	0	0
Klebsiella spp	1	2	0	1
Pseudomonas sp	1	0	0	0
Enterobacter	0	1	0	0
Acinetobacter	2	2	0	0
Candida	1	2	0	0

Table Eighteen illustrates the pathogens identified in episodes of catheter related sepsis. The expected predominance of Gram positive infections is seen in both groups.

Table Eighteen: Organisms causing IV catheter related sepsis

	SDD	Placebo	Withdrawn	Suitable
S.aureus	1	0	0	0
S.epidermidis	3	4	0	0
Enterococcus	0	1	0	0
Other *strep*	0	1	0	0
Klebsiella spp	1	1	0	0
Enterobacter	0	2	0	0
Acinetobacter	0	2	0	0

Table Nineteen illustrates the aetiological agents identified in episodes of urinary tract infection. Such infections were extremely uncommon. It is important to note however, that episodes of heavy *Candidal* colonisation of the bladder were all treated by amphotericin B bladder washes, which may have eliminated these infections.

Table Nineteen: Organisms causing urinary tract infections

	SDD	Placebo	Withdrawn	Suitable
S.epidermidis	1	1	0	0
E.coli	0	3	0	2
Enterobacter	1	0	0	0
Proteus spp	1	1	0	0

Table Twenty shows the organisms responsible for other episodes of infection. There were only two episodes of sinusitis, despite nasotracheal intubation being the norm, and

both occurred in patients receiving SDD. There were two soft tissue infections in the SDD group, while, as mentioned previously there were significantly more abscesses in the placebo group.

Table Twenty: Other Sites of Infection

	SDD	Placebo	Withdrawn	Suitable
S.aureus	2	3	0	0
S.epidermidis	2	0	0	0
Enterococcus	0	1	0	0
S. milleri	1	1	0	0
Other *strep*	1	1	0	0
E.coli	0	2	0	0
Enterobacter	0	1	0	0
Pseudomonas sp	0	1	0	0
Acinetobacter	0	1	0	0
Candida	0	3	0	0
Other	0	1	0	0

Pre-admission colonisation by aerobic Gram negative bacilli of the gastrointestinal tract was similar in both groups; in the SDD group, clearance of aerobic Gram-negative bacilli from the gastrointestinal tract was effective. Approximately 30% of the surveillance cultures of the stomach and oropharynx on admission, showed colonisation by aerobic Gram negative bacilli. The clearance of organisms from these sites with SDD occurred within approximately 72 hours of admission, whereas, the rectum, which was colonised in 90% of instances, took from two to three weeks to achieve a 90% reduction. There was a progressive increase in colonisation with aerobic Gram negative bacilli of the upper gastrointestinal tract in the placebo group. See Figure Two.

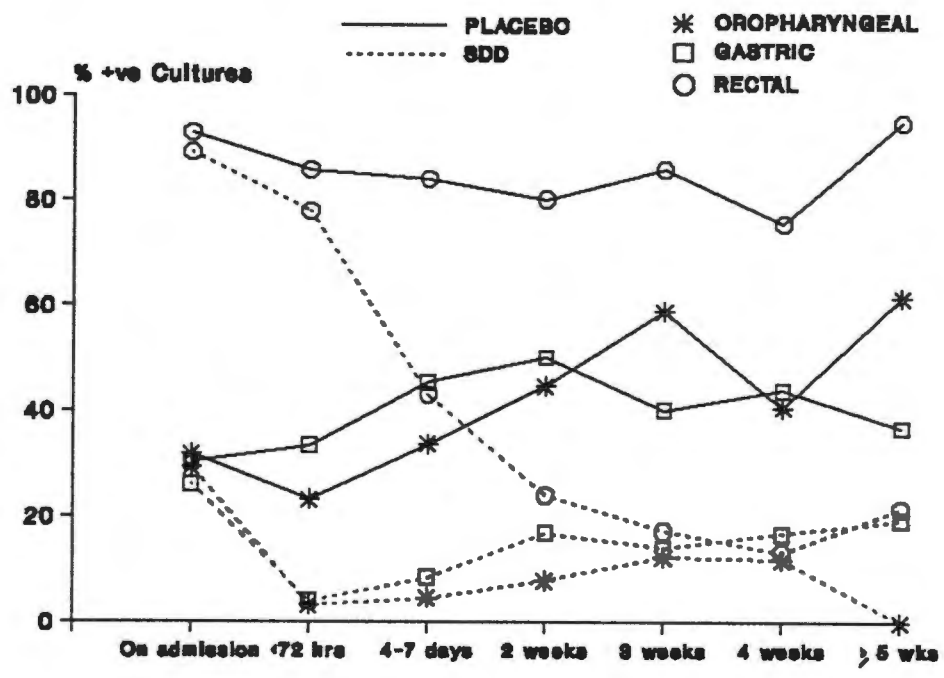


Fig. 2 Gastrointestinal Surveillance Samples

Enterococcal colonisation of the oropharynx became more common during the ICU stay in both groups. On admission, 16% and 10% of oropharyngeal samples from the SDD and placebo groups, respectively, were colonised with enterococci. By week two, 30% and 32% were colonised and after 4 weeks, 41% of samples in both groups were colonised. There was a similar increase in methicillin-resistant *S.aureus* colonisation, but it was significantly greater in the SDD than placebo group (SDD 0% on admission, 10% at 2 weeks, 13% at 4 weeks, vs placebo 2%,4%,5%; $p<0.005$, Fisher's test).

This surveillance data was withheld from the clinical staff for the duration of the study to prevent unblinding, and prejudice the diagnosis of infection by influencing the clinicians.

The effects of SDD on complications developing while in the ICU, morbidity and mortality are shown in Tables Twenty-one and Twenty-two. There were no differences

between the two groups in the incidence of complications, mean duration of ICU stay, hospital stay, or outcome. Most deaths were due to multiple organ system failure.

The incidence of multiple organ failure was similar in both groups, suggesting that the use of SDD did not protect against development of multiple organ failure, in spite of a significant reduction of the load of aerobic Gram negative bacilli in the gastrointestinal tract.

Table Twenty-one: Complications while in the ICU*

	SDD n=114	Placebo n=125	Withdrawn n=83	Suitable n=36
Adverse drug react				
Trial drug	0	0	0	0
Other drug	3	3	0	0
Other complications				
GIT bleed	11	8	2	0
Hepatic failure	12	14	1	3
Cardiac failure	4	1	1	1
Renal failure	7	7	1	0
Haematol failure	4	3	1	0
CNS (coma)	7	3	1	1
Shock (SBP < 70mmHg)	8	2	10	1
Aspiration gastric	2	1	0	0
Aspiration feed	4	3	1	0
Pulmonary embolus	0	0	1	1
Pneumothorax	3	6	1	0
Other vent comp	0	0	0	5
Failed wean	10	14	1	4
Diarrhoea	19	20	1	1
Venous thrombosis	8	7	3	3
Other	0	2	2	2
Total no complics	104	99	24	17
No (%)of patients	46(40)	49(39)	15(18)	11(30)

** There was no statistical difference between the active and placebo groups using Chi-square testing.*

There was no overall effect of SDD on mortality (see Table Twenty-two). When the patients in the active and placebo groups were analysed according to severity of illness as calculated by the APACHE II score, the mortality was 13% for those with APACHE II scores of less than 17 (SDD 9/78 vs 11/77), 22.5% for those with APACHE II scores between 17 and 30 (9/33 vs 9/47) and all those with an APACHE II of more than 30 died (3/3 and 2/2). There was no difference in mortality in any of these categories of severity of illness.

Table Twenty-Two: Effect of SDD on morbidity and mortality

	SDD n=114	Placebo n=125	Withdrawn n=83	Suitable n=36
Mean stay(days)				
In ICU	16.2 ± 14.3	16.8 ± 12.3	4.8 ± 13.2	15.2 ± 12.8
In hospital	29.9 ± 25.0	31.9 ± 22.2	14.6 ± 25.0	30.4 ± 31.3
Deaths				
In ICU	14	15	25	2
In hospital	7	6	3	2
Total	21	21	28	4
(%)	(18)	(17)	(34)	(11)

± values denotes standard deviation

There was no statistical difference between the active and placebo groups for any of the above variables using chi-square and student's t testing. A significant difference in the incidence of secondary infection was however demonstrated in the patients who developed multiple infections using contingency tables.

The cause of death was categorised according to the main organ system failure which was clinically thought to have resulted in death. Respiratory failure and the sequelae of septicaemia, which occurred equally frequently in both groups, were the major causes. In a number of patients in both groups, death occurred following withdrawal of therapy when the outcome was determined to be hopeless.

The relationship to nosocomial infection was assessed clinically and at autopsy, where possible. 3 deaths in each group were assessed as being directly attributable to secondary infection, and in a further 9 deaths, this was thought to have been a possible contributory factor.

Autopsies were performed in 11 of the patients in the active and placebo groups (3 in the active and 8 in the placebo group). In all these patients, the clinical diagnosis of secondary infection was confirmed at autopsy, with 3 deaths being directly attributable to secondary infections with *Pseudomonas spp* and *Acinetobacter spp* being the pathogens in one of these patients, and in two no organisms were identified. In a further four patients, nosocomial infections were considered to be a contributory cause of death, and this was not determined ante-mortem in only one of these patients. In five of these patients, autopsy suggested that the death might have been preventable: two of these patients were found to have undiagnosed disseminated tuberculosis, one died of staphylococcal septicaemia which had developed in hospital prior to ICU entry, and two patients died of ICU acquired infections. This may have been misleading, as autopsy was more likely to have been performed in those cases where the exact cause of death was uncertain.

Table Twenty-Three: Causes of Death

	SDD	Placebo	Withdrawn	Suitable
Cause of death				
Cardiac	2	1	3	0
Neurological	1	1	6	2
Respiratory	5	5	6	2
Septicaemia	4	7	6	0
Active support withdrawn	6	7	5	1
Other	3	0	2	1
Total	21	21	28	4
Relationship to nosocomial infection				
Definite	3	3	0	1
Possible	4	5	0	0
Unrelated	14	13	28	3

There was no statistical difference between the active and placebo groups using chi-square testing.

The costs of applying the technique of SDD include the costs of the topical and parenteral antibiotics, as well as the nursing time required to apply the technique, and the cost of microbiological surveillance, which is recommended to detect potential outbreaks of resistance. The reduction of antibiotic use for the treatment of secondary infections, with the attendant reductions in morbidity and mortality are hoped to produce cost-benefit from the use of SDD. Table Twenty-four indicates the measurable costs of antibiotics in all groups. The costs of treating secondary infection were

significantly higher in the SDD patients, probably as a result of the significant increased prescription of vancomycin that was required.

Table Twenty-Four: Antibiotics used and Costs for treating and preventing Infection

	SDD	Placebo	Withdrawn	Suitable
Acyclovir	0	1	0	0
Amikacin	5	14 p=0.32	1	4
AmphotericinB	1	4	0	0
Ampicillin	1	1	0	1
Ceftazidime	2	3	1	0
Ceftriaxone	2	7 p=0.4	0	1
Clindamycin	1	1	0	1
Cloxacillin	9	8	0	3
Cotrimoxazole	10	18 p=0.84	1	6
Erythromycin	2	0	0	0
Fucidin	1	0	0	0
Gentamicin	0	6	0	1
Imipenem	1	2	0	2
Penicillin	3	0	0	0
Piperacillin	0	6	1	0
Quinolones	0	3	1	0
Tobramycin	1	1	1	0
Vancomycin	15	9 p=0.01	1	1
State cost*(R)	24 015	33 337	1 259	3 363
Total/patient**	1 710	266	15	93
Private cost*	47 308	59 491	3 283	8 167
Cost of SDD*	171 000	0	-	-

** Cost in rands at prices current during the years 1989-1990*

*** Total/patient denotes mean cost of SDD and antibiotics for secondary infections, at state rates for all patients.*

9.2.4 Discussion

In this trial of selective decontamination, 239 patients at high risk of nosocomial infection were fully evaluable in terms of criteria of duration of stay, and our protocol. No significant reduction in the infection rate in the active group was able to be demonstrated, either in the group as a whole, or in the various subgroups previously reported as being particularly likely to benefit from the use of this regimen, apart from in the patients with mid-range APACHE II scores. There was also no reduction in morbidity, as measured by the duration of ICU and hospital stay, complications, mortality or costs. Overall, 14% of deaths were assessed as being directly attributable to secondary infection, but this figure was not improved by the use of SDD. While it is acknowledged that the numbers of patients studied were probably too small for a significant improvement in mortality to have been achieved, despite such a finding having been reported in two studies [14,267], these findings have not been confirmed in meta-analysis [279] and the relationship between secondary infection and death may in fact be too tenuous for such benefit ever to be convincingly demonstrated.

The use of strict clinical definitions for the diagnosis of infection may have resulted in a lower reported incidence of infection in this study, but because of the concurrent and double-blind nature of the study, the effect would have been the same on both groups; this study design would thus have eliminated bias in the diagnosis of secondary infection which, is difficult, as has been discussed extensively in the previous sections, and dependent on subjective interpretation. The definitions in many of the reported studies of SDD have a heavy microbiological weighting, with rather loose clinical criteria; the net result being that the reported rates of nosocomial infection are far higher than previous studies reporting the incidence of secondary infection [5]. The definitions used in this study are also not necessarily the gold standard for diagnosing secondary infection, and may also be criticised. However, they were found to be workable, clinical definitions without the heavy microbiological weighting and its

attendant problems, so common to many of the studies of SDD, and if criticism should be levelled, it would be that there was a tendency for the over-diagnosis of nosocomial infection. These definitions were also not excessively invasive, nor was exotically expensive equipment required; and they were easy to apply on a day to day basis, which, in the longterm would have improved their reliability. Indeed, these definitions are still regularly used to define episodes of nosocomial infection in the Respiratory ICU. Both clinical and microbiological confirmation were required to establish a definitive diagnosis of secondary infection.

The use of concurrent controls avoided the potential influence that outbreaks of infection, changes in the infection rate, treatment, and the nursing workload might have had on the results if the study had used either historical or consecutive time periods. The similar results for the patients who were found to have fulfilled admission criteria but were not enrolled (the so-called "suitable" group), also demonstrates the absence of a possibility of selection bias. Similarly, inclusion of the "withdrawn group" (48 SDD, 35 placebo) in an intention-to-treat analysis, still showed no beneficial effect of SDD; the overall mortality then being 23% in the SDD group and 21% in the placebo group. Only 3 patients who satisfied the duration of stay criterion were withdrawn, and their inclusion in the analysis did not affect the results. The remainder did not receive SDD for sufficiently long to have benefited from it, or to have been at significant risk for the development of secondary infection, and so have not been included in the main analysis.

A further possible explanation for our negative findings is that our infection rate is lower than many previously reported studies of SDD [253,264,269,278]. The statistical power of our study was sufficient to have detected a 12% reduction in the incidence of infection with 80% certainty and 95% confidence intervals, despite our initially low infection rate. The high nurse to patient ratio, a modern working environment with the beds widely spaced, and a strictly enforced antibiotic policy are possible reasons for

this low infection rate. It is widely accepted that long-term immobilisation, especially after multiple trauma, is associated with increased morbidity [70]; the immunosuppressant effects of hypnotic agents is also well known [26]. For several years we have had a policy of using the minimum of sedation necessary for patient management and comfort in our ICU, and have encouraged early mobilisation of our patients, with the use of vigorous physiotherapy [222]. It is possible that all these factors may help to prevent the development of infections.

Surveillance cultures showed effective decontamination in all patients who received SDD, but the incidence of infection was not significantly reduced; however among the placebo group, there were significantly more infections due to *Enterobacteriaceae* and other Gram negative organisms. The incidence of Gram positive infections was significantly higher in the SDD-treated patients, which may be due to an increase in colonisation by the staphylococci, which are not sensitive to the agents used in the decontamination regimen. The most common infectious agents were multi-resistant bacteria, including *Acinetobacter spp* and, especially in the active group, *Staphylococcus aureus* and *Staphylococcus epidermidis*. Although fewer SDD-treated than placebo-treated patients had infections caused by *Acinetobacter spp*, the difference was not significant. Very few of these organisms are sensitive to the antibiotics used for SDD.

The mode of infection seems to be less straightforward than has been suggested previously in reports promoting the use of SDD. Endogenous infections from organisms colonising the patient's own gastrointestinal tract are undoubtedly important, but their role may have been over-emphasized[300-302]; results of administration of topical antibiotic prophylaxis to the respiratory tract are conflicting [222,233], and the idea that colonisation is probably one step away from infection is possibly over-simplistic. Most of our patients had no evidence of gastrointestinal colonisation before the infective episodes; thus exogenous infections from the patient's skin or cross-

infection, are the most likely routes, especially for organisms such as *S aureus*, *S epidermidis*, or *Acinetobacter spp*. A possible criticism of this study design is that the effect of SDD might result from its influence on the environment rather than on the individual [229], suggesting that the control group might have had a reduced incidence of infection as a spin-off from the overall reduced bacterial load. The incidence of secondary infection was noted not to have differed from that reported previously from the unit [148] so that this would seem extremely unlikely. We were also unable to show cross-infection with aerobic Gram negative bacteria, and all patients, including those in whom infection developed, had evidence of effective bowel decontamination.

All patients in the trial received cefotaxime; this agent eliminates organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* which tend to cause early nosocomial infections [17,263]. In a study using cefoxitin prophylaxis to prevent nosocomial pneumonia, there was no demonstrable reduction in infection [17], so it is unlikely that cefotaxime would have had an important role in this way.

There has been concern that increased use of topical antibiotics with the SDD regimen may lead to the development of infections with *S. aureus* and enterococci, which are not sensitive to the agents used; and may even exert pressure on sensitive organisms to acquire resistance. We have shown an increase in colonisation of the gastrointestinal tract with enterococci in both groups, although these organisms did not cause many infective episodes. Methicillin-resistant *S aureus* colonisation increased significantly in the SDD group, resulting in more infections. It might be possible to address this difficulty by use of a different regimen [142], although the use of topical vancomycin with it attendant high cost might promote the development of greater resistance amongst the staphylococci, which would be of extreme concern.

Although SDD may reduce the incidence of infection slightly, it has no effect on morbidity or mortality and adds substantially to the cost of ICU care, in terms of

antibiotics, microbiological surveillance and nursing time. From the results obtained in this study its use cannot be recommended for routine prophylaxis in the general ICU.

9.3 : Sub-Group Analyses

Analyses of the various subgroups, particularly patients with multiple trauma and mid-range APACHE II scores, previously reported by Ledingham [263] and Stoutenbeek [274] to benefit from this technique, as well as patients with primary neurological disease and a comparison with patients infected on admission versus those who were uninfected on admission are discussed in the following sections.

9.3.1 Neurological disease

Introduction

Patients with neurological disease are recognised to be at particularly high risk for the development of nosocomial infection in the ICU, because their stay is often prolonged, and ventilatory support is needed for protracted periods of time. Their protective reflexes, particularly bulbar and upper airway reflexes may be impaired as part of their disease or in association with a depressed level of consciousness; steroids, plasma-exchange and other immunosuppressive agents play a major part in the therapy of patients with neurological disease, and stress ulcer prophylaxis also, in the form of antacids and H-2 antagonists, may further serve to predispose to the development of infection.

Patients and Methods

These patients are a subset determined a priori of the total study on selective decontamination. The protocol and methods are therefore identical to the parent study.

Results

40 patients with neurological disease and respiratory failure were included in the study of selective decontamination. Their demographic features are shown in the following table.

Table Twenty-five : Demographic Features of Patients with Neurological Disease

	SDD	Placebo	Withdrawn
No of patients	13	20	7
Mean age	38.5 ± 14.4	40.5 ± 18.4	41.8 ± 14.8
Sex (male:female)	7:6	6:14	5:2
Mean APACHE II	9.7 ± 5.4	12.5 ± 7.7	25.4 ± 11.4
Mean organ failure	1.2 ± 0.4	1.5 ± 0.6	2.3 ± 0.9
Glasgow coma scale	13.8	10.8	5.1

The placebo and SDD groups were fully comparable in terms of age and sex distribution. The severity of illness parameters (APACHE II ($p = 0.2$), organ failure score and Glasgow coma scale) were not significantly different.

The patients who were withdrawn had a higher APACHE II and Glasgow coma score and all but one had primary central nervous system disturbance, either from trauma or hypoxic brain damage, with a consequently higher mortality. They were all withdrawn because of failure to meet the criteria of duration of intubation and ICU stay, and have not been included in the analysis , as there were no infections and the SDD had not been given sufficient time to be effective. Even when included in the analysis, they do not affect the results.

The spectrum of neurological diseases that required ICU admission during the trial is shown in Table Twenty-Six.

Table Twenty-Six : Spectrum of Neurological Diseases

	SDD	Placebo	Withdrawn
Status epilepticus	1	3	2
Myasthenia gravis	1	2	0
Guillain-Barre	4	6	1
Tetanus	4	2	0
Meningoencephalitis	2	3	1
Coma	1	4	3

The distribution of the different neurological diseases, and the number of patients who were immunosuppressed for the management of their disease, were equally represented in both groups. The distribution of associated underlying disease, and other compromising factors occurred in a small number of patients only - Table Twenty-Seven.

Table Twenty-Seven: Underlying diseases predisposing to infection

	SDD	Placebo	Withdrawn
Carcinoma	1	0	0
Immunosuppressing drugs	3	3	1
Plasma exchange	4	3	0
Diabetes mellitus	1	2	1
Peptic ulcer disease	0	0	0
H-2 antagonists	2	5	0
Malnourished	2	4	3
Alcohol abuse	2	4	5
Antibiotic on admission	4	8	2
Comatosed	5	10	6
Unconscious for 3 days	7	11	4
Bulbar dysfunction	8	6	0
Bedbound > 5 days	8	17	0

The neurological status was assessed according to the following schema:

1. Orientated: fully responsive and aware of surroundings

2. Confused: inappropriate response

3. Unconscious: not responding to verbal commands

4. Comatose: no purposeful response to pain (i.e. Glasgow coma scale <6)

Bulbar dysfunction was documented according to whether the patient was able to swallow his secretions or required dental suction and/or a vocal aid added to the tracheostomy.

Bedbound > 5 days: Mobility of the patient was documented as to whether the patient was able to be mobilised to a chair within 5 days.

The overall incidence of infection in patients with neurological disease, who required intubation for more than 2 days and stayed in the ICU for at least 5 days, was 46.1% in the SDD group and 31.5% in the placebo group, with an overall incidence of 37.5% for this subgroup, compared with only 30% for all evaluable patients. The various types of infection documented during the patients' stay are shown in Table Twenty-Eight.

Table Twenty-Eight: Efficacy of SDD

	SDD	Placebo	Withdrawn
Infections total	11	10	0
Patients infected	6	6	0
Bronchial	6	3	
Pneumonia	2	1	
UTI	0	3	
IV catheter	2	1	
Septicaemia	0	2	
Other	1	0	

The organisms causing secondary infection in the different groups are shown in Table Twenty-Nine. While there are too few infections for there to be any statistically significant differences, it is noteworthy that there were no infections due to *Escherichia coli* in the SDD group.

Table Twenty-Nine: Organisms causing infection

	SDD	Placebo
Staphylococcus aureus	5	4
Staphylococcus epidermidis	2	2
Pseudomonas spp	2	0
Escherichia coli	0	3
Acinetobacter spp	0	1
Unknown	1	0

Diarrhoea proved to be the most common complication, but was self-limiting, and usually responded to altering the feeds; this as well as other complications were equally distributed in both groups. (Table thirty.) All patients were routinely anti-coagulated using subcutaneous heparin, and anti-embolism stockings were worn; monitoring for venous thrombo-embolism was performed clinically.

Table Thirty: Complications

	SDD	Placebo	Withdrawn
Gastrointestinal haemorrhage	0	1	0
Hepatic failure	0	1	0
Renal failure	0	1	0
Haematological failure	0	1	0
Gastric aspiration	1	1	0
Aspiration of feeds	0	0	0
Venous thrombosis	1	0	0
Pulmonary embolism	0	0	0
Ventilatory complications	0	0	0
Diarrhoea	5	5	0

The duration of ventilation was longer in the SDD group, but this was not significant (p=0.075); however, the duration of tracheostomy was prolonged in the SDD group (p=0.0025). The duration of ICU and hospital stay appeared to be more prolonged in the patients who received SDD, however this did not achieve statistical significance, nor was there any difference in mortality.

Table Thirty-One: Ventilatory Therapy, Morbidity and Mortality

	SDD	Placebo	Withdrawn
Duration (days)			
IPPV	27.9 ± 19.9	16.1 ± 16.7	2.5 ± 1.1
Tracheostomy*	39.3 ± 22.3	14.8 ± 20.1	0.5 ± 1.1
ICU stay	30.1 ± 22.5	20.6 ± 17.7	2.6 ± 0.9
Hospital stay	49.3 ± 31.9	40.0 ± 33.4	10.9 ± 8.4
Mortality	15%	15%	75%

** Duration of tracheostomy p = 0.0025, Student's t test; remaining values for the SDD and placebo groups were not significantly different using Student's t testing.*

DISCUSSION

Neurological diseases requiring longterm ventilation are reported to be complicated by respiratory infections in 35 - 67% of cases, and infection contributes to death in 33% of patients with tetanus.[224-226] A recent multivariate analysis of critically ill patients in a multicentre study showed pneumonia to be an independent risk factor for death and found the presence of neuromuscular disease and impairment of airway reflexes on admission, to be risk factors for the development of infection.[186] Such patients are also at particularly high risk of developing secondary infection because of their unusually protracted stay in the ICU. Impaired muscle function and immobility predispose to atelectasis; depressed protective reflexes and impaired bulbar function

render these patients susceptible to aspiration; endotracheal tubes, tracheostomies and central lines as well as longterm urinary catheterisation, by breaching host defences, increase the risk of nosocomial infection.[30] Immunosuppression and plasmapheresis, which are used in the management of patients with acute inflammatory demyelinating polyneuropathy (Guillain-Barre Sydrome) and myasthenia gravis, and the profound sedation used in the management of tetanus, may reduce humoral defences and increase the risk of such patients developing infection.[26]

There have been no studies evaluating the SDD regimen in patients requiring ICU admission for neurological disease. However, such patients might be expected to show especial benefit from such a prophylactic regimen. The higher incidence of secondary infection in patients with neurological disease was confirmed in this study, where the incidence of secondary infection was 37.5%, whereas, in the parent study, in patients with other diseases requiring admission who fulfilled similar criteria for analysis, the incidence was 30%. There were no secondary infections in the patients in the group that were withdrawn from the study; they were not included as an "intent to treat group", because although they had been randomised, their short duration of ICU stay made them at low risk for the development of secondary infection.

We were unable to reduce the incidence of secondary infection with SDD, nor were any deaths related to secondary infection. Although patient numbers are small, because of the increased risk of infection in this group and their prolonged ICU stay, this study probably includes sufficient patients to make these negative findings important.

Our patients represent the usual spectrum of neurological diseases requiring longterm ventilatory support and, although the numbers are small, the distribution in the groups is similar; all other features also make them entirely comparable. The severity of illness does not appear to have favoured the development of infection in the active group, as the APACHE II score was actually higher in the placebo group. The Glasgow coma scale was lower in the placebo group which also might have been expected to have put this group at increased risk of infection. The duration of

ventilation, ICU stay and hospital stay were not significantly different in the 2 groups. Although the duration of tracheostomy was longer in the active group, the number of respiratory tract infections did not appear to be influenced by this, as the majority of infections occurred within 25 days; only one bronchial infection and one pneumonia developed later in each group. The timing of onset of infections was similar in both groups and most infected patients had more than one episode of infection.

The most common organisms causing infection in both groups were *Staphylococcus aureus* and *Staphylococcus epidermidis* which are frequent causes of nosocomial infection; colonisation with these organisms may even be increased by the use of SDD. A recent study from Spain in patients with head injuries requiring admission to a neurosurgical ICU, has shown that the most frequent pathogens in patients with a Glasgow coma scale of less than 9 are the staphylococci [303]. Marked regional differences with endemic organisms may occur in different ICUs, which may also influence the effects of SDD. In our unit, colonisation by *Acinetobacter spp.*, frequently resistant to tobramycin, was shown in surveillance cultures to be unaffected by SDD. The route of infection with these organisms is usually from the skin, but intestinal decontamination may actually promote their growth in the gut.

The concurrent design of our trial simultaneously allowed decontaminated and non-decontaminated patients in the ICU. This may have led to cross infection and increased infection in the SDD group; however, it was not possible to demonstrate spread from patient to patient. It may also be argued that by reducing the load of AGNBs in the ICU with SDD, there may have been some benefit to the control group. This is particularly relevant in this group of patients who are exposed to the ICU environment for prolonged periods, with the implied risk of colonisation by unit-pathogens. These potential drawbacks in the study design were clearly outweighed by the advantages of the concurrent blinded nature of the study, which made the diagnosis of infection more reliable and eliminated possible observer bias.

Reusser et al [300] were unable to demonstrate that gastric colonisation played a role in the development of nosocomial infection in neurosurgical patients requiring mechanical ventilation. Although our patients were primarily medical, rather than surgical, the role of exogenous infections may help to explain the lack of efficacy of this regimen demonstrated in our study.

The microbiological surveillance, which must be performed for early detection of antibiotic resistance, the increased nursing and laboratory workload, and the additional drugs all add considerably to the cost of hospitalisation. While the theoretical benefits of reducing nosocomial infections and preventing patient complications with the use of SDD are extremely attractive, this study has been unable to confirm any benefit in patients with neurological disease; such techniques as strict asepsis, hand-washing, care of ventilatory apparatus and respiratory care must continue to be the cornerstones of prophylaxis.

9.3.2 Trauma patients

Introduction

Patients who have sustained multiple trauma are generally regarded as being "clean" on admission and thus form an ideal group for the primary prevention of secondary infection. These patients have been demonstrated in many studies to be particularly susceptible to secondary infection, because of extremely suppressed host immune responsiveness, and in studies using historical controls with post hoc stratification [263,274], trauma has been described as being an area where selective decontamination is of especial benefit.

Patients and Methods

This section reports a subgroup selected a priori as being at high risk of secondary infection who have been shown to benefit from the use of SDD with both a reduction in

nosocomial infections and mortality [263,274]. The same protocol as described in detail above in section 9.1, was used.

Approximately 30% of all admissions to our respiratory ICU are secondary to trauma. Our hospital is the major hospital and referral centre in a city with an estimated population of over 2 million inhabitants. The majority of trauma patients admitted to our ICU are victims of motor vehicle accidents - most of these being pedestrians. The delay from the time of injury to the time of hospital admission was usually not more than 4 to 5 hours, and ICU admission followed within 3 to 4 hours after resuscitation and definitive treatment in our accident unit.

Trauma patients admitted to our ICU had predominantly blunt chest trauma and multiple injuries, that required intermittent positive pressure ventilation. Many had associated limb, head, and abdominal injuries, mostly due to motor vehicle accidents; however, those with predominant head injuries were treated in a separate neurosurgical ICU and were not included in this study. All thoracic trauma patients referred to our hospital requiring ICU therapy would have been admitted to our respiratory ICU and included in this study. Only one patient with extensive burns of 35% body surface area, who was randomised to receive placebo, was admitted to the study (the other burns patients requiring ICU management received treatment in our isolation ICU, where the study of SDD was not conducted).

Eighty seven trauma patients were randomised on admission and entered into the study. The demographic details of the two groups show that the patients were fully comparable in terms of age, sex, severity of illness, and are shown in Table Thirty-Two.

Table Thirty-Two: Demographic Details of Trauma Patients

	SDD	Placebo	Withdrawn
Number of patients	39	33	15
Mean age	40	38.7	39.9
ISS	29.5 ± 13.8	29.5 ± 13.5	21.6 ± 11
APACHE II	9.8 ± 6.1	10.5 ± 5.8	10.1 ± 6.5
Organ failure	1.2 ± 0.4	1.1 ± 0.3	1.3 ± 1

Those patients in the withdrawn group did not meet the criteria for full evaluation of the study, because their durations of ICU stay or intubation were too short; there was one patient in whom it was decided to break the code because of suspected drug allergy - he was found to be receiving placebo. One further patient, who would not tolerate the application of the oral gel, also had to be withdrawn; however, when these patients were included in the overall analysis, they did not affect the results.

The presence of pre-existing factors which might have predisposed to the development of infection was documented, and are shown in Table Thirty-Three. The only factors which were maldistributed and likely to predispose to infection, would have favoured the development of more infections in the placebo group.

Table Thirty-Three: Factors predisposing to infection

	SDD n=39	Placebo n=33
Carcinoma	0	0
Immunosuppressing drugs	0	0
Diabetes mellitus	2	0
Malnutrition	3	5
Albumin <30/mmol/l	23	19
Alcohol abuse	7	15 p=0.02*
Peptic ulcer disease	1	0
H-2 antagonists	5	6
Glasgow coma scale	12.3± 4.2	12.7 ± 3.6
Bedbound >5 days	30	24
Shocked on admission	0	4 p=0.08*
Emergency surgery	7	3

** Statistical analysis by Chi-square testing*

Alcohol abuse was defined as >4g alcohol/day: (>1 bottle wine/>4 tots/>5 beers/day).

Shocked on adm (admission) was defined as a systolic blood pressure for less than 70mm Hg for more than one hour.

The complications experienced during ICU stay are shown in Table Thirty-Four and were equally distributed in both groups.

Table Thirty-Four: Complications

	SDD	Placebo
Gastrointestinal haemorrhage	2	1
Hepatic failure	5	4
Cardiac failure	1	0
Renal failure	2	1
Shock (SBP < 70)	1	1
Aspiration	2	1
Pneumothorax	0	1
Ventilatory complications	6	5
Diarrhoea	6	1
Venous thrombosis	1	1

The overall incidence of secondary infection in the subgroup of trauma patients was slightly lower (27%), than for all patients enrolled in the study (30%), but the difference in incidence between those who received SDD (28.2%) and placebo (33.3%) was not significant. The distribution and the various types of secondary infection occurring are shown in Table Thirty-Five. One patient from the placebo group, who was withdrawn from the study because of possible drug toxicity, developed infections.

Table Thirty-Five: Efficacy of SDD

	SDD	Placebo	Withdrawn
No of patients infected	11	11	1
% patients	28.2	33.3	6.6
Bronchial	4	5	2
Pneumonia	6	1	1
Urinary tract infection	2	1	0
IV catheter related	2	2	0
Septicaemia	2	3	0
Other	1	4	0
Total infections	17	16	3

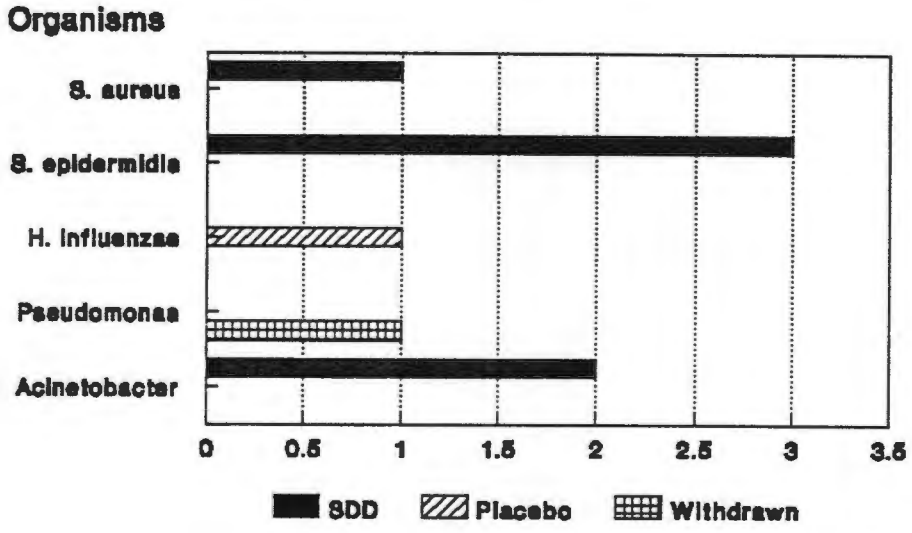
The organisms causing infection in the groups are shown in Table Thirty-Six. The majority of infections in those who received the active regimen were due to *Staphylococcus aureus* and *Staphylococcus epidermidis*.

Table Thirty-Six: Organisms causing secondary infection

	SDD	Placebo	Withdrawn
Staphylococcus aureus	4	4	0
Staphylococcus epidermidis	6	1	0
Enterobacteriaceae	2	5	1
Acinetobacter spp	3	1	1
Other Gram -ve	1	1	0
Other Gram +ve	1	2	0

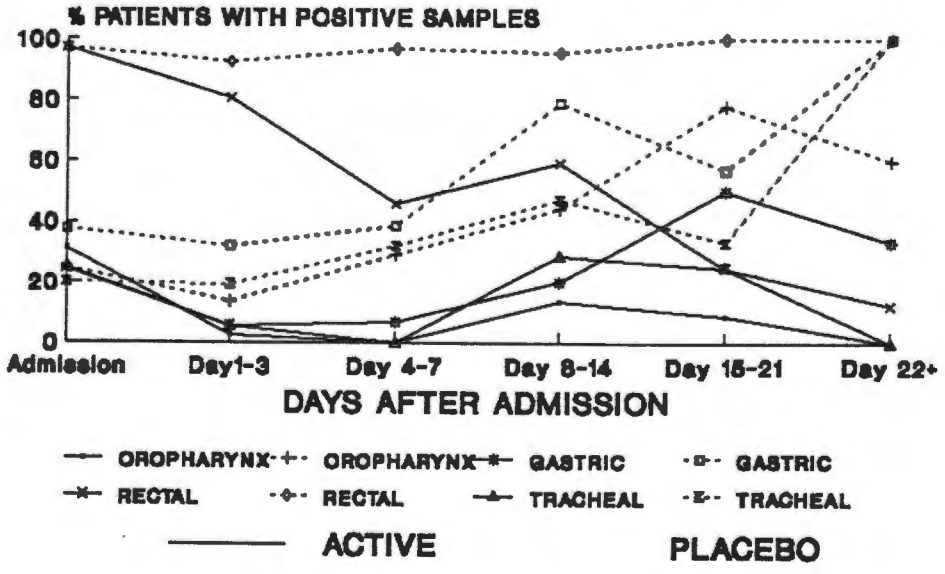
The organisms causing pneumonia in the active and placebo groups are shown in Figure Three. There were six patients in the active group and one in the placebo who developed pneumonia; the organisms causing pneumonia in the active group included *Staphylococcus epidermidis* 3, *Acinetobacter* 2, one patient in the placebo group developed pneumonia caused by *Haemophilus influenzae* and a patient who was withdrawn developed a pneumonia due to *Pseudomonas aeruginosa*. Bronchial infections were caused by *Staphylococcus aureus* in 3 patients in each group, *Acinetobacter spp* in one patient in each group, *Streptococcus pneumoniae* in one and *Moraxella catarrhalis* in one in the active and placebo groups respectively; there were two bronchial infections in the patients who were withdrawn caused by *Acinetobacter spp* and *Pseudomonas aeruginosa*.

Fig.3 Organisms causing Pneumonia



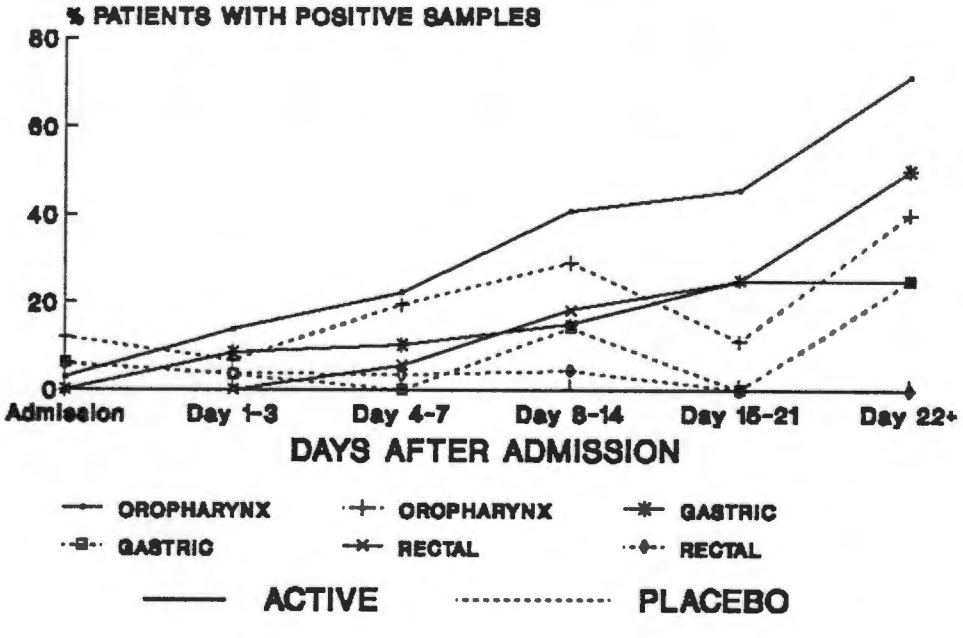
Surveillance cultures demonstrated that colonisation of the gastrointestinal tract by aerobic Gram negative bacilli was effective (Figure Four).

Fig.4 Surveillance samples



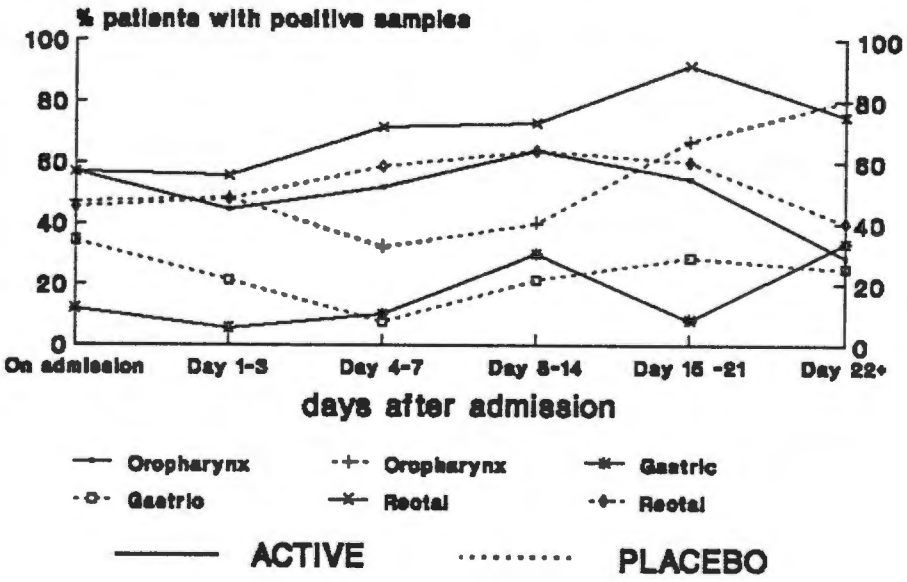
Colonisation of the gastrointestinal tract by the majority of organisms unaffected by the agents used as part of the decontamination regimen , however, was shown to increase progressively. Colonisation by methicillin-resistant *Staphylococcus aureus* increased signficantly in the active group at all sites (p=0.0002), particularly in the oropharynx (p=0.0006) during ICU stay (Figure five).

Fig.5 Colonisation by MRSA



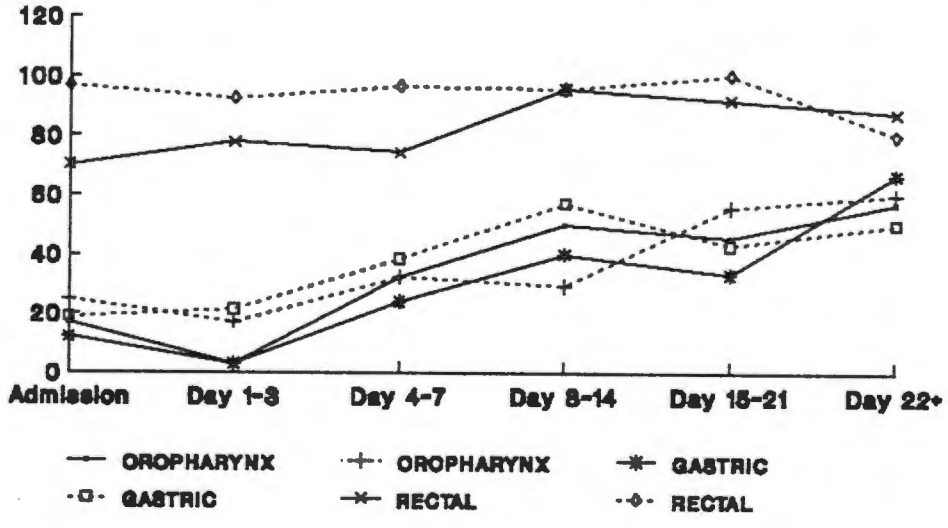
Persistently high levels of colonisation with *Staphylococcus epidermidis* were seen at all sites. (Figure Six)

Fig.6 S.epidermidis colonisation



Gastric and oropharyngeal colonisation by the enterococci occurred in 18.3% of patients on admission and increased in both groups to 56.2% at three weeks, while rectal colonisation was maintained in 83.7% of all patients. (Figure 7).

Fig.7 Enterococcal Colonisation



The duration of mechanical ventilation was similar, and although the duration of tracheostomy was more prolonged in the active group, this did not achieve statistical significance. The duration of ICU and hospital stay was similar in both active and placebo groups. Two deaths in each group were assessed as being directly attributable to secondary infection. In the patients who received SDD, there were 5 deaths (in 1 active treatment was discontinued because of primary neurological injury, there was 1 patient with a cardiac and 1 with a neurological cause of death), while in the placebo group, active treatment was discontinued in the third fatality. In the withdrawn group, active treatment was withdrawn in one, and there was an additional neurological death.

Table Thirty-Seven: Ventilatory Therapy, Morbidity and Mortality

	SDD	**Placebo**	**Withdrawn**
Duration (days)			
IPPV	6.5 ± 4.1	5.9 ± 2.9	2.4 ± 1.1
Tracheostomy	18.2 ± 12.1	13.4 ± 8.6	19.8 ± 14.8
ICU stay	15.5 ± 12.5	14.2 ± 9.7	11.3 ± 29.6
Hospital stay	26.3 ±18.5	25.5 ±16.3	20.2 ±43.3
Mortality	12.8%	9%	13.3%

DISCUSSION

This study of selective decontamination has been unable to show any reduction in the incidence of secondary infection, in this subgroup of trauma patients, there was also no reduction in the duration of ICU or hospital stay, nor other parameters of morbidity; the mortality also was similar, with death attributable to secondary infection occurring in 2 patients in each group. These findings are surprising as our patient population is similar to many studies which have shown a reduction in secondary infection, although only a few have been able to show any effect on mortality.[14,263,267] Most of

studies have, however, compared selective parenteral and enteral decontamination with no antibiotic regimen, whereas in this study, selective decontamination of the digestive tract only is being evaluated, as both limbs received cefotaxime for 72 hours (all enrolled patients received systemic prophylaxis with cefotaxime, as the administration of a parenteral placebo would have resulted in too many patients having to be withdrawn because of unblinding). The cefotaxime may have reduced the incidence of early-onset secondary infection in this study, as only 2 patients who received the active regimen developed infections within the first 5 days of admission (sinusitis and nosocomial pneumonia) compared with 3 who received placebo (septicaemia, wound infection and a bronchial infection). An early study by Stoutenbeek[274] using an enteral regimen alone showed only a moderate effect until cefotaxime was added to the initial regimen, to eliminate early onset pneumonia and achieve early decontamination.

Another possible explanation for the lack of efficacy of selective decontamination, may have been the inclusion of both decontaminated and contaminated patients in the same unit, necessitated by the blinded nature of the study, but this is unlikely to have had a major influence as there were no episodes of overt cross-infection detected [278]. Intestinal decontamination invariably takes a few days and thus, with the usual rapid patient turnover in any ICU, there will always be this reservoir of organisms in patients who are not fully decontaminated.

The surveillance cultures confirmed effective gastrointestinal elimination of aerobic Gram negative bacilli in the active group and few infections resulted from the *Enterobacteriaceae*. A high rate of colonisation by *Staphylococcus epidermidis* was seen in all patients. Increased colonisation by methicillin resistant *Staphylococcus aureus* was noted in the patients who received the active regimen and, although the incidence of infection with this organism was similar in both groups, this was of concern. An increase in colonisation with *Acinetobacter spp* and *Enterococci* was also noted in both groups. The infections caused by *Staphylococcus aureus* and

Acinetobacter spp were not necessarily preceded by gastrointestinal colonisation, particularly in the case of *Acinetobacter spp*, suggesting that other routes of infection, or alterations in adherence mechanisms, may have played a role.[33]

It is of interest that the overall rate of secondary infection in multiple trauma patients (29%) during the study period, was lower than the 43% previously reported from our unit in this group of patients [148] - which is again still considerably lower than the incidence in many of the studies where selective decontamination of the digestive tract has been reported to be of benefit. This difference may have been due to a reduction in the incidence of early onset pneumonia by the use of cefotaxime in both limbs of our trial, and also the use of strict clinical criteria for diagnosis. The exceptionally high incidence of secondary infection reported in the controls of some of the studies[253,264,269] may have been due to the open nature of the studies and the predominantly microbiological definitions. The reduction in colonising organisms in surveillance cultures with the use of selective decontamination is striking. This reduction, whether real or due to the "carry-over effect of the topical antibiotics", may influence the interpretation of tracheal cultures and lead to the under-diagnosis of infection.

A recent study of selective decontamination of the digestive tract using vancomycin, polymyxin B and neomycin in selected surgical patients showed a significant reduction in infection but no influence on mortality.[17] With a similar regimen in our patient population, staphylococcal infections might have been prevented; however, it is unlikely that infections with *Acinetobacter spp* would have been prevented. Selective decontamination of the digestive tract may, however, show more positive benefits if the antibiotic regimens are specifically chosen to deal with the problem organisms specific to the unit or hospital.

The negative results of this study do not support the routine use of selective decontamination of the digestive tract in trauma patients in a polyvalent ICU with a low incidence of secondary infection.

9.3.3 Mid-range APACHE II

Introduction

Patients with APACHE II scores ranging between 16 and 31 have been shown in several studies [14,263] to benefit from the use of selective decontamination. The severity of illness which falls into this range may preselect certain disease categories, or a subset of patients in whom, with no further complications, the outcome is likely to be favourable. Should they, however, develop infective complications, these may significantly adversely affect their outcome. Although there is no evidence to support the above theory, this subset was prospectively chosen for subanalysis.

Patients and Methods

There were 103 patients enrolled in this study who fulfilled this criterion; 33 in the SDD group and 47 who received placebo were suitable for subanalysis. The details of the protocol and methods are identical to those described previously.

Results

The demographic features of these patients are shown in Table Thirty-eight. The severity of illness as measured by the various scoring systems was similar for both SDD and placebo groups.

Table Thirty-eight: Demographic features of Patients with mid-range APACHE II scores.

	SDD	Placebo	Withdrawn	Suitable
No of patients	33	47	23	8
Age	51	46.6	42.9	54.1
	± 13.6	± 17	± 19	± 18.5
Male:female	19:14	28:19	14:9	3:5
Mean APACHE II	22.1	20.6	22.9	22.4
	± 4.2	±3.3	± 3.5	± 4
Mean organ	1.6	1.6	1.9	1.4
failure	± 0.7	± 0.6	± 1.1	± 0.7
Mean ISS	n=5	n=10	n=2	n=1
	33.6	25.5	27.5	34
Glasgow coma	11.5	11.5	11	12.5
score	± 4.3	± 4.3	± 5.1	± 4.1

The diagnostic categories of the patients with mid-range APACHE II scores are shown in Table Thirty-Nine. There were more patients in the placebo group admitted with pneumonia and neurological disease, however, this did not achieve statistical significance.

Table Thirty-nine: Diagnostic Categories of Patients with mid-range APACHE II

	SDD	Placebo	Withdrawn	Suitable
Asthma/resp	7	4	6	3
ARDS	0	5	2	0
Pneumonia*	5	14	1	1
Cardiovascular	1	1	2	1
General Surgery	5	6	2	0
Neurological	2	6	4	1
Trauma	5	7	3	1
Other disease	8	4	3	1

** Pneumonia p=0.28 chi-square test*

Possible factors predisposing to the development of secondary infection are shown in Table Forty. These factors were uniformly distributed, apart from previous infections, which favoured the development of infection in the placebo group.

Table Forty: Underlying or Predisposing Factors for the Development of Infection

	SDD	Placebo	Withdrawn	Suitable
In hospital*				
>48 hrs	11	19	10	3
Infect on adm	21	31	9	7
Infect past month**	2	18	5	3
Carcinoma	0	2	4	0
Immune supp drug	5	2	4	0
Cytotoxics	0	0	2	0
Cylophosphamide	1	0	0	0
Steroids	4	2	0	0
Connect tissue disease	1	2	0	0
Diabetes	5	5	2	2
Obesity	4	6	1	2
Malnourished	1	6	1	0
Albumin <30	23	31	10	4
Alcohol abuse	8	14	7	1
Peptic ulcer	1	3	2	0
H-2 blockers	12	17	8	0
Shocked on admission	8	6	6	2
Emerg surgery	4	5	3	1
Bedbound >5 days	23	41	3	8
Bulbar dysfunct	0	2	0	0
Comatosed	9	16	8	2
Unconsc 3 days#	14	27	5	4

** Hospitalised for more than 48 hours before admission to the ICU: p=0.6 Chi-square test*

*** Infections in the past month prior to ICU admission p=0.002 Chi-square test*

 # Unconscious for 3 days: p= 0.27 Chi-square test

The neurological status was assessed according to the following schema:

1. *Orientated: fully responsive and aware of surroundings*
2. *Confused: inappropriate response*
3. *Unconscious: not responding to verbal commands*
4. *Comatose: no purposeful response to pain (i.e. Glasgow coma scale <6)*

Bulbar dysfunction was documented according to whether the patient was able to swallow his secretions or required dental suction and/or a vocal aid added to the tracheostomy.

Bedbound > 5 days: Mobility of the patient was documented as to whether the patient was able to be mobilised to a chair within 5 days.

The amount of invasive therapeutic and monitoring required by both groups, which might have influenced the incidence of infection, was similar, and is shown in Table Forty-one. The duration of ventilation, tracheostomy, ICU and hospital stay were similar for both groups.

Table Forty-One: Invasive Therapy

	SDD	Placebo	Withdrawn	Suitable
No of patients	33	47	23	8
Duration IPPV	11.6	11.8	4.3	7.9
	±11.2	± 8	± 6.1	± 12.3
Tracheostomy	n=10	n=25	n=3	n=2
	19.2	16.8	45	17
Duration*	16.6	19.3	9.2	12.4
ICU (days)	± 14	± 12.2	± 25	± 12.3
Duration**	30.4	35.1	18.2	21.8
hospital (days)	± 27.7	± 21.3	± 36.6	±19.1
Haemodialysis	6	8	1	1
TPN*	10	22	4	1
TPN >5 days	14	18	3	1
Enteral feeding**	27	42	11	7
Plasmapheresis	1	0	0	0
Chest drain	9	12	3	1
Arterial line	18	34	13	3
Central line	28	44	14	5
Peripheral line	33	47	23	8
Pulmonary artery#	23	32	13	3
catheter				

** Duration ICU stay p= 0.36 Student's t test*
*** Duration hospital stay p= 0.42 Student's t test*
** TPN p= 0.21 Chi Square test*
***Enteral feeding p=0.52 chi-square test*
 # Pulmonary artery catheter p=0.92 Chi-square test

The development of complications while in the ICU occurred with equal frequency in both SDD and placebo groups and these are demonstrated in Table Forty-two.

Table Forty-Two: Complications

	SDD	Placebo	Withdrawn	Suitable
GIT bleed	6	6	2	0
Hepatic failure	8	7	1	1
Cardiac failure	2	1	1	0
Renal failure	4	4	0	1
Haem failure	3	4	0	0
CNS coma	5	0	0	0
Shock (Sbp < 70)	5	0	6	0
Pneumothorax	2	2	1	0
Failed wean	3	7	1	0
Diarrhoea	6	9	1	1
Ven. thrombosis	3	2	1	0
Other	4	6	1	0

Table Forty-three illustrates the types of secondary infections. There was no significant difference in the incidence of infection between the SDD and placebo groups.

Table Forty-three: Types of Infections

	SDD	Placebo	Withdrawn	Suitable
No of patients*	10	21	2	3
Bronchial	6	8	3	2
Pneumonia	3	3	1	1
IV catheter	1	6	0	0
Urinary catheter	0	2	0	0
Septicaemia	2	7	0	0
Other	1	4	0	0
Total	13	30	4	3

** No of patients infected p=0.28 Chi-square test*

The distribution of the pathogens causing infection is demonstrated in Table Forty-four. Infections caused by the *Enterobacteriaceae* and yeasts, occurred predominantly in the placebo group.

Table Forty-Four:Organisms causing infection

	SDD	Placebo	Withdrawn	Suitable
H.influenzae	0	1	0	0
S. aureus	4	5	0	1
S. epidermidis	3	7	0	0
Escherichia coli	0	4	0	0
Klebsiella spp	1	2	0	1
Proteus spp	0	1	0	0
Enterobacter	0	2	0	0
Acinetobacter spp	5	4	2	1
Pseudomonas spp	0	1	0	2
Candida	0	3	0	0
Enterococcus	0	1	0	0
Other *streptococci*	0	1	0	0
Other	0	1	0	0

There was no statistical difference between the mortality in the active and placebo groups (Table Forty-five).

Table Forty-Five: Mortality

	SDD	**Placebo**	**Withdrawn**	**Suitable**
No of patients	33	47	23	8
Mortality in ICU	6	7	11	1
in hospital	3	2	1	1
% total deaths*	27.3	19.2	52.1	25

* *Overall mortality p=0.55 chi-square testing*

Discussion

Ledingham et al [263] identified the patients with mid-range APACHE II scores (17-33 inclusive), with post-hoc stratification, as a group in whom the mortality was significantly reduced by the use of selective decontamination; the mortality rate was 43% in this group, compared with 58% in the control group. The mid-range APACHE II score selected by Ledingham is possibly too high, as it includes patients with scores of over 30, where the outcome is always very poor. Survival with an APACHE II score of over 30 may relate more to the disease process itself, and be unlikely to be significantly influenced by therapy. An APACHE II score of 17-30 was accordingly selected a priori for analysis in our study, where only 2.8% of patients had APACHE II scores of over 33. In our patients, even using Ledingham's higher mid-range APACHE II scores (17-33), the overall mortality was only 32.4%, which is significantly lower. It is possibly because of the lower mortality rate that no significant difference with the use of SDD could be demonstrated in this study.

The infection rate was also similar in both groups, although infections with organisms sensitive to the SDD regimen occurred more frequently in the placebo group. Although statistical significance was not achieved in the reduction of the incidence of secondary infection with SDD, there was a trend in this direction. A number of infections caused by the staphylococci occurred in both groups, suggesting that enteral elimination of the *Enterobacteriaceae* is not sufficient to prevent secondary infections altogether, and that the exogenous route of pathogenesis of secondary infection remains important.

9.3.4 : Surgical Patients

Introduction

Post-operative and other surgical categories may also stand to benefit from the use of SDD[259]. Although this group of patients was not large enough in this study to provide any conclusive results, this subgroup is presented for completeness.

Patients and Methods

This subgroup of patients was part of the study on selective decontamination, the methods and protocol were therefore identical to that described above. Selective decontamination was commenced on admission to the ICU, following surgery. Routine perioperative antimicrobial prophylaxis was used where indicated.

There were no patients undergoing surgery who met enrollment criteria who were not included in the study i.e there is no "suitable group".

Results

Similar numbers of patients were enrolled into both groups, however, the patients in the placebo group tended to have a higher APACHE II score; the patients were otherwise comparable.

Table Forty-six: Demographics of General Surgical Patients

	SDD	Placebo	Withdrawn
No of patients	10	10	7
Age	56.8 ±15	58.3 ± 16.3	51.1 ± 16.8
Male:female	4:6	4:6	2:5
Hospitalised >48 hours	4	4	4
APACHE	12.8 ± 4.9	16.1 ± 7.1	12.9 ± 9
Organ failure	1 ± 0.5	1.2 ± 0.4	1.4 ± 0.5

Potential factors thought to predispose to infection were equally distributed in both active and placebo groups, and are shown in Table Forty-seven.

Table Forty-Seven: Factors Predisposing to Infection

	SDD	Placebo	Withdrawn
Infected on admission	4	5	2
Carcinoma	1	1	0
Immunsupp drugs	1	1	1
Steroids	1	1	1
Diabetes	3	1	1
Obesity	4	2	2
Malnourished	0	2	0
Alcohol abuse	1	1	2
Peptic ulcer	2	4	2
Shocked on adm	2	3	0
Emerg surg	9	8	5
Albumin <30 mmol/l	10	10	3
Bedbound >5 days	6	7	1
H-2 blocker	6	6	4

This group of patients received numerous invasive monitoring and therapeutic modalities, which were however, equally distributed between the two groups. Table Forty-eight.

Table Forty-eight: Invasive and Other Therapy

	SDD	Placebo	Withdrawn
Haemodialysis	1	0	0
TPN	7	8	1
Enteral feed	4	7	2
Plasmapheresis	0	1	0
Chest drain	0	1	1
Arterial line	7	8	5
Central line	10	10	7
Periph line	10	10	7
Pulmonary a cath	8	5	2
TPN >5 days	8	6	1
Duration (days)			
IPPV	8.7 ± 4.4	9.2 ± 6.4	2.1 ± 1.2
Tracheostomy	n=1 19	n=6 11.9	n=0

The patients admitted to the Respiratory ICU following surgery, were largely emergency and non-elective cases, and the numerous complications reflect the severity of their disease, which is not accurately conveyed by the relatively low APACHE II scores on admission. Table Forty-nine.

Table Forty-Nine: Complications in ICU

	SDD	Placebo	Withdrawn
GIT bleed	2	1	1
Hepatic failure	2	2	0
Cardiac failure	1	0	0
Renal failure	2	0	0
CNS coma	3	0	0
Shock(Sbp < 70)	2	0	1
Failed wean	0	2	0
Diarrhoea	0	3	0
Ven thrombosis	0	1	0
Other	0	1	1

The morbidity for patients in the placebo group was higher in this subgroup, and the patients remained in both the ICU and hospital for significantly longer; however, the mortality in both groups was similar.

Table Fifty-Two: Morbidity and Mortality

	SDD	Placebo	Withdrawn
Duration	13.1	20.7	3.4
in ICU	±8.8	± 13.3	1.9
Duration	22.6	40.2*	17.5
in Hospital	± 12.9	± 16.8	10.8
Mortality			
in ICU	1	1	1
in hospital	2	1	0
Overall	30%	20%	14.3%

** $p = 0.017$ for difference from active subgroup for duration in hospital.*

Discussion

This subgroup of patients is unfortunately too small for any meaningful conclusions to be drawn. It is also not possibly representative of the patients admitted to a general surgical ICU for elective post-operative care. The lack of infections due to *Enterobacteriaceae* and yeasts in the SDD group suggests that the regimen may have been of benefit in preventing this type of infection, however, the greater incidence of staphylococcal infections is of concern.

9.3.5: Patients infected within the previous month of admission to the ICU

Introduction

Viral infections are well known to cause immunosuppression and to alter the indigenous colonising flora by alterations in bacterial adhesion [46]. More recently, a number of studies have reported an increase in incidence of repeated infections, following severe pneumonia requiring hospitalisation [304]. Infections in the month prior to admission to ICU were regarded as a potential major risk factor for the development of nosocomial infection. These patients were selected a priori to be analysed as a subset, in order to determine if the possible breach in adherence mechanisms and consequent predisposition to infection might be demonstrated to be prevented by SDD.

Patients and Methods

This subset was determined from the history taken on admission to the ICU. 95 patients fulfilled criteria for inclusion in this subgroup, and a further 11 patients not enrolled proved to have been suitable, and are shown separately. Previous antibiotic administration was documented. The protocol was identical to that described previously.

Results

The demographic details of the patients who fulfilled criteria for inclusion in this subgroup are shown in Table Fifty-three. The patients' characteristics were similar in both groups.

Table Fifty-Three: Demographics of Patients recently infected

	SDD	Placebo	Withdrawn	Suitable
No of patients	30	46	19	11
Age	41.3	45.2	42.8	52.5
	± 12	± 17.7	± 18.2	± 10.9
Male:female	13:17	24:22	6:13	2:9
Hospital >48 hrs	19	25	11	5
Rec'd antibiotics*	30	42	16	8
Community acq*	20	34	12	8
Nosocomial*	10	12	7	3
APACHE II	14.2	15.1	17.3	13.5
	± 8.5	± 7.1	± 11	± 3.9
Organ failure	1.5	1.5	1.5	1
	± 0.7	± 0.7	± 0.7	± 0.4
ISS	(n=3)	(n=2)	(n=1)	(n=3)
	20.3	45.5	9	18.3

** Number of patients who had already received antibiotic therapy, and whether the infection was acquired in the community or hospital.*

The risk factors which might have influenced the development of secondary infection were equally distributed in both groups and are shown in Table Fifty-four.

Table Fifty-four: Underlying Factors Predisposing to Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients	30	46	19	11
Carcinoma	2	2	2	0
Immunosupp drugs	0	4	2	3
Cyclphos	0	1	0	0
Steroids	0	3	2	3
Diabetes	2	5	2	3
Conn tissue dis	0	3	1	0
Obesity	3	0	1	2
Malnourished	6	5	1	1
Alcohol abuse	6	12	3	1
Other	1	1	0	0
Peptic ulcer	1	2	1	1
Shocked on adm	7	3	3	1
Emerg surg	7	6	1	0
Albumin <30	22	37	12	5
Bedbound >5days*	21	39	1	9
H-2 blocker	8	12	3	1

p=0.208 Chi-square test

The admitting diagnoses of the patients are shown in Table fifty-five. The numbers are small, and there is no statistical difference between the SDD and placebo groups.

The admitting diagnoses of the patients are shown in Table fifty-five. The numbers are small, and there is no statistical difference between the SDD and placebo groups.

Table Fifty-Five: Diagnostic Categories of Patients admitted with Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients	30	46	19	11
Respiratory dis.	4	7	6	4
Pneumonia*	5	13	4	1
ARDS	2	4	1	0
Cardiovasc	1	0	0	1
Surgery	7	6	3	1
Neurological	3	6	2	0
Other dis	6	8	2	1
Trauma	3	2	1	3

**p = 0.37 Chi-square testing*

Equally frequent use was made of therapy which might have influenced the development of secondary infection in both groups; apart from the use of chest drains, which were inserted more frequently into the placebo patients. The data is shown in Table Fifty-six. This difference in the use of chest drains might have influenced the incidence of secondary infection, however, no empyemata were encountered and chest drains appear to be an infrequent source of infection.

Table Fifty-Six: Invasive and other therapy

	SDD	Placebo	Withdrawn	Suitable
No of patients	30	46	19	11
Haemodialysis	4	6	0	0
TPN	14	22	0	2
Enteral feed	25	42	9	11
Chest drain*	3	16	0	4
Arterial line	21	31	8	4
Central line	30	46	19	11
Peripheral line	30	46	19	11
Pulm art cath	24	31	10	9
TPN >5 days	16	19	0	1
Duration IPPV	7.5	9.8	2.4	8.9
	± 4.7	± 5.4	± 1.3	± 7.9
Tracheostomy	n=7	n=19	n=1	n=2
	21.3	14.4	2	29.5
	± 24.6	± 13.7		

** p= 0.03 Chi-square testing.*

The complications that occurred while in the ICU and which might have contributed to the development of secondary infection are shown in table Fifty-seven.

Table Fifty-Seven: Complications Developing in ICU

	SDD	Placebo	Withdrawn	Suitable
No of patients	30	46	19	11
GIT Bleed	1	4	0	0
Hepatic failure	3	7	0	1
Cardiac failure	0	1	1	0
Renal failure	0	2	0	0
Haem failure	2	2	0	0
CNS coma	1	1	0	0
Shock(SBP <70)	2	0	3	1
Gastric aspirat	1	1	0	0
Pneumothorax	1	4	0	0
Failed wean	1	5	0	3
Diarrhoea*	4	10	0	2
Ven thrombosis	2	2	0	1
Other	3	2	0	1

* *$p= 0.53$ Chi-square testing*

The types of infection in the two groups are demonstrated in Table Fifty-eight. Respiratory tract infections again predominated, but there was no statistical difference between the SDD and placebo patients.

Table Fifty-Eight: Types of Secondary Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients	30	46	19	11
No of infections	8	19	0	8
No of patients*	5	15	0	4
Bronchial	3	7	0	5
Pneumonia	1	2	0	1
IV cath	1	2	0	1
Urinary cath	0	0	0	1
Septicaemia	2	4	0	0
Abscess	1	6	0	0

** p= 0.2 Chi-square testing*

The pathogens causing infection are illustrated in Table Fifty-nine. There was a predominance of staphylococcal infections and infections caused by *Acinetobacter spp*.

Table Fifty-Nine: Organisms causing Infection

	SDD	Placebo	Withdrawn	Suitable
S. aureus	4	5	0	1
S epidermidis	1	3	0	1
Enterococcus	0	2	0	0
E. coli	0	1	0	1
Klebsiella spp	0	1	0	1
Enterobacter	0	1	0	0
Pseudomonas spp	1	2	0	0
Acinetobacter sp	2	6	0	3
Candida	0	3	0	0
Other	0	1	0	1

The morbidity, as measured in terms of duration of ICU and hospital stay, was similar in both active and placebo groups; there was also no significant difference in mortality. (Table Sixty).

Table Sixty: Morbidity and Mortality

	SDD	Placebo	Withdrawn	Suitable
ICU stay	15.2	18.2	2.9	17.5
	± 14.5	± 11.9	± 1.3	± 13
Hospital stay	32.5	32.3	17.7	31.5
	± 21.4	± 17.5	± 27.9	± 20.7
Mortality				
in ICU#	3	10	9	1
in hosp	3	3	1	0
Total	20%	28.3%	52.6%	9%

p= 0.309 Chi square test

Discussion

This group of patients who had a history of recent infection, comprise a large subset (95 patients) of those admitted to the study of selective decontamination. The factors likely to predispose to secondary infection, particularly a greater incidence of alcohol abuse, lower serum albumin, and more invasive procedures occurred more frequently in the placebo group. This group also had twice as many patients admitted with primary pneumonia. A large proportion of patients in both groups had already received prior antibiotic therapy. The incidence of infections appeared to be higher in the placebo patients, although this did not achieve statistical significance, and the outcome of this

subset would suggest that no conclusive benefit from the use of SDD is found, even in patients with potentially abnormal bacterial adherence mechanisms.

When all the patients in the study are combined, no difference in the number of patients who developed secondary infections who had previously been infected, compared with the group as a whole ($p=0.65$) could be demonstrated, suggesting that this factor may not play an important role.

9.3.6 Patients infected on admission to the ICU

Introduction

A major proportion of patients admitted to the ICU are admitted with infection and the mortality in these patients is appreciably higher than for other disease categories. These patients have been excluded from many previous studies of SDD either by study design [261,270], or by selecting groups unlikely to be primarily infected Eg multiple trauma or post-surgical cases. In this study, these patients were specifically included and prospectively gathered to evaluate the efficacy of selective decontamination in reducing morbidity and mortality in this high risk group.

Patients and Methods

This study was a prospectively selected subgroup of the parent study on selective decontamination, using the protocol and methods described previously. 164 patients fulfilled criteria for enrollment and subanalysis, and a further 27 were suitable, but were not enrolled to the study on ICU admission.

The antibiotics that were used to treat the infections present on admission were continued, unless cefotaxime could be substituted; other agents thought to have an adverse effect on colonisation resistance were avoided if possible.

Results

The patients in the SDD and placebo groups were comparable in terms of demographic features. About 20-30% of all infections present on admission were acquired in hospital, and were equally distributed in both groups. Table Sixty-one.

Table Sixty-One: Demographic Details of Patients Infected on Admission

	SDD	Placebo	Withdrawn	Suitable
No of patients	59	76	29	27
Age	42.4	45.8	43	46.6
	±15.2	± 16.8	± 16.4	±15.7
Male:female	27:32	30:45	18:11	18:9
Hospit >48hrs	29	36	12	9
Community acq	47	64	23	21
Nosocomial	12	12	6	6
Infec past 1/12	29	43	29	24
APACHE	15.2	15.1	20.8	14.1
	± 8.3	± 7.3	± 11.7	± 6.6
Organ failure	1.4	1.4	1.8	1.7
	± 0.6	± 0.6	± 1.1	± 0.7

Hospit > 48 hrs: hospitalised for more than 48 hours before ICU admission

Community acqu, Nosocomial : Community or Nosocomial origin of infections present on ICU admission.

Infec past 1/12: Infection in month prior to ICU admission.

** p=0.42 Chi-square test.*

The diagnostic categories of the patients are shown in Table Sixty-two. The various diseases were not significantly differently distributed between the two groups.

Table Sixty-Two: Diagnostic Categories of Patients Admitted with Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients	59	76	29	27
ARDS	3	5	1	6
Respiratory dis	11	7	6	3
Surgery	9	12	3	2
CVS	2	0	0	0
Neurological	8	9	4	3
Other	6	9	5	2
Pneumonia*	12	23	7	3
Trauma	8	11	3	8

p=0.26 Chi-square test

Factors thought likely to predispose to the development of secondary infection were equally distributed between the active and placebo groups, except for immobilisation: significantly more patients in the SDD group had more prolonged immobilisation.

Table Sixty-Three: Factors Potentially Predisposing to the Development of Secondary Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients	59	76	29	27
Carcinoma	4	2	2	0
Immunosup drugs	5	2	2	5
Diabetes	4	6	3	4
Conn tiss dis	0	3	1	0
Malnutrition	10	8	3	0
Obesity	4	8	2	6
Alcohol abuse*	13	25	6	4
Peptic ulcer	3	6	2	2
Shocked	12	9	4	2
Emergency surg	10	12	5	2
Albumin < 30mmol/l	43	60	20	14
Bedbound > 5days#	42	33	5	12
H-2 blocker	15	22	6	3

*** p= 0.23 Chi-square test**

 # p = 0.002 Chi-square test

The invasive and therapeutic monitoring procedures including ventilatory requirement during ICU stay are shown in Table Sixty-four and were equally distributed between both groups, apart from a significantly increased requirement for total parenteral nutrition in the placebo group.

Table Sixty-Four: Invasive Therapeutic and Monitoring Procedures

	SDD	Placebo	Withdrawn	Suitable
No of patients	59	76	29	27
Dialysis	6	9	1	1
TPN*	17	38	4	7
Enteral feed	49	69	14	23
Plasmapheresis	1	2	0	0
Chest drain	10	24	2	6
Arterial line	31	51	13	10
Central line	47	71	22	18
Peripheral line	59	76	29	43
Pulm art cath	43	51	11	16
TPN >5 days*	21	30*	3	5
Duration IPPV	12.7	13.6	34	10.2
	± 13.8	±11.3	± 5.2	± 10
Tracheostomy	(n=21)	(n=34)	(n=2)	(n=7)
	21.9	19.8	8.9	14.7

**p = 0.02 Chi-square test*

Complications occurred with equal frequency in both groups and are shown in Table Sixty-five.

Table Sixty-Five: Complications developing in the ICU

	SDD	Placebo	Withdrawn	Suitable
No of patients	59	76	29	27
GIT bleed	6	7	1	0
Hepatic failure	6	10	1	2
Cardiac failure	0	1	0	0
Renal failure	2	6	0	0
Haem failure	2	3	0	0
CNS coma	2	2	0	0
Shock (SBP < 70)	3	1	7	1
Gastric aspirat	2	1	0	1
Feed aspiration	1	2	10	0
Pulmon embolus	0	0	0	0
Pneumothorax	2	5	1	0
Other vent comp	0	0	0	0
Failed wean*	2	10	1	5
Diarrhoea	12	17	1	3
Ven thrombosis	3	2	0	1
Other	7	7	1	2

* *p = 0.09 Chi-square testing*

There were significantly more infections in the placebo group, and these occurred at all sites.(Table Sixty-six).

Table Sixty-Six: Types of Infection

	SDD	**Placebo**	**Withdrawn**	**Suitable**
No of patients	59	76	29	27
No of patients*	13	32	2	9
No infections	19	49	4	16
Bronchial	7	13	3	10
Nosocom pneumon.	1	7	1	1
IV catheter	5	7	0	0
Septicaemia	4	7	0	0
UTI	0	3	0	3
Other	2	9	0	0

** $p = 0.023$ Chi-square test*

Gram positive infections occurred with equal frequency in both groups, however, there was a significantly increased frequency of all Gram negative infections in the placebo group (p=0.02). No infections were caused by the *Enterobacteriaceae* in the SDD patients, whereas there were 12 infections in the placebo group (p=0.03).

Table Sixty-Seven: Organisms causing Secondary Infection

	SDD	Placebo	Withdrawn	Suitable
S.aureus	7	5	0	2
S.epidermidis	4	5	0	1
Streptococci	0	1	0	0
Enterococcus	0	3	0	0
H.influenzae	0	1	0	1
E.coli	0	6	0	3
Enterobacter spp	0	3	0	1
Klebsiella spp	0	3	0	1
Pseudomonas spp	1	4	2	0
Acinetobacter sp	6	9	2	5
Candida spp	0	3	0	0
Other	1	2	0	1

The morbidity and mortality were similar in both active and placebo groups, although there were more deaths in the ICU in patients who did not receive SDD. The relationship of death to secondary infection was assessed as: "definite" in 3 patients in the placebo group, "possible" in the 2 patients who received SDD and 4 who received placebo, and "unlikely" in the remainder.

Table Sixty-Eight: Morbidity and Mortality

	SDD	Placebo	Withdrawn	Suitable
No of patients	59	76	29	27
ICU stay	17.5 ± 15.5	18.8 ± 13.9	7.8 ± 22.4	14 ± 10.9
Hospital stay	32.7 ± 23.8	34.2 ± 21	17.6 ± 34.1	31.21 ± 34.6
ICU deaths*	5	11	14	1
Hospital deaths	5	6	1	1
% Mortality	17%	22.3%	51.7%	7.4%

* p = 0.42 Chi-square testing

Discussion

It has been suggested that part of the explanation for the lack of efficacy of SDD in units admitting predominantly medical patients [265], has been that such patients are often primarily infected and thus less likely to demonstrate benefit from the use of SDD. These patients form a considerable proportion of the patients requiring admission to the medical ICU. However, in our study significant benefit has been demonstrated from the use of this technique in this subgroup, whereas no benefit was found in either the surgical or trauma subgroups. This suggests that there must be another explanation

for the failure of SDD to reduce the incidence of nosocomial infection, morbidity or mortality in medical patients.

The overall incidence of secondary infections was not higher in primarily infected patients (29.3%) compared with the entire study group; however, the incidence was significantly reduced in those who received SDD (22%), with complete elimination of the *Enterobacteriaceae* as nosocomial pathogens. In spite of this reduction in the incidence of secondary infection, there was no significant effect on morbidity or mortality. When the causes of death were analysed, however, only two deaths in the SDD patients were related to secondary infection, compared with seven in the placebo group; in the placebo group, three of these deaths were directly attributable to secondary infection, while in four, nosocomial infection played a contributory role. Had the numbers been larger, this might have achieved statistical significance.

The organisms identified in the three placebo patients as responsible for death were *Candida spp* in one, *Candida spp* and *Staphylococcus aureus* in another, and *Enterococcus* in the third. This suggests that the use of amphotericin B in the prophylactic regimen may be extremely important, particularly in patients who receive prolonged therapy with broad-spectrum antibiotics. The overgrowth of *Staphylococcus aureus* and *Enterococcus* in the gastrointestinal surveillance samples of all patients may have resulted from the use of SDD and contributed to the higher incidence of infections caused by those organisms inherently resistant to the agents used in the regimen.

Some authors have suggested that the reservoir of microorganisms in uncontaminated patients may have explained the lack of efficacy shown in some studies; however, even in those studies where infected patients were excluded, but nevertheless treated within the same ICU, effective decontamination was reported [263,264,268]. This suggests that treating decontaminated and undecontaminated patients in the same unit, plays no part in the incidence of secondary infection.

More studies evaluating the efficacy of SDD in infected patients, particularly using enteral antifungal prophylaxis alone, or in combination with drugs which will also prevent staphylococcal infections, are clearly required to assess its potential benefits. The potentially lethal consequences of systemic fungal infections, and its difficulty of diagnosis may well be sufficient to justify even costly therapy with enteral amphotericin B in certain at-risk groups of patients. However, the greater ease in detecting staphylococcal superinfection and the concern over the emergence of further antimicrobial resistance in the Gram positive organisms may mitigate against the use of anti-staphylococcal prophylactic regimens.

9.3.7 Patients with Primary Pneumonia

Introduction

Patients with primary pneumonia requiring ICU admission have a particularly high mortality (29%) [141]. These patients usually require prolonged ventilation, and antibiotic therapy for a number of weeks. Pneumonia itself has been shown to predispose to further episodes of respiratory tract infection [304] and this may apply to secondary infection occurring during the hospital stay. This subgroup who thus may be at particular risk for the development of secondary infection, has not previously been assessed with regard to the efficacy of selective decontamination.

Patients and Methods

This prospectively selected subgroup formed part of the parent study on selective decontamination, and the protocol and methods were thus identical. Primary pneumonia was defined as an acute febrile illness, with clinical signs of consolidation and crackles and radiological opacification, in patients who had not been hospitalised in the previous month.

Results

Forty-four patients fulfilled criteria for inclusion in this subgroup, and there were a further three who were suitable but not included. There was no difference between the SDD and placebo groups, as is demonstrated in Table Sixty-nine. The patients who were withdrawn were unable to be included because they did not meet the criterion for duration of ICU stay or intubation (6 early deaths).

Table Sixty-Nine: Demographic Details of Patients with Pneumonia

	SDD	Placebo	Withdrawn	Suitable
No of patients*	12	24	8	3
Age	43.2	45.7	56.9	47
	± 13.1	±18.3	± 14.4	± 3.5
Male:female	8:4	16:8	2:5	1:2
Hospit >48hrs	6	13	1	3
APACHE**	14.6	17.1	27.4	15
	± 6.4	± 5.9	±13.7	2.65
Organ failure	1.4	1.5	1.7	1
	± 0.7	± 0.6	± 1	0

** p =0.09 Chi-square test*

*** p = 0.25 Student's t test*

The factors which have previously been described as predisposing to the development of secondary infection were equally distributed between the active and placebo groups. (Table Seventy). There were more patients who were shocked on admission included in the SDD group, but because of the small numbers in the study, this did not achieve statistical significance.

Table Seventy: Possible Predisposing Factors to the Development of Secondary Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients*	12	24	8	3
Carcinoma	1	1	1	0
Immunosup drugs	1	2	0	0
Diabetes	1	2	3	0
Conn tiss dis	0	1	0	0
Malnutrition	2	1	1	0
Obesity	2	2	0	0
Alcohol abuse	5	8	5	1
Peptic ulcer	1	1	2	0
Shocked*	4	1	2	0
Albumin <30	10	20	4	3
Bedbound >5days	7	22	0	2

* $p = 0.06$ Chi-square test

The use of invasive and therapeutic monitoring procedures whilst in the ICU was of equal frequency in both SDD and placebo groups. (Table Seventy-one).

Table Seventy-One: Invasive Therapeutic and Monitoring Procedures

	SDD	**Placebo**	**Withdrawn**	**Suitable**
No of patients*	12	24	8	3
Dialysis	2	3	0	0
TPN	4	15	1	0
Enteral feed	11	22	3	3
Plasmapheresis	0	0	0	0
Chest drain	3	10	1	1
Arterial line	7	19	4	0
Central line	10	23	4	3
Peripheral line	12	24	7	3
Pulm art cath	9	18	3	3
TPN >5 days	3	12	0	1
Duration IPPV	11.1	12.8	1.9	19.3
	± 9.7	±5.6	± 1.2	± 16.2
Tracheostomy	(n=4)	(n=9)	0	
	16.3	17.2	0	

Complications occurred infrequently in both groups. Five patients developed pneumothoraces, related to positive pressure ventilation.(Table Seventy-Two)

Table Seventy-Two: Complications Developing Within the ICU

	SDD	Placebo	Withdrawn	Suitable
No of patients*	12	24	8	3
GIT bleed	1	3	0	0
Hepatic failure	2	3	0	0
Cardiac failure	0	1	1	0
Renal failure	1	2	0	0
Haem failure	0	2	0	0
CNS coma	0	1	0	0
Shock (Sbp < 70)	0	1	2	0
Gastric aspirat	0	0	0	0
Feed aspiration	0	1	0	1
Pulmon embolus	0	0	0	0
Pneumothorax	1	4	0	0
Other vent comp	0	0	0	0
Failed wean	2	2	0	0
Diarrhoea	1	6	0	0
Ven thrombosis	1	0	0	0
Other	2	1	0	0

Only one nosocomial infection occurred in the patients who received SDD, compared with 10 infections in the placebo group. Five of the infections in the placebo group were respiratory. Table Seventy-three.

Table Seventy-Three: Types of Secondary Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients*	12	24	8	3
No of patients*	1	8	0	1
Infections	1	10	0	1
Bronchial	1	3	0	1
Nosocom pneum	0	2	0	0
IV catheter	0	3	0	0
Septicaemia	0	2	0	0

* p = 0.24 Chi-square test

The organisms causing infection are shown in Table Seventy-Four. Infections were predominantly caused by Gram negative bacilli.

Table Seventy-Four: Organisms Causing Secondary Infection

	SDD	Placebo	Withdrawn	Suitable
S.epidermidis	0	1	0	0
Enterobacter	0	1	0	0
Klebsiella spp	0	1	0	0
Pseudomonas spp	0	2	0	0
Acinetobacter spp	1	2	0	1
Candida spp	0	1	0	0
Other	0	1	0	0

Morbidity and mortality were similar for active and placebo groups, although unfortunately the numbers are too small for meaningful comparison.

Table Seventy-Five: Morbidity and Mortality

	SDD	Placebo	Withdrawn	Suitable
No of patients*	12	24	8	3
ICU stay	18 ± 16.1	17.7 ± 11.3	2.1 ± 1.2	22.7 ± 16.9
Hospital stay	32.3 ± 22.3	35.4 ± 20.4	5.9 ± 8.6	41 ± 22.5
ICU deaths	0	5	6	0
Hospital deaths	1	1	0	0
Mortality#	8.3%	25%	75%	0%

 # p = 0.45 Chi-square test

Discussion

Only one patient in the SDD group died: this patient's therapy was withdrawn because of hypoxic brain damage sustained following cardiac arrest on intubation and prior to ICU admission. Four of the twelve patients enrolled to the SDD group were shocked on admission, compared with only one in the control group: this alone, although not statistically significant, should have predisposed to a higher mortality rate in this group, as shock in pneumonia has been shown to be a poor predictor of outcome (Hammond, unpublished data). There was a total of 13 deaths, of which six occurred early from respiratory failure or multiple organ failure in the withdrawn group. There were six deaths in the placebo group of which one was definitely related to secondary infection (*Candida* septicaemia), and one possibly related to secondary infection.

Although 47 patients with pneumonia were admitted over the study period, only 36 met criteria for analysis, and these numbers are insufficient to show statistically relevant differences. It is however very suggestive that SDD exerted a protective effect in patients with pneumonia, and may prevent mortality, as two of the patients in the placebo group died from secondary infection.

9.4 Microbiological Surveillance during SDD

Introduction

While the use of antimicrobial prophylaxis with SDD has been shown to reduce the incidence of secondary infection [261,263,274], mortality has not been influenced [279], and there has been concern that the longterm application of topical and systemic antibiotics may lead to the development of increasing antimicrobial resistance. Surveillance cultures thus form an important and integral part of the technique [263].

Previous studies have suggested that SDD has very little influence on the resistance patterns of aerobic Gram negative bacilli [275,276], although most of the studies have not monitored the resistance patterns of the microorgansisms for prolonged periods. There are reports to suggest that the overgrowth of organisms not susceptible to the agents used in the decontamination regimen may be promoted by SDD, and that the incidence of infections due to *Staphylococcus aureus*, coagulase negative staphylococci and enterococci may actually increase [305].

This section reports the results of surveillance cultures taken during the double-blind randomised study of selective parenteral and enteral decontamination in our respiratory intensive care unit over a two year period. The clinical results suggested that although the incidence of infections caused by the *Enterobacteriaceae* was significantly reduced, infections due to staphylococci actually increased in those who received the trial drugs, with a resultant non-significant reduction in the overall incidence of nosocomial infection.[305]

Patients and Methods

This double-blind randomised placebo controlled trial of selective decontamination of the digestive tract (SDD) was performed in the two five-bedded open plan units of the Respiratory ICU of our hospital, admitting all categories of medical, surgical and trauma patients. All patients who were expected to be intubated for more than 48 hours and to remain in the ICU for more than 5 days, were randomised on admission, by computer generated numbers, to receive either the active decontamination regimen (2 ml methylcellulose gel containing 2% wt/vol each of tobramycin, polymyxin E and amphotericin B, applied to the oropharynx with a gloved finger 6 hourly; 10 ml of an enteral solution containing amphotericin B 500 mg, tobramycin 80 mg and polymyxin E 100mg, 6 hourly by mouth or nasogastric tube) or indistinguishable, inert, placebo compounds. Both groups of patients received intravenous cefotaxime 1g 8 hourly for the first 72 hours of admission. The study was approved by the ethics committee of the University of Cape Town.

322 patients were enrolled, but 83 patients were withdrawn (3 protocol violations, 80 with too short a duration of stay) and these withdrawals have not been included in the microbiological surveillance analysis. 239 patients were suitable for analysis: 114 received the active regimen and 125 placebo; the patients in the two groups were fully comparable in terms of age, sex distribution ratio, disease categories and severity of illness parameters.

All ICU and laboratory staff were blinded until the end of the trial. The results of microbiological surveillance cultures were not reported to the clinical staff or diagnostic section of the microbiological laboratory, as they were expected to reveal a difference between verum and placebo groups. A diagnosis of infection was made on the basis of clinical evaluation and diagnostic microbiological specimens only.

Microbiological surveillance specimens included swabs from the oropharynx and the rectum, samples of urine and aspirates of gastric and tracheal secretions. These specimens were obtained on admission and then twice weekly, being taken shortly before the morning administration of medications. Collection of the gastric and tracheal secretions continued until extubation, whilst the remaining specimens were collected throughout ICU admission, and final specimens was taken three days after discharge from the ICU.

Processing of specimens was as follows: Gram-stains and semiquantitative leucocyte counts were carried out on the samples of urine and tracheal aspirate specimens in the diagnostic section of the microbiology laboratory. Urines were cultured semiquantitatively on MacConkey agar, while tracheal aspirates were plated onto boiled blood, 5% horse blood and MacConkey agars. After processing and interpretation, these cultures were passed to the surveillance section. Gastric aspirates and swabs from the oropharynx were cultured as for tracheal aspirates, but in addition were plated onto sodium azide-aesculin agar and Saboraud's agar. Rectal swabs were cultured in the same way but without a boiled blood agar plate.

To minimise the effect of any residual antimicrobial, these swabs (or swab of the gastric aspirate fluid) were inoculated into 10ml amounts of brain-heart infusion broth. These swabs were subcultured when absence of growth on the agar plates indicated such an effect. All incubations were in air overnight at $37^{o}C$, except for the boiled blood agar plates which were incubated in 5-10% CO_2.

Morphologically distinct colonies were identified by standard methods [306]. Susceptibility testing was by the disc diffusion method. Isolates of *Pseudomonas* species were tested for susceptibility to piperacillin, ceftazidime, gentamicin, tobramycin and amikacin, while other AGNB and non-fermenters were tested for susceptibility to amoxycillin, cefamandole, cefotaxime, gentamicin, tobramycin, amikacin, co-trimoxazole and chloramphenicol.

Tobramycin resistant isolates of non-fermenters (usually one morphologically distinct isolate per patient) were stored on Dorset egg slopes at room temperature. Where these non-fermenters were identified as *Xanthomonas* or *Flavobacterium* species, polymyxin susceptibility was determined by multi-point inoculation of agar containing up to 1000 mg/L polymyxin B.

Definitions.

Aerobic Gram negative bacilli (AGNB) were *Enterobacteriaceae* and *P. aeruginosa*.

An organism was "acquired" when no prior specimen from the same site grew an organism with the same identification and susceptibility profile.

"Colonisation" was the isolation in two or more consecutive specimens from the same site of organisms with the same identification and susceptibility profile.

Pseudomonas aeruginosa was assumed resistant to cefotaxime and *Proteus, Providencia* and *Morganella species* were assumed resistant to polymyxin [275].

Resistant AGNB were these bacteria and *Enterobacteriaceae* resistant to cefotaxime or tobramycin on susceptibility testing.

"Infection" was diagnosed using strict clinical and microbiological criteria and was defined as secondary infection when signs developed more than 48 hours after admission to the ICU [305]

Statistical analysis.

The presence of organisms isolated from the various specimens was analysed in intervals determined by the duration of ICU stay. [263] These intervals were: On admission, 8-72 hours, 3-7 days, second week, third week and fourth to eighth weeks. The numbers of samples, isolates or patients were the denominators for proportions [263,275,277,278]. The difference between proportions was tested by chi-squared

without Yate's correction, or Fisher's exact test (alpha= 0,05) and, where relevant, 95% confidence intervals for the difference between proportions were obtained.

Results

Specimens for microbiological surveillance were obtained from 239 patients (Verum: 114 Placebo: 125). The specimens were equally distributed between the two groups. with a total of 3806 gastrointestinal specimens, a mean of 15.2 verum and 16.6 placebo specimens per patient. Tracheal aspirates totalled 1207 (V5.1, P5.0) and urinary specimens 947 (V3.9, P4).

Colonisation of the gastrointestinal tract by AGNB in the decontaminated patients was significantly reduced, but not completely eliminated, with early clearance being evident in the oropharyngeal and gastric surveillance samples within 3 days, while requiring a week or longer to achieve a similar degree of rectal clearance. (Figures 8, 9, and 10)

Fig. 8 Oropharyngeal Surveillance

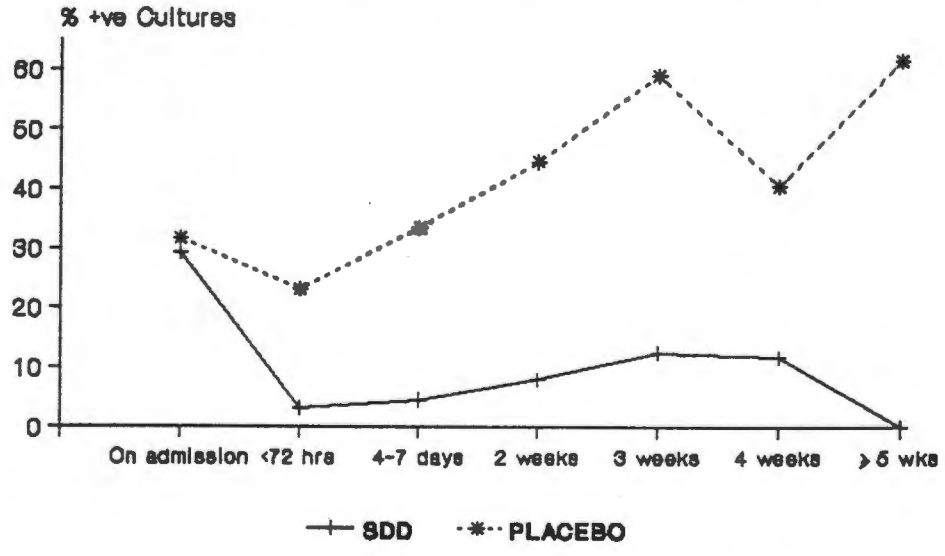


Fig. 9 Gastric Surveillance

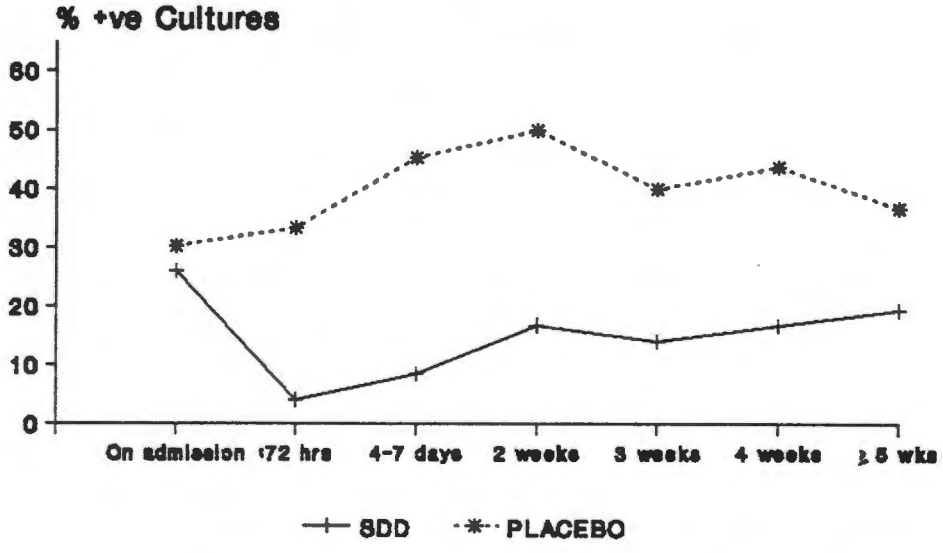
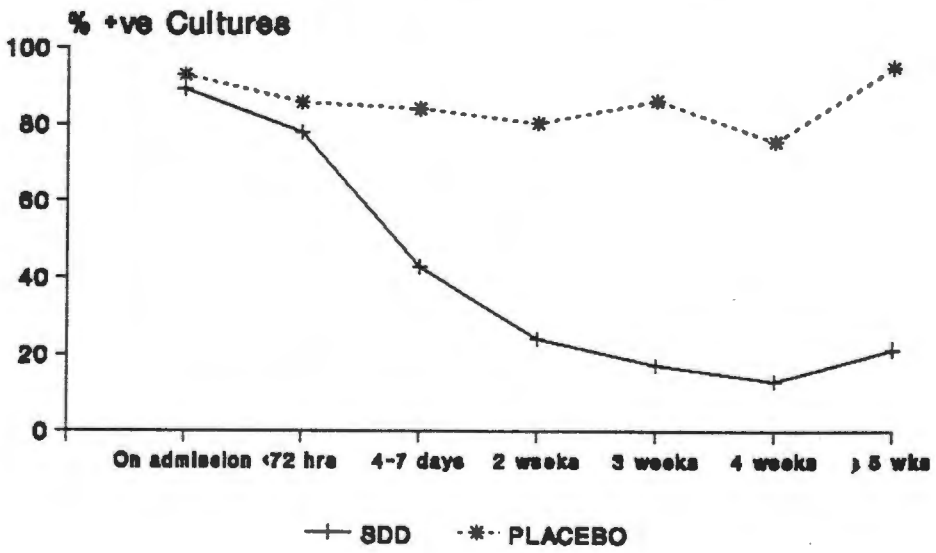


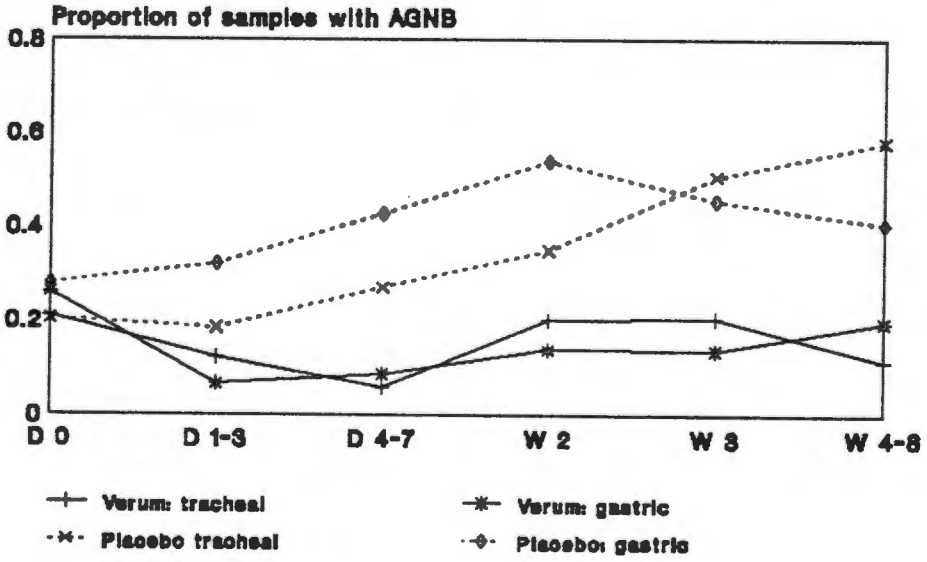
Fig. 10 Rectal Surveillance



Colonisation of the gastrointestinal tract by AGNB that had been present from admission occurred infrequently in all patients. Those who were treated with SDD had significantly less gastrointestinal colonisation (V: 0,16 P: 0,32 $p < 0,005$). None of the organisms which persisted as colonisers caused infection.

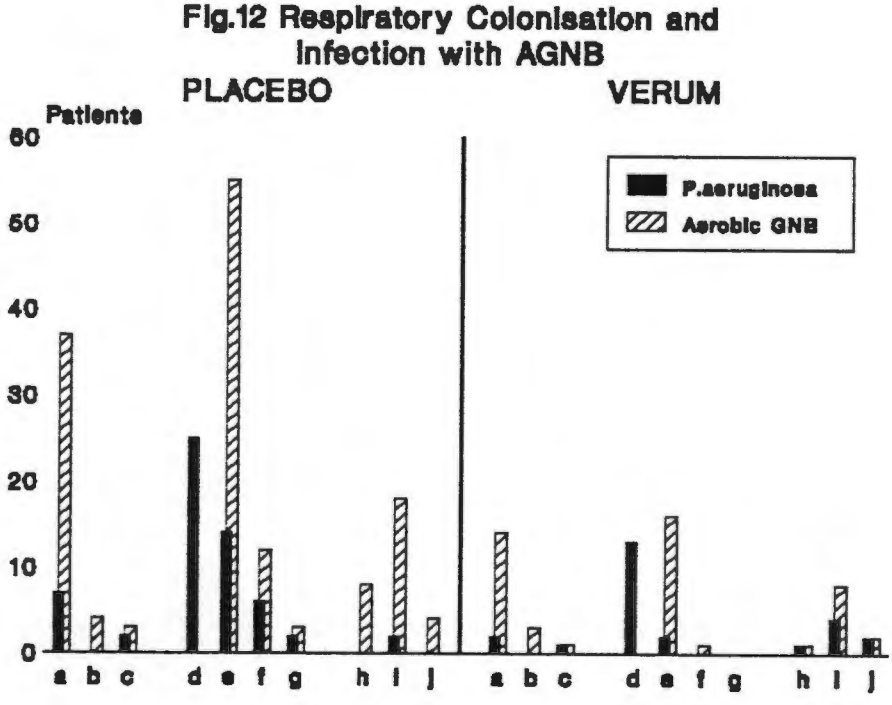
Tracheal and gastric colonisation by AGNB remained at very low levels in the active group, but increased significantly in the placebo group with more prolonged duration of stay The progression from colonisation of the digestive tract by AGNB acquired in the ICU, to colonisation of the trachea, with the subsequent development of secondary lower respiratory tract infections was only detected in placebo patients (V: 0 P: 7 $p < 0,01$). (Figure Eleven) The acquisition, colonisation and infection that occurred with AGNB in the patients during their ICU stay are shown in Figure Twelve.

Fig.11 AGNB in surveillance



In all secondary lower respiratory tract infections caused by_*P. aeruginosa*, in the patients who received the active regimen, the organisms were either present in the

trachea from admission, or acquired directly into the trachea, without evidence of prior gut colonisation. (Figure Twelve).



(a) colonisation from admission

(b) acquired tracheal colonisation

(c) unit-acquired infection

(d) unit-acquired Pseudomonas aeruginosa only

(e) unit-acquired gut colonisation

(f) unit-acquired tracheal colonisation

(g) unit-acquired infection

(h) co-incident gut colonisation

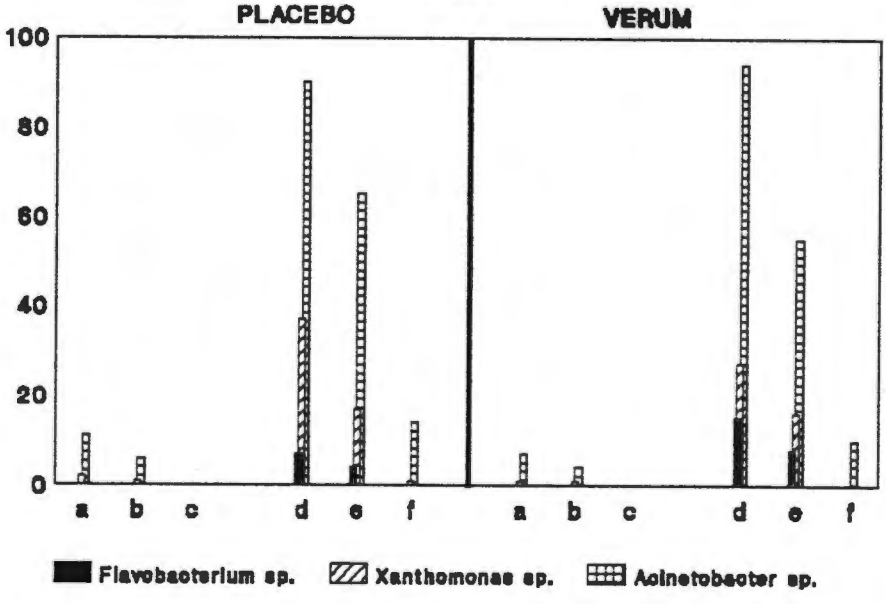
(i) unit-acquired tracheal colonisation

(j) unit-acquired infection

P. aeruginosa was less common in the digestive tract of verum patients when measured as isolates from specimens, but when measured by colonisation of patients, (V: 4 P: 12) this difference was not significant.

The 1174 non-fermenters isolated were identified as: *Acinetobacter* species (809), *Xanthomonas maltophilia* (195), *Flavobacterium* species (57) and non-aeruginosa pseudomonads. Non-fermenters were isolated with equal frequency from both groups of patients. These organisms were mainly isolated from tracheal aspirates (740 versus 354 specimens from other sites), but were uncommon until 8-72 hours after admission. The isolation of non-fermenters from other sites was uncommon in patients who received SDD (V: 0,047 P: 0,142 $p < 0,0001$). Acquired tracheal colonisation by *Acinetobacter* species was common, usually became evident during the first week of admission, (85/108 patients) and occurred throughout the trial. *Acinetobacter* species caused equal numbers of lower respiratory tract infections in both groups of patients and was the most common Gram negative organism resulting in unit-acquired colonisation and infection. The respiratory tract was the most frequent site of infection caused by this organism and, as with *Pseudomonas spp*, preceding gastrointestinal colonisation was not identified, suggesting an alternative route of acquisition. (Figure Thirteen).

Fig. 13 Acquisition, Colonisation and Infection with Non-Fermenters



(a) on admission

(b) persistent tracheal colonisation

(c) unit-acquired infection

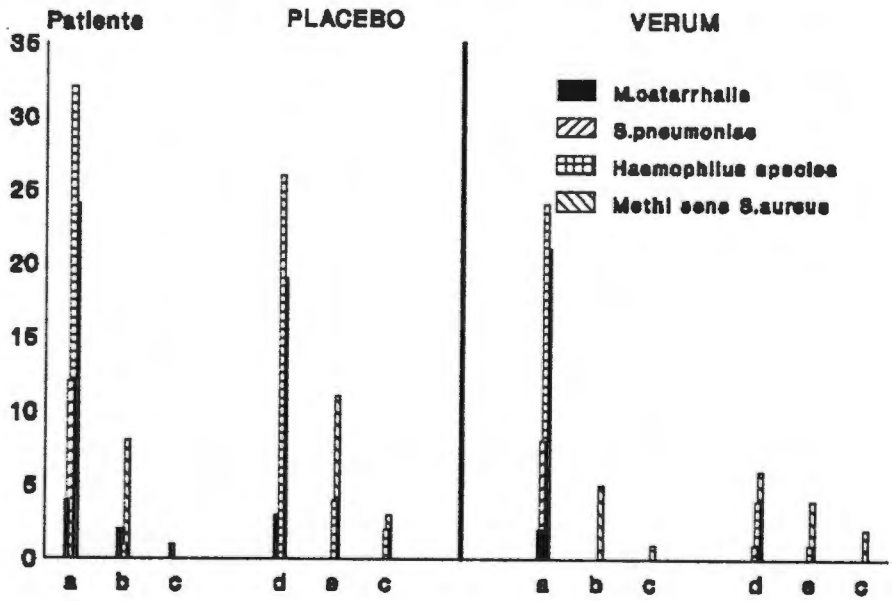
(d) unit-acquired

(e) unit-acquired tracheal colonisation

(f) unit-acquired infection

Most secondary lower respiratory tract infections were caused by "community-acquired" respiratory pathogens, particularly methicillin sensitive *Staphylococcus aureus* and, in placebo patients, *Haemophilus* species. The acquisition of *Streptococcus pneumoniae* and *Moraxella catarrhalis* after admission to the ICU was uncommon, and did not lead to either colonisation or infection (Figure Fourteen).

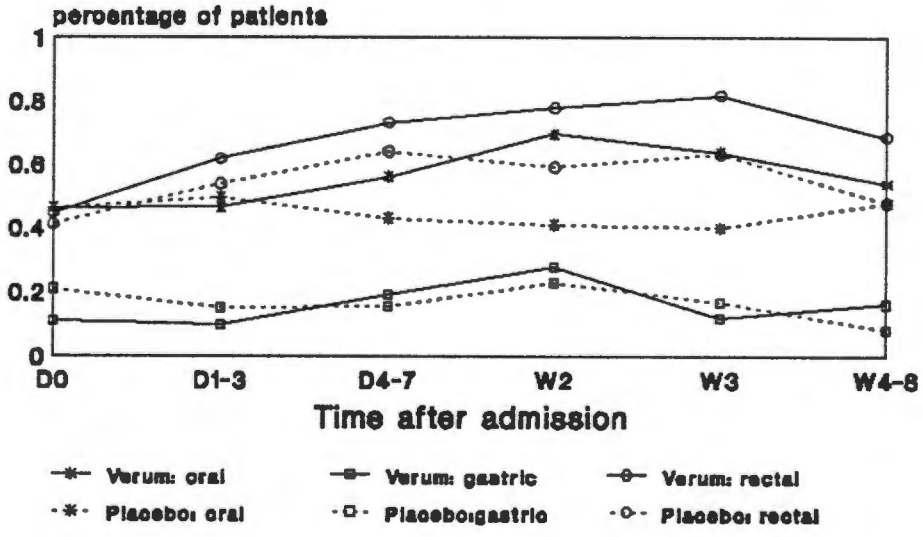
Fig. 14 Colonisation and Infection with "Normal" Oropharyngeal Flora



Both the acquisition and colonisation by "community-acquired" respiratory pathogens were more common in placebo than verum patients ($p < 0,05$). In neither group of patients were episodes of "early" hospital-acquired infection (48 hours to 5 days after admission) attributable to "community-acquired" pathogens such as *Streptococcus pneumoniae, Moraxella catarrhalis*, or *Haemophilus spp.*

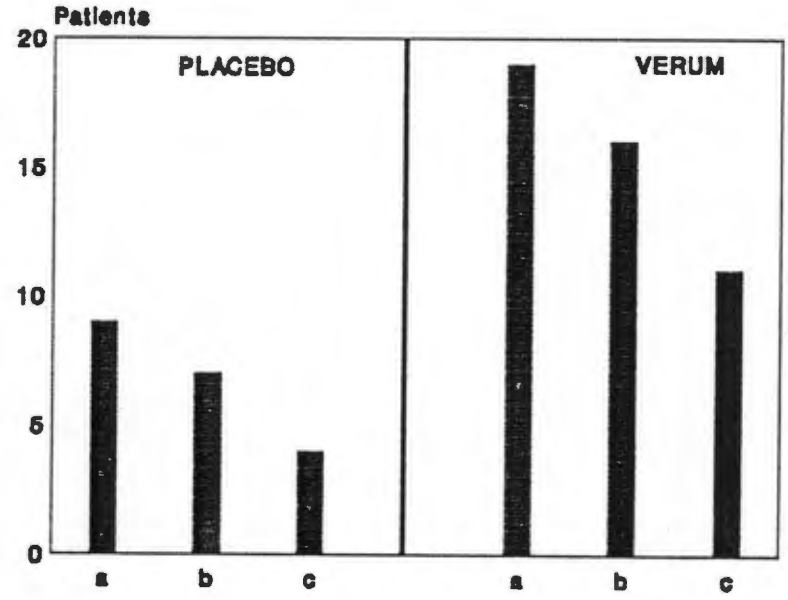
Colonisation of the gastrointestinal tract by DNase negative, methicillin- resistant and sensitive staphylococci showed an increase in all patients, but this was significantly greater in those who received SDD. (Figure Fifteen).

Fig.15 Colonisation with Staphylococcus Epidermidis



The majority of secondary lower respiratory tract infections were due to methicillin sensitive *Staphylococcus aureus* (Figure Fourteen). There were no identified outbreaks of methicillin-resistant staphylococcal infection during the study period, however, there was an increase in both colonisation and infection with this organism in the patients who received the active regimen. (Figure Sixteen).

Fig.16 Acquistion, Colonisation and Infection with MRSA



(a) unit-acquired isolates

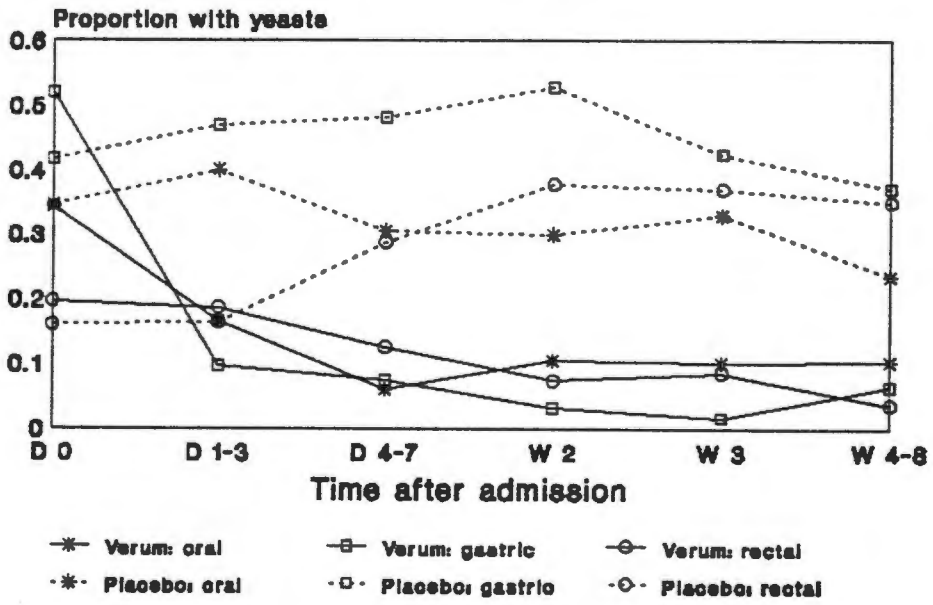
(b) unit-acquired colonisation

(c) unit-acquired infection

There were significantly more Gram postive infections caused by all the staphylococci in the patients who received SDD, than in the placebo group (26 infections vs 16, p= 0.003); in some of these the route was gastrointestinal, but in others direct acquisition via the exogenous route played a role.

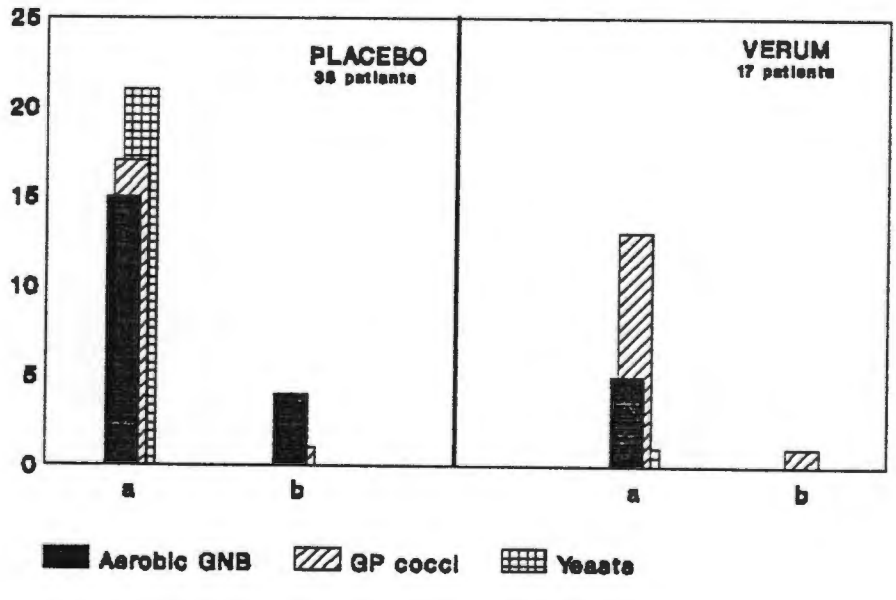
The overgrowth of yeasts was controlled by the use of SDD. The topical application of amphotericin B almost completely abolished colonisation by yeasts in the decontaminated patients; there was however no difference in the incidence of infection caused by *Candida albicans* in the two groups, and in one decontaminated patient infection which failed to respond to amphotericin B was detected. (Figure Seventeen). *Candida albicans* was identified in two patients who died from secondary infection acquired in the ICU.

Fig.17 Yeast Overgrowth



The enteral amphotericin decontamination was sufficient to eliminate virtually all urinary fungal colonisation. The low incidence of fungal infection in the placebo patients may have been partly due to active topical oropharyngeal and urinary anti-fungal therapy commenced whenever significant and persistent colonisation was noted in the clinical samples. The effect of SDD on urinary tract colonisation and infection is illustrated in Figure Eighteen.

Fig.18 Urinary Colonisation and Infection

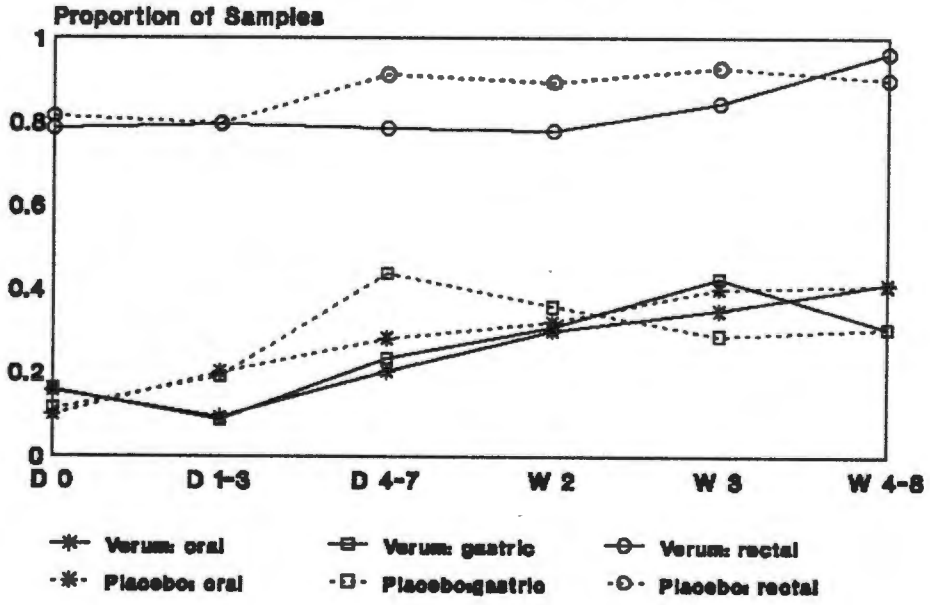


(a) Colonisation

(b) Infection

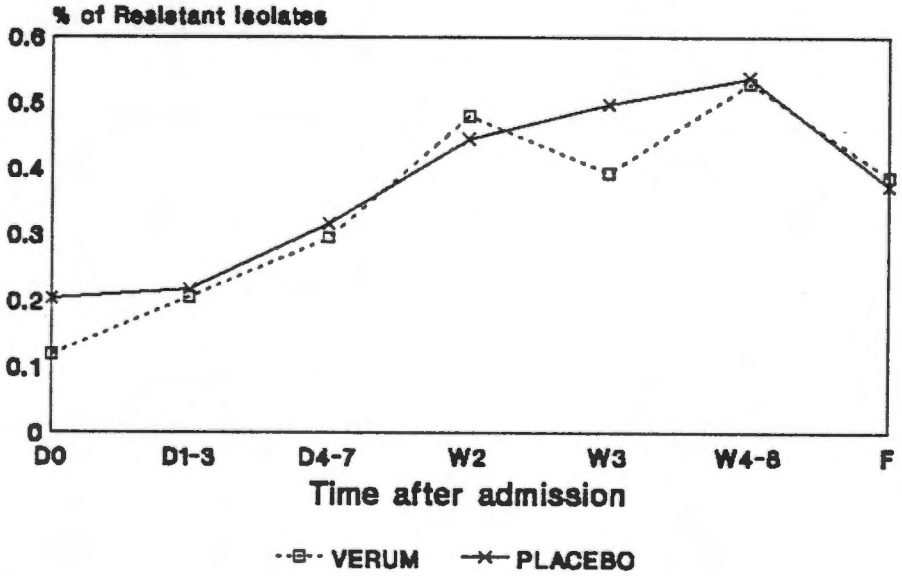
The use of SDD appeared to have no influence in promoting overgrowth or infection by enterococci. Increasing colonisation of the gastrointestinal tract by enterococci occurred to a similar extent in all patients throughout the patients'stay: 16% of SDD patients were colonised on admission, and this increased to 30% by the second week, and 41% of patients were colonised by the fourth week. In the placebo group, 10% were colonised on admission, 32% by week 2, and 41% after four weeks. There were three enterococcal infections which occurred in the placebo group: one IV catheter related infection which lead to death and two abscesses. (Figure Nineteen).

Fig.19 Enterococcal Overgrowth



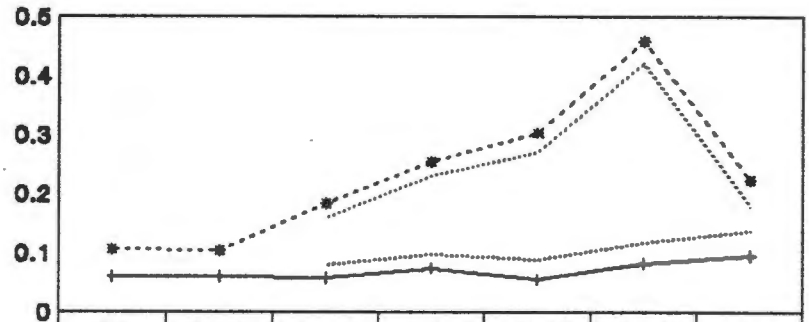
The percentage of resistant Gram negative organisms increased in both groups from soon after admission.(Figure Twenty).

Fig.20 Colonisation by Resistant Gram Negative Micro-organisms



When comparing the total number of resistant isolates, there was a significant increase of resistant Gram negative isolates in the placebo group (Figure Twenty-One).

Fig.21 Proportion of Resistant Gram Negative Isolates

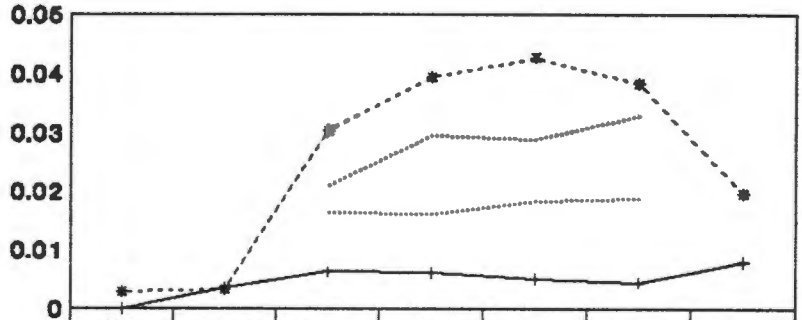


	D0	D1-3	D4-7	W2	W3	W4-8	F
VERUM	0.059	0.059	0.058	0.073	0.055	0.081	0.094
PLACEBO	0.105	0.103	0.183	0.263	0.302	0.457	0.221
95%			0.06	0.097	0.088	0.117	0.136
CI			0.159	0.228	0.268	0.421	0.179

VERUM PLACEBO 95% CI

Although no increase in antibiotic resistance by the AGNB was seen in the SDD group, in the placebo group a significantly increasing number of isolates resistant to tobramycin and cefotaxime was found. (Figure Twenty-Two)

Fig. 22 Proportion of Cefotaxime Resistance in Surveillance Cultures

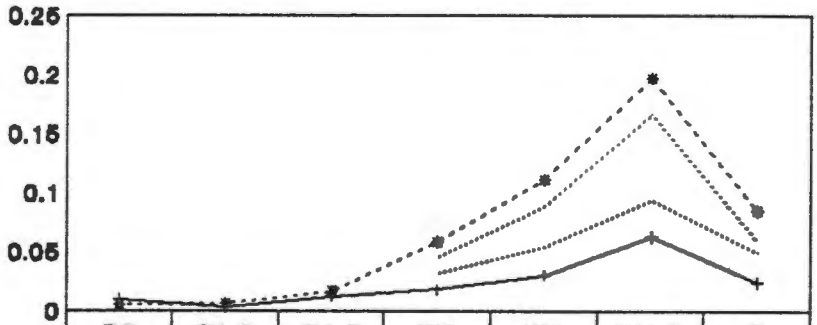


	D0	D1-3	D4-7	W2	W3	W4-8	F
VERUM	0	0.003	0.006	0.006	0.005	0.004	0.008
PLACEBO	0.003	0.003	0.03	0.039	0.043	0.038	0.019
95% CI			0.016	0.016	0.018	0.019	
lower limits			0.021	0.029	0.029	0.033	

VERUM PLACEBO 95% CI lower limits

The isolation of both cefotaxime and tobramycin resistant *Enterobacteriaceae* was less common in the digestive tract of patients receiving SDD, whether measured as isolates from specimens or as colonisation of patients (cefotaxime resistant, tobramycin susceptible V: 2 P: 20 $p < 0{,}001$ and tobramycin resistant V: 2 P: 19 $p < 0{,}001$). (figure Twenty-Three)

Fig. 23 Proportion of Tobramycin Resistance in Surveillance Samples

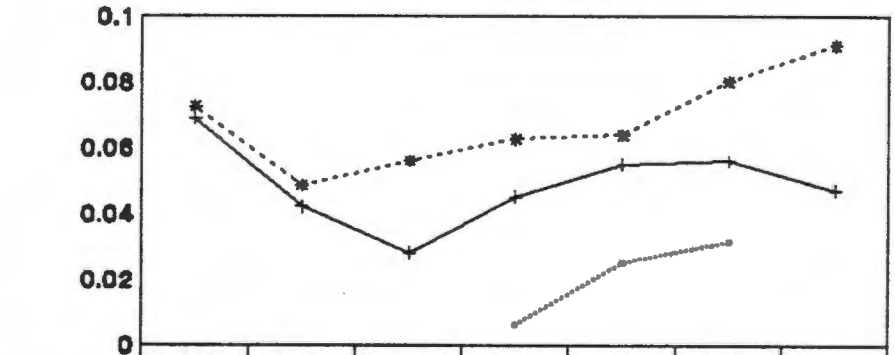


	D0	D1-3	D4-7	W2	W3	W4-8	F
VERUM	0.009	0.003	0.013	0.018	0.03	0.063	0.024
PLACEBO	0.006	0.006	0.017	0.058	0.111	0.197	0.084
95% CI				0.031	0.053	0.093	0.049
lower limit				0.045	0.087	0.166	0.059

VERUM PLACEBO 95% CI lower limit

Proteus, Providencia and *Morganella* species, which are intrinsically resistant to Polymyxin, were isolated with equal frequency in both groups and the colonisation of patients was also similar in both groups (V: 6 P: 8). In three patients who received SDD, these isolates were also found to be Tobramycin resistant. There was only one respiratory tract infection in a patient receiving SDD that could have been attributed to prior gut colonisation with *Proteus mirabilis*; this was an episode of sinusitis related to a nasogastric tube caused by a tobramycin sensitive organism. (Figure Twenty-four)

Fig.24 Proteus, Providencia Morganella spp and Tobramycin Resistance



	D0	D1-3	D4-7	W2	W3	W4-8	F
VERUM	0.069	0.042	0.028	0.045	0.055	0.068	0.047
PLACEBO	0.072	0.049	0.056	0.063	0.064	0.08	0.091
TOBRA R				0.006	0.025	0.031	

The majority of non-fermenters were resistant to the agents used in the decontamination regimen, apart from polymyxin E; most isolates of these organisms (92%) were resistant to cefotaxime. Although tobramycin resistant *Acinetobacter species* were isolated less often in the patients who received SDD (V: 0,46 P: 0,59 $p < 0,0005$) colonisation (V: 27 P: 34) was not significantly different. Most isolates of other non-fermenters (94%) were resistant to tobramycin. All isolates of *Flavobacterium* species were resistant to 1000 mg/L polymyxin. Acquired tracheal colonisation by

Xanthomonas maltophilia and *Flavobacterium* species was recognised more often in the second year of the trial (9/14 and 11/12 patients, respectively). Colonisation by *X. maltophilia* occurred equally in both groups of patients, and, although colonisation by *Flavobacterium* species was more common in verum than placebo patients (V: 8 P: 4), the difference was not significant. *X. maltophilia* was responsible for one catheter-related (verum) and one respiratory (placebo) infection. No infections were attributed to *Flavobacterium species*.

Methicillin resistant *Staphylococcus aureus* (MRSA) were more commonly acquired in the ICU in patients who received SDD, whether measured as total isolates, or as number of patients with colonisation (isolates in consecutive specimens from the same site: V: 16 P: 7 $p < 0{,}025$). However, secondary infections caused by MRSA were not more common in verum patients (V: 7 P: 5).

Contamination of urine with yeasts and AGNB was less common in verum patients (V: 6 P: 34 $p < 0{,}001$, Figure Eighteen). Urinary tract infection was infrequent. In 50% of the 8 patients who developed urinary tract infection, rectal isolation of the causative AGNB was noted to precede infection.

Discussion

The aim of this detailed microbiological surveillance was to detect the effects of SDD on colonising and pathogenic flora, and to monitor for the emergence of antibiotic resistance and overgrowth by organisms not susceptible to the agents used in the decontamination regimen.

Our study design differed from the other studies of SDD in that patients in both the active and placebo groups were given intravenous cefotaxime for 72 hours following admission. Cefotaxime was given to both groups to avoid the frequent unblinding which might otherwise have been necessary, because of uncertainty as to whether the patients were receiving an antibiotic. The absence of early infections by "community"

pathogens may have been due to the initial effect of the systemic cefotaxime administered to all patients. This may be one of the reasons why our study of SDD failed to demonstrate a significant reduction in the number of patients with secondary infections. A recent paper [17] using cefoxitin prophylaxis to prevent the development of early onset pneumonia in patients requiring mechanical ventilation, however, failed to find any benefit from its use, suggesting that this alone was not the reason.

Despite successful clearance of the *Enterobacteriaceae* from the gastrointestinal tract of decontaminated patients, and the clear reduction in incidence of nosocomial infections caused by this group of organisms, the overall incidence of secondary infections was not significantly reduced in the patients who received SDD. There may be several reasons for this: 1) the primarily low incidence of secondary infections caused by the *Enterobacteriaceae* in our patient population, 2) the increased incidence of Gram positive infections in the decontaminated patients, 3) continuing infections caused both by the *Pseudomonads* and other non-fermenters and 4) routes other than the gastrointestinal tract contributing significantly to infection.

The overall incidence of nosocomial infection in our ICU during the two year period of SDD was 23.2%. The incidence of secondary infections caused by the *Enterobacteriaceae* was 29.7% in the placebo group [305]; the year prior to the commencement of the SDD study, 30% of nosocomial infections in the ICU were caused by *Enterobacteriaceae* (unpublished data). Although significantly higher than the incidence in the decontaminated patients (9.1%), this incidence is far lower than the incidence of over 80% reported in the studies where the most dramatic benefit from SDD was found [253,264,269,278].

Direct acquisition and colonisation of the trachea by sensitive organisms did occur in the patients who were decontaminated. *Pseudomonas aeruginosa* was the most important cause of such episodes and was isolated primarily from this site. Primary colonisation of the trachea by this organism is thought to occur because of bacterial

adherence mechanisms [33], which facilitate its adherence to the epithelium with resultant colonisation of the lower respiratory tract. Certainly, SDD appears to have had no influence in preventing this organism from causing respiratory tract infection, nor did it prevent gastrointestinal colonisation. The incidence of infections caused by this organism was not significantly different in the active and placebo groups (2 vs 5 infections).

Amongst the other non-fermenters, *Acinetobacter spp* was the most common pathogen, resulting most commonly in respiratory tract infections. This organism was not frequently isolated from surveillance samples of the gastrointestinal tract, and as with *P. aeruginosa* was frequently primarily isolated from the respiratory tract; its route of spread is generally accepted to be exogenous, and although less is known about its adherence to the epithelium of the lower respiratory tract, it appears that selective decontamination is not an effective way of preventing secondary infection with this organism. This organism was the most frequently isolated Gram negative pathogen, and appears to be increasing in importance as an opportunistic nosocomial pathogen in the ICU. This may well have contributed to the limited efficacy of SDD.

The significance of gastric colonisation and its relationship to secondary respiratory tract infection with both the *Enterobacteriaceae* and other Gram negative organisms has been questioned [39,300]; and mechanisms of direct tracheal or oropharyngeal acquisition and infection have been suggested to be of greater importance than may have been recognised by the protagonists of SDD. Our findings would support this.

Although the number of staphylococcal infections was significantly higher in the decontaminated patients, when comparing methicillin-resistant, methicillin-sensitive and DNase negative infections, the numbers were too small individually to achieve significance. This increase in infections with Gram positive organisms diminished the positive effect of SDD on the overall incidence of secondary infections. Whilst the staphylococcal infection rate was not excessively high in our unit, a much higher rate

of infection with this organism has been found in neurosurgical patients [199] during a study of SDD. The infections due to these organisms in our study were not necessarily related to gastrointestinal colonisation, and although gastrointestinal colonisation with these organisms actually increased during the study period. In many cases the route of infection appeared to have been via direct acquisition of these organisms.

There was concern that the use of SDD might promote an outbreak of methicillin-resistant *Staphylococcus aureus* infections; however, methicillin-resistant staphylococcal infections occurred with equal frequency in both groups, and no outbreaks were identified. It is nevertheless of concern that this increasing colonisation by resistant organisms might eventually have resulted in infection if the regimen had been continued for much longer. The use of alternative agents in the decontamination regimen to address the problem of staphylococcal infection has been reported to be successful [142]. The potential induction of resistance to vancomycin with the topical, prophylactic use of this drug however, needs careful evaluation.

Surveillance cultures showed a significantly increased incidence of both cefotaxime and tobramycin resistance by the non-fermenters in both groups, but there was also an increase in resistance to these agents by the *Enterobacteriaceae* isolated from the placebo group; however, during the trial period, there was no increase in the incidence of antibiotic resistance by the AGNB in early surveillance cultures. There were no outbreaks of multi-resistant organisms during the trial of SDD, or in the subsequent 12 months.

Topical amphotericin B proved highly effective in eliminating yeasts from both the gastrointestinal and urinary tracts. There were fewer systemic infections with *Candida albicans* in the patients who received the active regimen; however, this reduction was not significant. The incidence of fungal infection in the placebo limb may have been reduced with the use of topical therapy, whenever colonisation was clinically detected. The high mortality and difficulty in diagnosis associated with systemic fungal

infections, may be a sufficient reason for the more general use of topical antifungal prophylaxis, despite the expense and controversial role of amphotericin B in SDD.

Gastrointestinal surveillance cultures were of little value in detecting microorganisms likely to cause infection at other sites; however, the value of the surveillance cultures of tracheal aspirates was highlighted by their having detected in advance the presence of colonising organisms, which subsequently gave rise to the development of respiratory tract infections or septicaemias. The routine use of tracheal and urinary surveillance should help to predict the early development of infection and its likely aetiology, and assist in the choice of appropriate therapy.

9.5 Antibiotic resistance patterns and the long-term effects of selective decontamination

We recently reported the effect of the use of amikacin as the primary aminoglycoside on antibiotic resistance profiles in our ICU [34], during this time of increased amikacin usage, the rate of amikacin resistance increased from 8.5% to 39.6% with an associated increase in resistance to the other aminoglycosides. There has been much concern internationally that the use of selective decontamination, where clinically important antibiotics are used prophylactically and topically, might likewise have a detrimental effect on microbial resistance patterns. Surveillance cultures have been an integral part of the majority of studies on SDD, and assessment of resistance patterns during the use of SDD have shown no increase in the incidence of resistance in Gram negative organisms to the agents used. A number of studies have shown some increase in the number of organisms, not sensitive to the regimen, which has further heightened concern about the potential long-term effects of SDD [263,275,276,305]. None of these studies was designed to demonstrate, over an extended time period, the influence of SDD on the overall antimicrobial resistance patterns.

This prospective study compares the resistance patterns before the introduction of SDD with those obtained during the two year period of the trial of SDD, and those during the subsequent year, in an attempt to evaluate the effect of SDD on the long-term antibiotic resistance patterns in the ICU.

Methods

All patients admitted to the respiratory ICU were included in this four year study from January 1988 through December 1991. The clinical features and episodes of nosocomial infection were documented in a similar manner to those reported during the study of SDD.

Nosocomial infection was diagnosed if signs developed more than 48 hours after admission to the ICU. The following definitions of infection were used:

Septicaemia was diagnosed as the clinical observation of all of the following with no obvious localising site of infection:

a positive blood culture

a rise or fall in temperature ($> 38^{o}C$ or $<35.5^{o}C$)

a rise in white blood cell count ($>10\ 000$/ml), or a left shift in its morphology

evidence of organ dysfunction. Criteria for organ dysfunction were defined as follows:

lung: PaO_2 <8kPa on 40% oxygen, or respiratory rate <5/minute or >49/minute, or $PaCO_2$ > 6kPa, or $AaDO_2$ >46 kPa, or dependent on ventilator for >4 days.

kidney: urine output < 479ml/24 hours, or < 159ml/8 hours, or serum creatinine >300 mmol/l, or serum urea >20 mmol/l.

liver: liver enzymes more than twice normal or total bilirubin > 50 mmol/l.

central nervous system: unconscious with a Glasgow coma scale of <6 without the use of sedatives for more than 24 hours

haematological: white cell count < 1 000/ml, or platelets 20 000/ml.

cardiovascular: mean blood pressure <49 mm Hg, or pH < 7.24.

Nosocomial pneumonia was defined as a new infiltrate on the chest radiograph more than 48 hours after admission to the ICU, purulent bronchial secretions with many leukocytes, temperature above 38°C, white blood cell count > 10^{10}/l , increasing or showing a left shift, substantial numbers of organisms shown by Gram staining of the tracheal aspirate, with a pure growth cultured from the tracheal aspirate, and a deterioration in gas exchange of 2kPa or more.

Bronchial infection was defined by the presence of all the features of pneumonia, except the radiographic changes.

Urinary tract infection in patients who had been catheterised for at least 48 hours before collection of the specimen, was defined by the presence of local or systemic signs of infection, with culture of bacteria or yeasts, and the presence of more than 10^8 white cells per litre of urine.

Vascular-catheter related sepsis was defined as temperature above 38°C, white blood cell count above 10^{10}/l or left shift, with relief of signs on removal of the catheter; a positive catheter tip culture, blood culture, or the presence of local inflammation were not required for the diagnosis.

If a nosocomial infection was diagnosed, appropriate cultures were taken for isolation, identification and sensitivity testing of the causative organisms. All central venous catheters were cultured on removal.

Routine surveillance cultures of tracheal aspirates in intubated patients and urine samples, as well as from other clinically relevant sites, were performed twice weekly and when clinically indicated, in addition to the surveillance cultures taken as part of the study on SDD.

Clinically significant bacterial isolates only were considered for analysis, and resistance patterns of organisms deemed to be colonisers were excluded. A clinically significant

bacterial isolate was defined as a culture of an organism accompanied by clinical evidence of systemic infection which required antibiotic treatment. Repeated culture of the same organism was recorded as the initial specimen only, and all organisms considered to be colonisers or contaminants were disregarded. The method used to determine resistance for the initial period was that of Stokes and Ridgway[306,307], using a 10 microgram aminoglycoside disc which was subsequently changed to the Kirby-Bauer method, where 30 ug aminoglycoside discs were used [308]. 30ug discs of cephalosporin were used throughout the study.

Results

The demographic data of the patients admitted to the Respiratory ICU over the three time intervals studied are shown in the Table Seventy-six. Although similar numbers of patients were admitted over the four years, and there was no statistical difference in age, in the year post SDD, there was an unexplained increase in the number of women admitted, and the APACHE II score was significantly lower than in the year prior to SDD. The duration of tracheostomy was shorter in the year after SDD. There was however no difference in the number of patients who required ventilation or other invasive procedures, and the overall mortality for the three time periods was similar.

Table Seventy-Six :Patient profiles and invasive procedures

	Pre-SDD	SDD	Post-SDD
No of patients	406	719	403
Age	42.7	41.4	40
	± 18.2	± 16.5	± 17.9
Male:female	208:198	371:348	193:210
APACHE	14.3*	13.3	12.9*
	± 8.3	± 8.1	± 6.8
Ventilated	75.9%	79.6%	76.9%
Duration ETT	5.1 ± 4.8	5.2	5 ± 3.8
Tracheostomy	n=68	n=132	n=75
	18.1	18.3	12.9
ICU stay	9.6	9.9	9.1
	± 13.3	± 11.6	± 10.8
PA catheter	61	115	62
Mortality	14.5%	13.9%	13.4%

** Student's t test p=0.0088 comparing APACHE II pre and post SDD.*

The incidence of different diseases requiring ICU admission was also similar and is shown in Table Seventy-seven.

Table Seventy-Seven: Incidence of disease requiring ICU admission

	Pre SDD	SDD	Post-SDD
No of patients	406(%)	719(%)	403(%)
Asthma	46(11.3)	72(10)	30(7)
Pneumonia	62(15)	87(12)	50(12)
ARDS	21(5)	65(9)	34(8)
COPD	18(4)	29(4)	15(4)
Other lung dis.	37(9)	62(9)	37(9)
Neurologic dis.	39(10)	54(8)	40(10)
Overdose/poison	34(8)	43(6)	26(6)
Elective surgery	41(10)	63(9)	45(11)
Blunt chest trauma	44(11)	112(16)	47(12)
Other disease	64(16)	132(18)	79(20)

The number of patients who received antibiotics during the three time intervals is shown in table Seventy-eight. The differences in antibiotics used over the time intervals studied, were largely the result of drug studies (a quinolone was studied as part of a Phase III study in the year pre-SDD), or owing to hospital policy and cheaper tenders for antibiotics. Cefotaxime usage during the SDD interval was higher, as this antibiotic was often continued for therapeutic purposes, if microbial sensitivities were appropriate over this time period; thereafter, however, the drug was no longer available on hospital code and other cephalosporins were substituted, so that overall cephalosporin usage remained similar. The overall antibiotic prescribing over the three time intervals was thus comparable.

Table Seventy-Eight : Number of Patients for whom antibiotics were prescribed during the pre, post and SDD study periods

No of patients	Pre SDD 406	SDD 719	Post SDD 403
Penicillin	119	187	148
Ampicillin	69	67	58
Cotrimoxazole	40	74	49
Gentamicin	2	55	127
Amikacin	135	160	37
Cefamandole	0	1	0
Cefoxitin	0	1	0
Cefuroxime	1	0	5
Cefotaxime	52	195	1
Ceftriaxone	11	106	77
Ceftazidime	14	15	10
Piperacillin	9	14	5
Imipenem	1	8	3
Quinolone	26	8	18
Cloxacillin	57	97	59
Fucidin	3	10	11
Macrolides	39	60	43
Vancomycin	25	48	28
Metronidazole	83	176	117
TB drugs	16	46	28
Amphotericin B	8	14	12
Nystatin	4	3	1
Acyclovir	1	4	3
Other	28	18	12
Total no.antibiotics	743	1367	852

(Other: chloramphenicol, tetracycline, nalidixic acid)

The overall incidence of nosocomial infection was not statistically different during any of the time periods studied, although the incidence of respiratory tract infections was significantly higher in the year following SDD than during the two year SDD study

period. There were no clusters of nosocomial infection during any of the time periods, and the incidence of infection was considered to be the usual pattern with no exceptional increases. No outbreak of nosocomial infections with resistant organisms was identified and the incidence of different pathogens was similar during all the intervals that were monitored. (Table Seventy-Nine).

Table Seventy-Nine: Incidence of Nosocomial Infection

	Pre-SDD	SDD	Post-SDD
No of patients	406	719	403
Respiratory	42	68*	55*
Septicaemia	23	35	17
Urinary tract	13	18	16
Endocarditis	0	1	1
Other	2	10	5
Total infections	80	132**	94

** Chi-square: p=0.039 difference between incidence of respiratory tract infections during SDD and year post SDD.*

*** p= 0.055 difference between overall incidence of nosocomial infections during and after SDD.*

The clinically significant bacterial isolates obtained during the study periods are shown in Table Eighty. There was a significantly increased number of clinically significant organisms isolated in the year following SDD compared with the SDD period (p=0.0005), and the year preceding SDD (p=0.024); however, there was no difference in the incidence of infection between the year preceding SDD and the SDD period (p=0.43). The increase in the different types of pathogens in the year following SDD was proportional.

Table Eighty : Clinically Significant Bacterial Isolates

	Pre-SDD	SDD	Post-SDD
Gram positive	49	79	44
S. pneumoniae	12	5	5
S.aureus	25	42	29
S.epidermidis	7	23	8
Enterococcus	3	6	2
S.milleri	1	1	0
Other strep.	1	2	0
Gram negative	69	111	95
E.coli	6	10	12
Klebsiella spp	19	16	12
Proteus spp	1	3	7
Enterobacter	1	12	4
Serratia spp	0	0	2
Acinetobacter	21	45	36
Pseudomonas spp	9	15	13
H.influenzae	10	9	6
M.catarrhalis	2	1	3
Candida	10	13	9
Viruses	0	2	0
Other	1	6	12

The resistance patterns of the clinically significant isolates cultured are shown in Table Eighty-one. Tobramycin resistance in the year following SDD was unfortunately not tested, except for *Pseudomonas spp*.

Table Eighty-One: Resistance patterns of organisms causing clinical infection, cultured 48 hours after ICU admission.

	Pre-SDD		SDD		Post-SDD	
Organism	**Isol**	**Resist**	**Isol**	**Resist**	**Isol**	**Resist**
AGNB	28		38		36	
Tobramycin		17.8%		23.1%		N.T.
Amikacin		4%		5%		3%
Gentamicin[1]		18%		5%		8%
Cephalosporin[2]		25%		26%		3%
Cotrimoxazole		32%		39%		39%
Amoxycillin		86%		82%		86%
Pseudomonas	9		14		13	
Tobramycin		0		8%		8%
Amikacin		0		7%		0
Gentamicin		0		7%		15%
Ceftazidime		11%		14%		8%
Piperacillin		11%		14%		8%
Acinetobacter	20		45		35	
Tobramycin		-		-		-
Amikacin[3]		60%		51%		6%
Gentamicin		95%		98%		91%
Cephalosporin		100%		100%		100%
Cotrimoxazole		5%		0%		6%
S.aureus	23		39		26	
Tobramycin[4]		48%		38%		23%
Amikacin		17%		36%		23%
Penicillin		100%		90%		92%
Cloxacillin		48%		38%		23%
Vancomycin		0%		0%		0%
Cotrimoxazole		30%		23%		15%
S.epidermidis	5		22		8	
Tobramycin		N.T.		N.T.		N.T.
Amikacin		20%		68%		N.T.
Penicillin		100%		95%		100%
Cloxacillin		60%		64%		62%
Vancomycin		0%		0%		0%
Cotrimoxazole		60%		77%		100%

AGNB : Enterobacteriaceae
N.T. = not tested
Cephalosporin : cefotaxime, ceftriaxone.
1 p=0.44 *2 p=0.02*
3 p=0.000037 *4 p=0.19*

Discussion

This four year clinical study in which a similar population of 1528 patients were admitted to the respiratory ICU, has shown a very consistent pattern of nosocomial infections and causative organisms, with no major changes in antimicrobial resistance patterns, despite the extensive use of antimicrobial prophylaxis with topical and systemic therapy. It is however interesting to note that the incidence of respiratory tract infections was higher in the year subsequent to SDD than during the trial period. The reasons for this are not clear, and there was no statistical difference between the incidence of respiratory infections during and before SDD.

There was no discernible increase in the microbial resistance patterns of clinically significant isolates, as a result of selective decontamination. The number of isolates of specific organisms tested during the three time intervals studied was similar, confirming that there were no outbreaks of any particular organism. A decrease in resistance to the cephalosporins and gentamicin was noted in the period following SDD, which was almost certainly attributable to the change in the method of sensitivity testing. A similar resistance pattern was also seen in isolates from the rest of the hospital over the same time period.

The level of aminoglycoside resistance by the *Enterobacteriaceae*, following SDD, was unfortunately not tested for tobramycin, and the level of gentamicin resistance in this case may be unhelpful, as resistance to the aminoglycosides may occur independently. 86% of isolates of *Enterbacteriaceae* were resistant to amoxycillin, 39% to cotrimoxazole, 8% to gentamicin and 1 isolate only to amikacin and ceftriaxone.

Antimicrobial resistance of *Pseudomonas spp* following SDD to tobramycin, ceftazidime and piperacillin was detected in 8% of isolates, while 15% of isolates were resistant to gentamicin, and all were sensitive to amikacin. Previous studies [276] have suggested that SDD may alter adherence mechanisms and the colonisation resistance of

patients, allowing an increased colonisation and possibly infection with this organism. In our study, this problem was not encountered, as colonisation was uncommon and in the few infections that did occur, the organism was either present on admission, or acquired directly into the trachea. In this long-term surveillance, no influence on aminoglycoside resistance was detected.

All isolates of *Acinetobacter spp*, which was the most commonly isolated Gram negative organism other than the *Enterobacteriaceae*, were resistant to ceftriaxone, 91% to gentamicin, and only 6% to amikacin and cotrimoxazole. These resistance patterns were seen both during SDD and in the year preceding and after the study, demonstrating no adverse effects with the use of SDD, despite its inherent lack of sensitivity to the regimen (apart from polymyxin E). A previous study [271] has expressed concern that SDD might promote the incidence of infections with this organism, and although the incidence of nosocomial infections with this agent is high, no long-term effects relating to SDD could be found. It appears that this organism is emerging as a consistently important ICU pathogen, unrelated to the use of SDD.

Despite the increase noted in gastrointestinal colonisation by methicillin resistant staphylococci, with an associated higher frequency of infections caused by *S aureus* in the patients who received the active decontamination regimen during the SDD trial period, the percentage of clinically significant methicillin-resistant isolates did not increase with SDD. Reassuringly, in the year after SDD the number of clinically significant methicillin-resistant isolates of *S aureus* was actually lower than previously, so that there would appear to have been no long-term adverse effects on the Gram positive flora in the ICU. There has previously been concern that the use of SDD might cause such major disturbances to the microbial flora of the ICU that its former equilibrium might not be restored. This study would suggest that once SDD has been withdrawn, the potential problem with Gram positive organisms, intrinsically resistant to the agents used in SDD, subsides to its previous level [277,278].

Despite major concern that the long-term effects of SDD might adversely affect the "ecological" balance of the microbial flora within the intensive care unit, this study has demonstrated that there would appear to be no immediate or long-term sequelae associated with this prophylactic regimen.

CHAPTER 10 CONCLUSION

For over a decade attempts at reducing the incidence of nosocomial infection in the ICU with the technique of selective decontamination of the digestive tract have been attempted, yet its role remains controversial. This is not surprising, as the reported incidence of secondary infection varies widely between different populations and institutions; no conformity in the diagnostic criteria for secondary infections has been achieved, and the actual influence of secondary infection on morbidity and mortality in ventilated patients remains unknown, further contributing to the dilemma.

Attempts to elucidate the pathogenetic mechanisms involved, have lead to the recognition of the important role of colonisation of the host, leading to endogenous infection.[5] The natural progression from this greater understanding of the role of the gastrointestinal tract in the pathogenesis of nosocomial infection, was the emergence of selective decontamination of the digestive tract, using non-absorbable oropharyngeal and enterally administered, prophylactic antibiotics.

Initial attempts using enteral prophylaxis alone by Stoutenbeek et al [243], failed to reduce the incidence of early onset nosocomial pneumonia, until parenteral cefotaxime was added for the initial few days of ICU admission. With a combination of parenteral and enteral prophylaxis, the Groningen group reported a dramatic reduction particularly in the incidence of secondary respiratory tract infection from over 80% to less than 20% [274]. Especial benefit was shown in patients who had sustained multiple trauma[14]; subsequently Ledingham et al [263] confirmed these results and showed a reduction in mortality in this subset of patients. While initial studies reported reductions in the incidence of all types of secondary infections, particularly of the respiratory and urinary tracts, subsequent emphasis has largely been on the prevention of respiratory tract infection.

The previous adverse experience encountered with the use of aerosolised polymyxin [233], and the inherent resistance of physicians to the use of topically administered antimicrobial prophylaxis, for fear of the development of resistance, has resulted in there having been at least a further twenty to thirty reported studies, with varying success. Meta-analysis [279] of the effect of selective decontamination of the digestive tract on the incidence of respiratory tract infections and mortality, where the technique had been used for varying indications in different patient groups, with either historical or concurrent controls, and different prophylactic regimens, found a significant reduction of the frequency of respiratory tract infections, but the effect on mortality was not clearly shown. The studies of Stoutenbeek [274], using an historical control group, and Ulrich [267], were largely responsible for any reduction in mortality, and when these studies were excluded from the meta-analysis, no benefit was found. Criticism of all these studies was the accuracy of diagnosis of secondary pulmonary infection, particularly in ventilated patients, and the lack of uniformity in the definitions.

More recently, the publication of two large, double-blind studies has shown less convincing benefit from the use of SDD in both medical patients [265], and in the general ICU, where a large subgroup of trauma patients [305] was included. Although these studies showed a trend towards a reduction in infection, particularly with *Enterobacteriaceae*, in the 684 patients reported the reduction in secondary infection did not achieve statistical significance. Microbiological surveillance was only reported in one of these studies and demonstrated effective clearance of AGNB from the digestive tract; no episodes of pneumonia followed oropharyngeal colonisation with AGNB in the decontaminated patients. Although the infections with aerobic Gram negative bacilli were virtually eliminated, infection with non-fermenters persisted, and Staphylococcal infections increased significantly in the decontaminated patients, so that there was no overall benefit. There was a complete absence of early onset pneumonia (<5 days), possibly because both trial groups received cefotaxime, which may also

have effectively reduced the observed benefit of decontamination, and thereby supporting Stoutenbeek's early observation that initial use of a parenteral agent was essential [243].

Many of the studies which have shown maximal benefit from the use of SDD, have used control groups, with an exceptionally high incidence of pneumonia (40-80%) [14,253,278]. Previous descriptive studies of ICU infection have shown the incidence of nosocomial pneumonia to be much lower, than that reported with SDD, with an incidence of approximately 20 % [30,148]. This suggests that in the trials of SDD, there was, a priori, an exceptionally high incidence of both exogenous and endogenous nosocomial infection; any trial under such circumstances, particularly if not blinded, would have been likely to have shown benefit. While the reduction in infection could have been directly attributed to SDD, other peripheral phenomena such as awareness, improved hand-washing and aseptic techniques fostered by the routine imposed by the regimen may also have contributed significantly.

Another important detractor from the benefit shown in these studies, is the recognised inadequacy of the diagnosis of pneumonia in ventilated patients. This difficulty is best recognised in the setting of ARDS, where 29% of patients with ARDS were misdiagnosed as having pneumonia, and 36% of cases of nosocomial pneumonia were misdiagnosed as ARDS until autopsy [105]. SDD is well recognised to signficantly reduce colonisation of the upper airway and oropharynx, and this, combined with the suppressive effects of oral antibiotics on microbiological cultures [272], may influence the incidence of nosocomial pneumonia, particularly if the diagnosis is dependent on quantitative cultures.

The protected specimen brush has become widely accepted as the gold standard for the diagnosis of pneumonia, yet its sensitivity of only 70% makes it unreliable as a clinical means for the diagnosis of pneumonia [112]. Once again it relies heavily on quantitative cultures, which may be signficantly affected by the carry-over effects of high dose oral

aminoglycosides and polymyxin. The levels in serum and bronchial secretions have been shown to exceed the MIC for *Enterobacteriaceae*, following the administration of SDD [272].

The best way to minimise bias in the diagnosis of ventilator-associated pneumonia in clinical trials, is with the use of well defined clinical criteria, which should include the presence of purulent tracheal secretions, a new pulmonary infiltrate on the chest radiograph, an increasing white cell count, fever and a deterioration in oxygen exchange, in well designed, controlled and preferably double-blind studies. While the high specificity of the protected specimen brush ensures an accurate aetiological diagnosis, its lower sensitivity makes it less valuable in clinical trials evaluating therapeutic and preventative modalities [110,111,115]. The treatment of bronchial infection, which usually precedes pneumonia, is essential to ensure optimal outcome, while awaiting the development of parenchymal involvement, may prejudice survival. In this setting, the use of routine surveillance cultures of tracheal secretions, may provide an early indication of the progression from colonisation to respiratory infection.

The more recent studies which have shown no benefit, suggest that while the gut is important as a source of endogenous infection, either by colonisation of the oropharynx and aspiration or possible translocation, other mechanisms, particularly enhanced bacterial adherence [51], may play a more major role when the gut has been decontaminated. This seems to be relevant with altered patterns of infection with *Pseudomonas aeruginosa* [276] and *Acinetobacter spp* [147]. In addition, part of the normal flora, which is eliminated by decontamination, may also be important in colonisation resistance. Its removal may account for increasing colonisation by enterococci and staphylococci, which has been encountered in a number of studies; this may lead to an increased incidence of infection by these organisms. The use of alternative agents in the decontamination regimen may obviate some of these problems.

that the incidence of both Gram negative and staphylococcal pneumonia was reduced by using enteral vancomycin, neomycin and vancomycin, although the long-term effects on antimicrobial resistance remain of concern. Despite careful microbiological surveillance conducted during most of the studies of SDD, there has, to date, been very little antimicrobial resistance reported by the aerobic Gram negative bacteria to the agents used in the regimen [275,276]. Few of the studies have monitored the resistance patterns of the Gram positive organisms, but in those studies that have analysed this, there has been concern that there may be an increasing incidence of both methicillin resistant and sensitive *Staphylococcus aureus* and coagulase negative staphylococci [277,278,305]. Long-term follow-up, on discontinuation of SDD, has shown that disturbances in the microbial flora and its resistance patterns should revert to their previous levels.

The relationship between nosocomial infection and death may be indirect, and related to the development of multiple organ failure. This may be related to the release of cytokines or endotoxin from the bowel or the site of infection. It was postulated that the reduction in the bacillary load in the gastrointestinal tract achieved with SDD might reduce the translocation of endotoxin from the gut during periods of ischaemia, and thus not only reduce the incidence of nosocomial infections, but also prevent the development of mutiple organ failure. This hypothesis has however not been confirmed in any of the studies of SDD, as no reduction in mortality nor the incidence of multiple organ failure has been observed despite effective bowel decontamination.[255,305]

The cost of SDD in terms of drug costs, pharmacy time, nursing time for the application of the medication, and microbiological surveillance, which is considered an essential part of the regimen, all add considerably to the expense of hospitalisation with little obvious benefit in terms of morbidity and mortality and would question the wisdom of widespread use of this technique. SDD has, however, been successfully used to curtail the spread of multiply-resistant *Enterobacteriaceae* [249]. There may also

be a role for elements of the SDD regimen, in particular, the use of topical antifungal therapy may be effective in preventing systemic superinfection with yeasts in susceptible patients [257,258,309].

CHAPTER 11 BIBLIOGRAPHY

1. Duguid JP, Marmion BP, Swain RHA. Mackie and McCartny: Medical Microbiology. 13th ed. Edinburgh: Churchill Livingstone, 1978:

2. Eickhoff TC. Nosocomial Infections. N Engl J Med 1982; 306:1545-1546.

3. Eickhoff TC. Nosocomial infections - a 1980 view: progress, priorities and prognosis. Am J Med 1981; 70:381-388.

4. Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalised patients. N Engl J Med 1969; 281:1137-1140.

5. Johanson WG, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with Gram negative bacilli: the significance of colonisatiion of the respiratory tract. Ann Intern Med 1972; 77:701-706.

6. Schimpff SC, Miller RM, Polkavetz SH, Hornick RB. Infection in the severely traumatised patient. Ann Surg 1974; 179:352-357.

7. Le Frock JL, Ellis CA, Weinstein L. The impact of hospitalisation on the aerobic fecal microflora. Am J Med Sci 1979; 277:269-274.

8. Brown RB, Hosmer D, Chen C, et al. A comparison of infections in different ICUs within the same hospital. Crit Care Med 1985; 13,no6:472-476.

9. Daschner FD, Frey P, Wolff G, Baumann PC, Suter P. Nosocomial infections in intensive care wards: a multicentre prospective study. Intensive Care Med 1982; 8:5-9.

10. Craven DE, Kunches LM, Lichtenberg DA, et al. Nosocomial Infection and Fatality in Medical and surgical intensive care unit patients. Arch Intern Med 1988; 148:1161-1168.

11. Daschner FD. Cost effectiveness in hospital infection control - lessons for the 1990s. J Hosp Infect 1989; 13:325-326.

12. Clasener HAL, Vollaard EJ, Van Saene HKF. Long term prophylaxis of infection by selective decontamination in leukopenia and in mechanical ventilation. Rev Infect Dis 1987; 9,no2:295-328.

13. Guiot HFL, Van der Meer JWM, Van Furth R. Selective antimicrobial modulation of human microbial flora: infection prevention in patients witn decreased host defense mechanisms by selective elimination of potentially pathogenic bacteria. J Infect Dis 1981; 143:644-654.

14. Stoutenbeek CP, Van Saene HKF, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 1984; 10:185-192.

15. van Saene H.K.F., Stoutenbeek C.P., Zandstra D.F. Eleven Important Definitions, 1991 First European Consensus Conference on Selective Decontamination.

16. Bone RC. Sepsis, the sepsis syndrome, multi-organ failure: a plea for comparable definitions. Ann Intern Med 1991; 114:332-333.

17. Mandelli M, Mosconi P, Langer M, Cigada M. Prevention of pneumonia in an intensive care unit : a randomised multicentre clinical trial. Crit Care Med 1989; 17:501-505.

18. Gorbach SL, Barza M, Giulano M, Jacobus NV. Colonisation Resistance of the human intestinal microflora: testing the hypothesis in normal volunteers. Eur J Clin Microbiol Infect Dis 1988; 7:98-102.

19. Wells CL, Maddaus MA, Jechorek RP, Simmons RL. Role of intestinal anaerobic bacteria in colonisation resistance. Eur J Clin Microbiol Infect Dis 1988; 7:107-113.

20. Van Saene HKF, Stoutenbeek CP, Zandstra DF, Gilbertson AA, Murray A, Hart CA. Nosocomial infections in severely traumatised patients: magnitude of problem, pathogenesis, prevention and therapy. Acta Anaesthesiol Belg 1987; 38:347-353.

21. Geddes DM. Infection versus Colonisation. Intensive Care Med 1990; 16s3:s201-s205.

22. Niederman MS, Rafferty TD, Sasaki CT, Merrill WW, Matthay RA, Reynolds hY. Comparison of bacterial adherence to ciliated and squamous epithelial cells obtained from the human respiratory tract. Am Rev Respir Dis 1983; 127:85-90.

23. Niederman MS, Merrill WW, Ferranti RD. Nutritional status and bacterial binding in the lower respiratory tract in patients with chronic tracheostomy. Ann Intern Med 1984; 100:795-800.

24. Todd TRJ, Franklin A, Mankinen-Irvin P, Gurman G, Irvin RT. Augmented bacterial adherence to tracheal epithelial cells is associated with Gram-negative pneumonia in an intensive care unit population. Am Rev Respir Dis 1989; 140:1585-1589.

25. Harada R, Repine JE. Pulmonary Host Defense Mechanisms. Chest 1985; 87:247-252.

26. Stevenson GW, Hall SC, Rudnick S, Seleny FL, Stevenson HC. The effect of anesthetic agents on the human immune response. Anesthesiology 1990; 72:542-552.

27. Gil-Egea MJ, Pi-Sunyer MT, Verdaguer A, Sanz F, Sitges-Serra A, Torre Eleizegui L. Surgical Wound Infections: Prospective study of 4 468 Clean Wounds. Infection Control 1987; 8:277-280.

28. Haley RW, Culver DH, Morgan WM, White JW, Emor TG, Hooton TM. Identifying patients at high risk of surgical wound infection: a simple multivariate index of patient susceptibility and wound contamination. Am J Epidemiol 1985; 121:206-215.

29. Cross AS, Roup B. Role of respiratory assistance devices in endemic nosocomial pneumonia. Am J Med 1981; 70:681-685.

30. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 1986; 133:792-796.

31. Berendt RF. Relationship of method of administration to respiratory virulence of *Klebsiella* pneumoniae for mice and squirrel monkeys. Infect Immun 1978; 20:581-583.

32. Nickel JC, Ruseka I, Wright JB. Tobramycin resistance of *Pseudomonas aeruginosa* cells growing as a biofilm on urinary catheter material. Antimicrob Agents Chemother 1985; 27:619-624.

33. Niederman MS, Craven DE, Fein AM, Schultz DE. Pneumonia in the critically ill hospitalised patient. Chest 1990; 97:170-181.

34. Hammond JMJ, Potgieter PD, Forder AA, Plumb H. Influence of amikacin as the primary aminoglycoside on bacterial isolates in the intensive care unit. Crit Care Med 1990; 18:607-610.

35. Kerver AJH, Rommes JH, Mevissen-Verhage EAE, et al. Colonisation and infection in surgical intensive care patients -a prospective study. Intensive Care Med 1987; 13:347-351.

36. White R, Dilworth P. Pneumonia in Hospital. Br J Dis Chest 1988; 82:121-126.

37. Meduri GU. Ventilator associated pneumonia in patients with respiratory failure: a diagnostic approach. Chest 1990; 97:1208-1219.

38. Graybill JR, Marshall LW, Charache P, Wallace CK, Melvin VB. Nosocomial Pneumonia : a continuing major problem. Am Rev Respir Dis 1973; 108:1130-1140.

39. Schwartz SN, Dowling JN, Benkovic C. Sources of Gram negative bacilli colonising the tracheae of intubated patients. J Infect Dis 1978; 138:227-231.

40. Potgieter PD, Tinker J, Warren DE, Hambraeus A. The Influence of Design on Nosocomial Infections in ICUs. HOST 1992; 6:8-10.

41. Doebbeling BN, Stanley GL, Sheetz CT, et al. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. N Engl J Med 1992; 327:88-93.

42. Goldmann D, Larson E. Hand-washing and nosocomial infections. N Engl J Med 1992; 327:120-122.

43. Preston GA, Larson EL, Stamm WE. The effect of private isolation rooms on patient care practices, colonisation and infection in an Intensive Care Unit. Am J Med 1981; 70:641-645.

44. Cobley M, Atkins M, Jones PL. Environmental contamination during tracheal suction. Anaes 1991; 46:957-961.

45. Valenti WM, Trundell RG, Bentley DW. Factors predisposing to orophayngeal colonisation with Gram-negative bacilli in the aged. N Engl J Med 1978; 298:1108-1111.

46. Ramirez-Ronda CH, Fuxench-Lopez Z, Nevarez M. Increased pharyngeal bacterial pharyngeal colonisation during viral illness. Arch Intern Med 1981; 141:1599-1603.

47. Glover J, Jolly L. Gram negative colonisation of the respiratory tract in post-operative patients. Am J Med Sci 1971; 261:24-26.

48. Johanson WG, Higuchi JH, Chauduri TR, Woods DE. Bacterial adherence to epithelial cells in bacillary colonisation of the respiratory tract. Am Rev Respir Dis 1980; 121:55-64.

49. Hasty D, Simpson WA. Effect of fibronectin and other salivary macromolecules on the adherence of *Escherichia coli* to buccal epithelial cells. Infect Immun 1987; 55:2103-2109.

50. Niederman MS, Ferranti RD, Ziegler A, Merrill WW, Reynolds hY. Respiratory infection complicating long-term tracheostomy: the implication of persistent Gram negative tracheobronchial colonisation. Chest 1984; 85:39-44.

51. Niederman MS, Mantovani R, Schoch P, Pappas J, Fein AM. Patterns and routes of tracheobronchial colonisation in mechanically ventilated patients: the role of the nutritional status in colonisation of the lower airway by Pseudomonas species. Chest 1989; 95?:155?-161.

52. Atherton ST, White DJ. Stomach as source of bacteria colonising respiratory tract during artificial ventilation. Lancet 1978; iv:968-969.

53. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med 1978; 64:564-568.

54. Du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid treated patients: a frequent cause of postoperative colonisation of the airway. Lancet 1982; 1:242-245.

55. Tryba M. Risk of acute stress bleeing and nosocomial pneumonia in ventilated intensive care unit patients : sucralfated versus antacids. Am J Med 1987; 83s3b:117-124.

56. Heyland D, Mandell LA. Gastric colonisation by Gram -negative bacilli and nosocomial pneumonia in the ICU patient. Chest 1992; 101:187-193.

57. Ruddell WSJ, Axon ATR, Findlay JM, Bartholomew BA, Hill MJ. Effect of gastric cimetidine on the gastric bacterial flora. Lancet 1980; i:672-674.

58. Pingleton SK, Hinthorn DR, Liu C. Enteral nutrition in patients receiving mechanical ventilation: multiple sources of tracheal colonisation include the stomach. Am J Med 1986; 80:827-832.

59. Tryba M, Mantey-Stiers F. Antibacterial activity of sucralfate in human gastric juice. Am J Med 1987; 83s3b:125-127.

60. Inglis TJJ. Pulmonary Infection in Intensive Care Units. British Journal of Anaesthesia 1990; 65:94-106.

61. Snepar R, Poporad GA, Romano JM, Kobasa WD, Kaye D. Effect of cimetidine and antacid on gastric microbial flora. Infect Immun 1982; 36:518-524.

62. Driks MR, Craven DE, Celli BR, et al. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. N Engl J Med 1987; 317:1376-1382.

63. Cook DJ, Laine LA, Guyatt GH, Raffin TA. Nosocomial pneumonia and the role of gastric pH: a meta analysis. Chest 1991; 100:7-13.

64. McCarthy DM. Drug therapy: Sucralfate. N Engl J Med 1991; 325:1017-1025.

65. A'Court C, Garrard CS. Nosocomial pneumonia in the intensive care unit: mechanisms and significance. Thorax 1992; 47:465-473.

66. Langer M, Mosconi P, Cigada M, Mandelli M. Long term respiratory support and risk of pneumonia in critically ill patients. Am Rev Respir Dis 1989; 140:302-305.

67. Reinarz JA, Pierce AK, Mays BB, Sanford JP. The potential role of inhalation therapy equipment in nosocomial pulmonary infection. J Clin Invest 1965; 44:831-839.

68. Inglis TJJ, Millar MR, Jones JG, Robinson DA. Tracheal tube biofilm as a source of bacterial colonisation of the lung. J Clin Microbiol 1989; 274:2014-2018.

69. Inglis T.J.J. Colonisation of the Ventilated Airway 1990, MD Thesis, Leeds University.

70. Seibel R, Laduca J, Hassett JM, et al. Blunt multiple trauma (ISS 36),femur traction, and the pulmonary failure septic state. Ann Surg 1985; 202:283-295.

71. Behrman SW, Fabian TC, Kudsk KA, Taylor JC. Improved outcome with femur fractures : early versus delayed fixation. J trauma 1990; 30:792-798.

72. Caplan ES, Hoyt NJ. Nosocomial sinusitis. JAMA 1982; 647:639-643.

73. Im SWK, Fung JPH, So SY, Yu DYC. Unusual dissemination of pseudomonads by ventilators. Anaes 1982; 37:1074-1077.

74. Irwin RS, Demers RR, Pratter MR, et al. An Outbreak of *Acinetobacter* Infection Associated with the Use of a Ventilator Spirometer. Resp Care 1980; 25:232-237.

75. Leu HS, Kaiser DL, Mori M, Woolson RF, Wenzel RP. Hospital-acquired pneumonia attributable mortality and morbidity. Am J Epidemiol 1989; 129:1258-1267.

76. Krieger JN, Kaiser DL, Wenzel RP. Urinary tract etiology of bloodstream infections in hospitalised patients. J Infect Dis 1983; 148:57-62.

77. Finkelberg Z, Kunin CM. Clinical evaluation of closed urinary drainaage systems. JAMA 1969; 207:1657-1662.

78. Warren JW. Nosocomial urinary tract infections. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and practice of Infectious Disease. 3rd ed. New York: Churchill Livingstone, 1990:2205-2215.

79. Quercia R.A, Hills SW, Klimek JJ, et al. Bacteriologic contamination of intravenous infusion delivery systems in an Intensive Care Unit. Am J Med 1986; 80:364-368.

80. Maki DG, Goldmann DA, Rhame FS. Infection control in intravenous therapy. Ann Intern Med 1973; 79:867-887.

81. Ryan JA, Abel RM, Abbott WM, et al. Catheter complications in total parenteral nutrition. N Engl J Med 1974; 290:757-761.

82. Collignon P, Sorrell TC, Uther JB. Prevention of sepsis associated with the insertion of intraavenous cannulae: the experience in a coronary care unit. Med J Aust 1985; 142:346-348.

83. Maki DG, Ringer M. Evaluation of dressing rgimens for prevention of infection with peripheral intravenous catheters: Gauze, a transparent polyurethane dressing, and an iodophor dressing. JAMA 1987; 258:2396-2403.

84. Eyer S, Brummitt C, Crossley K, Siegel R, Cerra F. Catheter related sepsis: Prospecitve, randomised study of three methods of long-term catheter maintenance. Crit Care Med 1990; 18:1073-1079.

85. Samsoondar W, Freeman JB, Coultish I, Oxley C. Colonisation of intravascular catheters in the intensive care unit. Am J Surg 1985; 149:730-731.

86. Rhame FS, Maki DG, Bennett JV. Hospital Infections. Boston: Little Brown, 1979:433-442.

87. Miller JJ, Venus B, Mathru M. Comparison of the sterility of longterm central venous catheterisation using single lumen , triple lumen, and pulmonary artery catheters. Crit Care Med 1984; 12:634-637.

88. Linder LE, Curelaru I, Gustavsson B. Material thrombogenicity in central venous catheterisation:A comparison between soft, antebrachia catheters of silicone elastomer and polyurethane. J Parenter Enteral Nutr 1984; 8:399-406.

89. Kelly CS, Ligas JR, Smith CA, Madden GM, Ross KR, Becker DR. Sepsis due to triple lumen central venous catheters. Surg Gynecol Obstet 1986; 163:14-16.

90. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter related sepsis: critical level of quantitative tip cultures. Arch Intern Med 1987; 147:873-877.

91. Goldman DA, Maki DG. Infection control in total parenteral nutrition. JAMA 1973; 223:1360-1364.

92. Press OW, Ramsey PG, Larson EB. Hickman catheter infections in patients with malignancies. Medicine (Baltimore) 1984; 63:189-200.

93. Forgacs IC, Eykyn SJ, Bradley RD. Serious infection in the Intensive Therapy Unit: a 15 year study of bacteraemia. Quart J Med 1986; 60:773-779.

94. Sheagreen JN. Significance of blood culture isolates of *Staphylococcus epidermidis*. Arch Intern Med 1987; 147:635.

95. Fiddian-Green RG, Baker S. Nosocomial pneumonia in the critically ill: product of aspiration or translocation? Crit Care Med 1991; 19:763-769.

96. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. Arch Surg 1990; 125:403-404.

97. Deitch EA. Intestinal bacterial translocation in sepsis. Highlights from infections in surgery 1992;

98. Veterans Affairs Total Patenteral Nutrition Cooperative Study Group . Perioperative Total Parenteral Nutrition in surgical patients. N Engl J Med 1991; 3325:525-532.

99. Guedon C, Schmitz J, Lerebours E. Decreased brush border hydrolase activities without gross morphological changes in human intestinal mucosa after prolonged total parenteral nutrition of adults. Gastroenterology 1986; 90:373-374.

100. Levine GM, Deren JJ, Steiger E, Zinno R. Role of oral intake in maintenance of gut mass and disaccharide activity. Gastroenterology 1974; 67:975-982.

101. Alverdy JC, Aoys E, Moss GS. TPN promotes bacterial translocation from the gut. Surg 1988; 104:185-190.

102. Souba W, Herskowitz K, Salloum RM, Chen MK, Austgen TR. Gut glutamine metabolism. J Parenter Enteral Nutr 1990; 14:s45-s50.

103. Jacobs S, Chang RW, Lee B, Bartlett FW. Continuous enteral feeding: a major cause of pneumonia among ventilated intensive care unit patients. J Parenter Enteral Nutr 1990; 14:353-356.

104. Tobin MJ, Grenvik A. Nosocomial lung infection and its diagnosis. Crit Care Med 1984; 12:191-199.

105. Andrews CP, Coalson JJ, Smith JD, Johanson WG. Diagnosis of Nosocomial Bacterial Pneumonia in Acute Diffuse Lung Injury. Chest 1981; 80:254-258.

106. Winterbauer RH, Hutchinson JF, Reinhardt N, et al. The use of quantitative cultures and antibody coating of bacteria to diagnose bacterial pneumonia by fibreoptic bronchoscopy. Am Rev Respir Dis 1983; 128:98-103.

107. Wilkinson PJ, Ball AJ, Gillespie WA, Orton VS. Routine laboratory assessment of postoperative chest infection: a prospective study. J Clin Path 1977; 30:417-420.

108. Torres A, Puig de la Bellacasa J, Xaubet A, et al. Diagnostic value of quantitative cultures of bronchoalveolar lavage and telescoping plugged catheters in mechanically ventilated patients with bacterial pneumonia. Am Rev Respir Dis 1989; 140:306-310.

109. Meduri GU. Introduction to the Consensus Conference on Ventilator-Associated Pneumonia. Chest 1992; 102s1:551s-552s.

110. Wunderink RG, Mayhall CG, Gibert C. Methodology for Clinical Investigation of Ventilator-Associated Pneumonia; Epidemiology and Therapeutic Intervention. Chest 1992; 102s1:580s-588s.

111. Pingleton SK, Fagon JY, Leeper KV. Patient Selection for Clinical Investigation of Ventilator-Associated Pneumonia; Criteria for Evaluating Diagnostic Techniques. Chest 1992; 102s1:553s-556s.

112. Chastre J. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections. Am Rev Respir Dis 1984; 130:924-929.

113. Bartlett JG, Alexander J, Mayhew J, Sullivan-Sigler N, Gorbach S. Should fibreoptic bronchoscopy aspirates be cultured? Am Rev Respir Dis 1976; 114:73-78.

114. Donowitz GR, Mandell GL. Acute Pneumonia. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and Practice of Infectious Diseases. 3rd ed. New York: Churchill Livingstone, 1990:540-555.

115. Meduri GU, Chastre J. The Standardisation of Bronchoscopic Techniques for Ventilator-Associated Pneumonia. Chest 1992; 102s:557s-564s.

116. Baselski VS, El-Torky M, Coalson JJ, Griffin JP. The Standardisation of Criteria for Processing and Interpreting Laboratory Specimens. Chest 1992; 102s1:571s-579s.

117. Wimberley N, Faling LJ, Bartlett JG. A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secrections for bacterial culture. Am Rev Respir Dis 1979; 119:337-343.

118. Baughman RP, Thorpe JE, Staneck J, Rashkin M, Frame PT. Use of the protected specimen brush in patients with endotracheal or tracheostomy tubes. Chest 1987; 91:233-236.

119. Torres A, Puig de la Bellacasa J, Rodriguez-Roisin R, Jimenez de Anta MT, Agusti-Vidal A. Diagnostic value of telescoping plugged catheters in mechanically ventilated patients with bacterial pneumonia using the Metras Catheter. Am Rev Respir Dis 1988; 138:117-120.

120. Torzillo PJ, McWilliam DB, Young IH, Woog RH, Benn R. Use of protected telescoping brush system in the management of bacterial pulmonary infection in intubated patients. Br J Dis Chest 1985; 79:125-131.

121. Chastre J, Fagon JY, Soler P, et al. Diagnosis of nosocomial bacterial pneumonia in intubated patients undergoing ventilation: comparison of the usefulness of bronchoalveolar lavage and the protected specimen brush. Am J Med 1988; 85:499-506.

122. Fagon JY, Chastre J, Hance AJ, et al. Detection of nosocomial lung infection in ventilated patients: use of a protected specimen brush and quantitative culture techniques in 147 patients. Am Rev Respir Dis 1988; 138:110-116.

123. Fagon JY, Chastre J, Domart Y, et al. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 1989; 139:877-884.

124. Faling LJ. A tale of two brushes. Chest 1981; 79:155-156.

125. Zavala DC, Schoell JE. Ultrathin needle aspiration of the lung in infectious and malignant disease. Am Rev Respir Dis 1981; 123:125-131.

126. Ha Pham L, Brun-Buisson C, Legrand P, et al. Diagnosis of nosocomial pneumonia in mechanically ventilated patients: comparison of a plugged telescoping catheter with the protected specimen brush. Am Rev Respir Dis 1991; 143:1055-1061.

127. Bates JH, Campbell GD, Barron AL, et al. Microbial aetiology of acute pneumonia in hospitalised patients. Chest 1992; 101:1005-1012.

128. Faling LJ. New advances in diagnosing nosocomial pneumonia in intubated patients: editorial. Am Rev Respir Dis 1988; 137:253-255.

129. Johanson WG, Seidenfeld JJ, Gomez P, De Los Santos R, Coalson JJ. Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. Am Rev Respir Dis 1988; 137:259-264.

130. Meduri GU, Wunderink RG, Leeper KV. Management of bacterial pneumonia in ventilated patients: protected bronchoalveolar lavage as a diagnostic tool. Chest 1992; 101:500-508.

131. Meduri GU, Beals DH, Maijub AG, Baselski V. Protected bronchoalveolar lavage: A new bronchoscopic technique to retrieve uncontaminated distal airway secretions. Am Rev Respir Dis 1991; 143:855-864.

132. Johanson WG. Ventilator-Associated Pneumonia: light at the end of the tunnel? Chest 1990; 97:1026-1027.

133. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am Rev Respir Dis 1991; 143:1121-1129.

134. Pugin J, Auckenthaler R, Delaspre O, van Gessel E, Suter P. Rapid diagnosis of Gram negative pneumonia by assay of endotoxin in bronchoalveolar lavage fluid. Thorax 1992; 47:547-549.

135. Davidson M, Tempest B, Palmer DL. Bacteriologic diagnosis of acute pneumonia. Comparison of sputum, transtracheal aspirates and lung aspirates. JAMA 1976; 235:158-163.

136. Wunderink RG, Russell GB, Mezger E, Adams D, Popovich J. The diagnostic utility of the antibody coated bacteria test in intubated patients. Chest 1991; 99:84-88.

137. Salata RA, Lederman MM, Shlaes DM, et al. Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. Am Rev Respir Dis 1987; 135:426-432.

138. Wunderink RG, Woldenburg LS, Zeiss J, Day CM, Ciemins J, Lacher DA. The radiologic diagnosis of autopsy-proven ventilator associated pneumonia. Chest 1992; 101:458-463.

139. Winer-Muram HT, Rubin SA, Ellis JV. Guidelines for Reading and Interpreting Chest Radiographs in Patients Receiving Mechanical Ventilation. Chest 1992; 102s1:565s-570s.

140. Bartlett JG, O'Keefe P, Tally FP, Louie T, Gorbach SL. Bacteriology of hospital acquired pneumonia. Arch Intern Med 1986; 146:868-871.

141. Potgieter PD, Hammond JMJ. Etiology and Diagnosis of Pneumonia Requiring ICU Admission. Chest 1992; 101:199-203.

142. Pugin J, Auckenthaler R, Lew DP, Suter PM. Oropharyngeal decontamination decreases incidence of ventilator associated pneumonia: a randomised , placebo controlled double blind clinical trial. JAMA 1991; 265:2704-2710.

143. Fagon JY, Chastre J, Trouillet JL, Domart Y, Scheimberg A, Darne C. Evaluation of patients suspected of having nosocomial pneumonia: are invasive procedures necessary for accurate decision making?(abstract). Am Rev Respir Dis 1988; 137:A219.

144. Maki D, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravascular catheter-related infection. N Engl J Med 1977; 296:1305.

145. Henderson DK. Bacteremia due to percutaneous intravascular devices. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and Practice of Infectious Diseases. 3rd ed. Boston: Churchill Livingstone, 1990:2189-2199.

146. Mosca R, Curtas S, Forbes B. The benefits of isolator cultures in the management of suspected catheter sepsis. Surg 1987; 102:718-723.

147. Haley RW, Schaberg DR, Crossley KB, Von Allmen SD, McGowan JE. Extra charges and prolongation of stay attributable to nosocomial infections: a prospective interhospital comparison. Am J Med 1981; 70:51-58.

148. Potgieter PD, Linton DM, Oliver S, Forder AA. Nosocomial infection in a respiratory intensive care unit. Crit Care Med 1987; 15:495-498.

149. Jimenez P, Torres A, Rodriguez-Roisin R, et al. Incidence and aetiology of pneumonia acquired during mechanical ventilation. Crit Care Med 1989; 17:882-885.

150. Ruiz-Santana S, Jimenez AG, Esteban A, et al. ICU pneumonias: a multi-institutional study. Crit Care Med 1987; 15:930-932.

151. Gross PA, Neu HC, Aswapokee P, Van Antwerpen C, Aswapokee N. Deaths from nosocomial infections: Experience in a university hospital and a community hospital. Am J Med 1980; 68:219-223.

152. Bryan CS, Reynolds KL. Bacteremic nosocomial pneumonia. Am Rev Respir Dis 1984; 129:668-671.

153. Mock CN, Burchard KW, Hasan F, Reed M. Surgical intensive care unit pneumonia. Surg 1988; 104:494-499.

154. Nielsen SL, Roder B, Magnussen P, Engquist A, Frimodt-Moller N. Nosocomial pneumonia in an intensive care unit in a Danish University Hospital: Incidence, Mortality and Aetiology. Scand J Infect Dis 1992; 24:65-70.

155. Rello J, Quintana E, Ausina V, et al. Incidence, etiology and outcome of nosocomial pneumonia in mechanically ventilated patients. Chest 1991; 100:439-444.

156. Thorp JM, Richards WC, Telfer ABM. A survey of infection in an intensive care unit. Anaes 1979; 34:643-650.

157. Chandrasekar PH, Kruse JA, Mathews MF. Nosocomial infection among patients in different types of intensive care units at a city hospital. Crit Care Med 1986; 14:508-510.

158. Torres A, Aznar R, Gatell JM, et al. Incidence, Risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 1990; 142:523-528.

159. Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132:485-489.

160. Campbell GD, Coalson JJ, Johanson WG. The effect of bacterial superinfection on lung function after diffuse alveolar damage. Am Rev Respir Dis 1984; 129:974-978.

161. Haley RW, Hooton TM, Culver DH, Stanley RC, Emori TG. Nosocomial infections in U.S. Hospitals 1975-1976: estimated frequency by selected characteristics of patients. Am J Med 1981; 70:947-959.

162. Donowitz LG, Wenzel RP, Hoyt JW. High risk of hospital acquired infection in the ICU patient. Crit Care Med 1982; 10:355-357.

163. Smith RL, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infections. Chest 1991; 100:164-167.

164. Detsky AS, Baker JP, O'Rourke K, Goel V. Perioperative Parenteral Nutrition: A Meta-Analysis. Ann Intern Med 1987; 107:195-203.

165. Wenzel RP. Preoperative Antibiotic Prophylaxis. N Engl J Med 1992; 326:337-339.

166. Kaiser AB. Antimicrobial proophylaxis in surgery. N Engl J Med 1986; 315:1129-1138.

167. Crossley K, Gardner LC. Antimicrobial Prophylaxis in Surgical Patients. JAMA 1981; 245:722-726.

168. Shapiro M, Townsend TR, Rosner B, Kass EH. Use of antimicrobial drugs in general hospitals: patterns of prophylaxis. N Engl J Med 1979; 301:351-355.

169. Bergquist EJ, Murphey SA. Prophylactic antibiotics for surgery. Med Clin North Am 1987; 71:357-368.

170. Hunt TK. Surgical Wound Infections: an overview. Am J Med 1981; 70:712-718.

171. Stone HH. Basic principles in the use of prophylactic antibiotics. J Antimicrob Chemo 1984; 14sB:33-37.

172. Polk HC, Lopez-Meyer JF. Postoperative wound infection; a prospective study of determinant factors and prevention. Surg 1969; 66:97-103.

173. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surg 1961; 50:161-168.

174. Ronald AR. Antimicrobial prophylaxis in surgery. Surg 1983; 93:172-173.

175. Green JW, Wenzel RP. Postoperative wound infection: a controlled study of the increased duration of hospital stay and direct cost of hospitalisation. Ann Surg 1977; 185:264-268.

176. Guglielmo BJ, Hohn DC, Koo PJ, Hunt TK, Sweet RL, Conte JE. Antibiotic Prophylaxis in Surgical Procedures. Arch Surg 1983; 118:943-955.

177. Burdon DW. Principles of antimicrobial prophylaxis. World J Surg 1992; 6:262-267.

178. Classen DC, Scott Evans R, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. N Engl J Med 1992; 326:281-286.

179. Allgower M, Durig M, Wolff G. Infection and Trauma. Surg Clin North Am 1980; 60:133-144.

180. Goris RJA, Draaisma J. Causes of death after blunt trauma. J Trauma 1982; 22:141-146.

181. Schmipff SC, Miller RM, Polakavetz S, Hornick RB. Infection in the severely traumatised patient. Ann Surg 1974; 179:352-357.

182. Harkness GA, Bentley DW, Roghmann KJ. Risk factors for nosocomial pneumonia in the elderly. Am J Med 1990; 89:457-463.

183. Kinnear WJM, Finch RG, Macfarlane JT. Nosocomial lower respiratory tract infections in surgical wards. Thorax 1990; 45:187-189.

184. Eykyn SJ, Gransden WR, Phillips I. The causative organisms of septicaemia and their epidemiology. J Antimicrob Chemo 1990; 25sC:41-58.

185. Celis R, Torres A, Gatell JM, Almela M, Rodriguez-Roisin R, Agusti-Vidal A. Nosocomial pneumonia: a multivariate analysis of risk and prognosis. Chest 1988; 93:318-324.

186. Mosconi P, Langer M, Cigada M. Epidemiology and risk factors of pneumonia in critically ill patients. European Journal of Epidemiology 1991; 7:320-327.

187. Deppe SA, Kelly JW, Thoi LL, et al. Incidence of colonisation, nosocomial pneumonia and mortality in critically ill patients using a Trach Care closed suction system versus an open suction system: Prospective randomised study. Crit Care Med 1990; 18:1389-1393.

188. Rogers LA, Osterhout S. Pneumonia following tracheostomy. Am Surg 1970; 59:39-46.

189. Bresalier RS, Grendell JH, Cello JP, Meyer AA. Sucralfate suspension versus titrated antacid for the prevention of acute stress related gastrointestinal hemorrhage in critically ill patients. Am J Med 1987; 83s3B:110-116.

190. Lacroix J, Infante-Rivard C, Jenicek M, Gauthier M. Prophylaxis of upper gastrointestinal bleeding in intensive care units: a meta-analysis. Crit Care Med 1989; 17:862-869.

191. Fiddian-Green RG. The potential for monitoring gastric intrmucosal pH to reduce the costs of critical care. In: Vincent JL, ed. Yearbook of Intensive Care and Emergency Medicine. Berlin: Springer-Verlag, 1992:259-268.

192. Goris RJA, van Bebber IPT, Mollen RMH, Koopman JP. Does selective decontamination of the gastrointestinal tract prevent multiple organ failure? Arch Surg 1991; 126:561-565.

193. Moiraghi A, Castellani Pastoris M, Barral C, et al. Nosocomial legionellosis associated with use of oxygen bubble humidifiers and underwater chest drains. J Hosp Infect 1987; 10:47-50.

194. Grayston JT, Diwan VK, Cooney M, Wang SP. Community and hospital acquired pneumonia associated with Chlamydia TWAR infection demonstrated serologically. Arch Intern Med 1988; 149:169-173.

195. Sanford JP. Lower respiratory tract infections. In: Bennett JV, Brachman PS, eds. Hospital Infections. Boston: Little,Brown, 1986:385-422.

196. Andrews BE, Bartlett CRL. Connolly CK, et al. Community acquired pneumonia in adults in British hospitals in 1982-1983: a survey of aetiology , mortality, prognostic factors and outcome. Quart J Med 1987; 62:195-220.

197. Johanson WG, Seidenfeld J, Gomez P, De Los Santos R, Coalson JJ. Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. Am Rev Respir Dis 1988; 137:259-264.

198. Crouch TW, Higuchi JH, Coalson JJ, Johanson WG. Pathogenesis and prevention of nosocomial pneumonia in a nonhuman primate model of acute respiratory failure. Am Rev Respir Dis 1984; 130:502-504.

199. Hong-Hao Hsieh A, Bishop MJ, Kubilis PS, Newell DW, Pierson DJ. Pneumonia following closed head injury. Am Rev Respir Dis 1992; 146:290-294.

200. Espersen F, Gabrielsen J. Pneumonia due to *Staphylococcus aureus* during mechanical ventilation. J Infect Dis 1981; 144:19-23.

201. Stevens RM, Teres D, Skillman JJ, Feingold DS. Pneumonia in an Intensive Care Unit. Arch Intern Med 1974; 134:106-111.

202. Silver DR, Cohen IL, Weinberg PF. Recurrent *Pseudomonas aeruginosa* Pneumonia in an Intensive Care Unit. Chest 1992; 101:194-198.

203. Tran DD, Groeneveld J, Van der Meulen J, Nauta JJP, Strack van Schijndel RJM, Thijs LG. Age, chronic disease, sepsis, organ system failure and mortality in a medical intensive care unit. Crit Care Med 1990; 18:474-479.

204. Seidenfeld JJ, Pohl DF, Bell RC, Harris GD, Johanson WG. Incidence, site and outcome of infections in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 1986; 134:12-16.

205. ACCP/SCCM consensus committee , Bone RC. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 101:1644-1655.

206. Mylotte JM, Beam TR. Comparison of Community-acquired and Nosocomial Pneumococcal bacteraemia. Am Rev Respir Dis 1981; 123:165-168.

207. Caplan ES, Hoyt N. Infection Surveillance and control in the severly traumatised patient. Am J Med 1981; 70:638-640.

208. Machiedo GW, LoVerme PJ, McGovern PJ, Blackwood JM. Patterns of mortality in a surgical intensive care unit. Surg Gynecol Obstet 1981; 152:757-759.

209. Meijer K, Van Saene HKF, Hill JC. Infection control in patients undergoing mechanical ventilation: traditional approach versus a new development - selective decontamination of the digestive tract. Heart Lung 1990; 19:11-20.

210. Haley RW, Culver DH, White JW. The efficacy of infection surveillance and control programs in preventing nosocomial infections in university hospitals. Am J Epidemiol 1985; 121:182-205.

211. Inglis TJJ, Sproat LJ, Hawkey PM, Knappett P. Infection control in intensive care units: U.K. national survey. British Journal of Anaesthesia 1992; 68:216-220.

212. Albert RK, Condie F. Hand-washing patterns in medical intensive care units. N Engl J Med 1981; 304:1465-1466.

213. Garner JS, Favero MS. CDC guidelines for the prevention and control of nosocomial infections. Am J Infect Control 1986; 14:110-129.

214. Hamilton-Miller JMT. The emergence of antibiotic resistance: myths and facts in clinical practice. Intensive Care Med 1990; 16s3:s206-s211.

215. Weinstein RA, Kabins SA. Strategies for prevention and control of multiple drug-resistant nosocomial infection. Am J Med 1981; 70:449-454.

216. Weber DJ, Wilson B, Rutala WA, Thomann CA. Manual ventilation bags as a source for bacterial colonisation of intubated patients. Am Rev Respir Dis 1990; 142:892-894.

217. Flournoy DJ, Plumlee CJ, Steffee RL. Volume Ventilator as a vehicle of airborne bacterial contamination from patients. Resp Care 1980; 25:57-60.

218. Nauseef WM, Maki DG. A study of the value of simple protective isolation in patients with granulocytopaenia. N Engl J Med 1981; 304:448-453.

219. Burke JF, Quinby WC, Bondoc CC, Sheehy EM, Moreno HC. The contribution of a bacterially isolated environment to the prevention of infection in seriously burned patients. Ann Surg 1977; 186:377-387.

220. Klein BS, Perloff WH, Maki DG. Reduction of nosocomial infection during paediatric intensive care by protective isolation. N Engl J Med 1989; 320:1714-1721.

221. Madge P, Paton JY, McColl JH, Mackie PLK. Prospective controlled study of four infection-control procedures ot prevent nosocomial infection with respiratory syncytial virus. Lancet 1992; 340:1079-1083.

222. Turner JS, Potgieter PD, Springhorn H, Briggs S. Patients' recollection of ICU experience. Crit Care Med 1990; 18:966-968.

223. Torres A, Serra-Batlles J, Ros E, et al. Pulmonary Aspiration of Gastric Contents in Patients Receiving Mechanical Ventilation: the effect of body position. Ann Intern Med 1992; 116:540-543.

224. Beale EO, Miller MT. The Guillain- Barre syndrome A review of admissions to an intensive care unit over 8 years. S Afr Med J 1985; 67:10-12.

225. Edmondson RS, Flowers MW. Intensive care in tetanus : management . complications and mortality in 100 cases. Br Med J 1979; 1:1401-1404.

226. Trujillo M, Castillo A, Espana JV, Guevara P, Eganez H. Tetanus in the adult: intensive care and management experience with 233 cases. Crit Care Med 1980; 8:419-423.

227. Apte NM, Karnad DP, Medhekar TP, Tilve GH, Morye S, Bhave GG. Gastric colonisation and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: A randomised, controlled trial. Crit Care Med 1992; 20:590-593.

228. Simmons BP, Wong ES. CDC Guidelines for the prevention and control of nosocomial infections: Guideline for the prevention of nosocomial pneumonia. Am J Infect Control 1983; 11:230-244.

229. Miranda DR, Van Saene HKF, Stoutenbeek CP, Zandstra DF. Environment and costs in surgical intensive care unit : The implication of selective decontamination. Acta Anaesthesiol Belg 1983; 3,September:223-232.

230. Allen KD, Green HT. Hospital outbreak of multiresistant *Acinetobacter* anitratus: an airborne mode of spread? J Hosp Infect 1987; 9:110-119.

231. Rodriguez-Roldan JM, Altuna-Cuesta A, Lopez A, et al. Prevention of nosocomial lung infection in ventilated patients: use of an antimicrobial pharyngeal nonabsorbable paste. Crit Care Med 1990; 18:1239-1242.

232. Klick JM, Du Moulin GC, Hedley-Whyte J, Teres D, Bushnell LS, Feingold DS. Prevention of Gram negative bacillary pneumonia using polymyxin aerosol as prophylaxis. J Clin Invest 1975; 55:514-519.

233. Feeley TW, Du Moulin GC, Hedley-Whyte J, Bushnell LS, Gilbert JP, Feingold DS. Aerosol Polymyxin and pneumonia in seriously ill patients. N Engl J Med 1975; 293:471-475.

234. Johanson WG, Seidenfeld J, De Los Santos R, Coalson JJ, Gomez P. Prevention of nosocomial pneumonia using topical and parenteral antimicrobial agents. Am Rev Respir Dis 1988; 137:265-272.

235. Faling LJ. Advances in Preventing Nosocomial Pneumonia Part II. Am Rev Respir Dis 1988; 137:256-258.

236. Burke J, Jacobson J, Garibaldi R. Evaluation of daily meatal care with poly-antibiotic ointment in prevention of urinary catheter-associated bacteriuria. J Urol 1983; 129:331-334.

237. Schaeffer AJ, Story KO, Johnson SM. Effect of silver oxide/trichloroisocyanuric acid antimicrobial urinary drainage system of catheter-associated bacteriuria. J Urol 1988; 139:69-73.

238. Garibaldi RA, Burke JP, Britt MR. Meatal colonisation and catheter-associated bacteriuria. N Engl J Med 1980; 303:3316-318.

239. Garibaldi RA, Mooney BR, Epstein BJ. An evaluation of daily bacteriologic monitoring to identify preventable episodes of catheter-associated urinary tract infection. Infection Control 1982; 3:466-470.

240. Olson ME, Lam K, Bodey GP, King EG, Costerton JW. Evaluation of strategies for central venous catheter replacement. Crit Care Med 1992; 20:797-804.

241. Bradley JA, Hamilton DNH, Brown MW, Cance W, Jackson VS, Ledingham IMA. Cellular defense in critically ill surgical patients. Crit Care Med 1984; 12:565-570.

242. Jackson GG. Considerations of antibiotic prophylaxis in nonsurgical high risk patients. Am J Med 1981; 70:467-473.

243. Stoutenbeek CP, Van Saene HKF, Miranda DR, Zandstra DF, Langrehr D. The effect of oropharyngeal decontamination using topical nonabsorbable antibiotics on the incidence of nosocomial respiratory tract infections in multiple trauma patients. J Trauma 1987; 27:357-364.

244. van der Waaij D. Evidence of immunoregulation of the composition of intestinal microflora and its practical consequences. Eur J Clin Microbiol Infect Dis 1988; 7:103-106.

245. Goldin BR, Lichtenstein AH, Gorbach SL. The roles of the intestinal flora. In: Shils ME, Young VR, eds. Modern Nutrition in Health and Disease. 7th ed. Philadelphia: Lea and Febiger, 1988:500-515.

246. Young LS. Antimicrobial prophylaxis in the neutropaenic host: lessons of the past and perspectives for the future. Eur J Clin Microbiol Infect Dis 1988; 7:93-97.

247. Wolfson JS, Hooper DC. Overview of Fluoroquinolone Safety. Am J Med 1991; 91s6A:s153-s161.

248. Van Uffelen R, Van Saene HKF, Fidler V, Lowenberg A. Oropharyngeal flora as a source of bacteria colonising the lower airways in patients on artificial ventilation. Intensive Care Med 1984; 10:233-237.

249. Brun-Buisson C, Legrand P, Rauss A, et al. Oral digestive tract decontamination (SDD) to control an outbreak of multiresistant Gram negative bacilli . Effect on endemic nosocomial infections. Intensive Care Med 1988; 14 supplement 311:

250. Brun-Buisson C, Legrand P, Rauss A, et al. Intestinal decontamination for control of nosocomial multiresistant Gram negative bacilli : study of an outbreak in an ICU. Ann Intern Med 1989; 110:873-881.

251. Goris RJA, Draaisma J. Death after blunt injury. Injury 1982; 14:7-10.

252. Van Saene HKF, Stoutenbeek CP, Miranda DR, Zandstra DF, Langrehr D. Recent advances in the control of infectiion in patients witb thoracic injury. Injury 1986; 17:332-335.

253. Kerver AJH, Rommes JH, Mevissen-Verhage EAE, et al. Prevention of colonization and infection in critically ill patients: a prospective randomised study. Crit Care Med 1988; 16:1087-1093.

254. Hartenauer U, Thulig B, Diemer W, et al. Effect of selective flora suppression on colonisation, infection, and mortality in critically ill patients : a one year, prospective consecutive study. Crit Care Med 1991; 19:463-473.

255. Cerra FB, Maddaus MA, Dunn DL, et al. Selective Gut Decontamination Reduces Nosocomial Infections and Length of Stay but Not Mortality or Organ Failure in Surgical Intensive Care Unit Patients. Arch Surg 1992; 127:163-169.

256. Wiesner RH. Selective bowel decontamination for infection prophylaxis in liver transplantation patients. Transplant Proc 1991; 23:1927-1928.

257. Rolando N, Harvey F, Brahm J. Prospective study of bacterial infection in acute liver failure. Hepatology 1990; 11:49-53.

258. Rolando N, Harvey F, Brahm J. Fungal infection: a common, unrecognised complication of acute liver failure. J Hepatol 1991; 12:1-9.

259. Tetteroo GWM, Wagenvoort JHT, Ince C, Bruining HA. Effects of selective decontamination on Gram negative colonisation, infections and development of bacterial resistance in esophageal resection. Intensive Care Med 1990; 16s3:s224-s228.

260. Tetteroo GWM, Wagenvoort JHT, Castelein A, Tilanus HW, Ince C, Bruining HA. Selective decontamination to reduce Gram negative colonisation and infections after oesophageal resection. Lancet 1990; 1:704-707.

261. Tetteroo GWM, Wagenvoort JHT, Bruining HA, Tilanus HW. A randomised study to the efficacy of selective decontamination in patients undergoing oesophageal resection, and it's epidemiological effects. Intensive Care Med 1988; 14 supplement 311:

262. McClelland P, Murray AE, Willians PS, et al. Reducing sepsis in severe combined acute renal and respiratory failure by selective decomtamination of the digestive tract. Crit Care Med 1990; 18:935-939.

263. Ledingham IMA, Alcock SR, Eastaway AT, McDonald JC, McKay IC, Ramsay G. Triple regimen of selective decontamination of the digestive tract, systemic cefotaxime, and microbiological surveillance for prevention of acquired infection in intensive care. Lancet 1988; 1:785-790.

264. Unertl K, Ruckdeshel G, Selbmann HK, et al. Prevention of colonisation and respiratory infections in long term ventilated patients by local antimicrobial prophylaxis. Intensive Care Med 1987; 13:106-113.

265. Gastinne H, Wolff MD, Delatour F, Faurisson F, Chevret S. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. N Engl J Med 1992; 326:594-599.

266. Van Uffelen R, Rommes JH, Van Saene HKF. Preventing lower airway colonisation and infection in mechanically ventilated patients. Crit Care Med 1987; 15:99-102.

267. Ulrich C, Harinck-de Weerd JE, Bakker NC, Jacz K, Doornbos L, de Ridder VA. Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU aquired infections : a prospective randomized study. Intensive Care Med 1989; 15:424-431.

268. Godard J, Guillaume C, Reverdy M-E, et al. Intestinal decontamination in a polyvalent ICU A double blind study. Intensive Care Med 1990; 16:307-311.

269. Aerdts SJA, Clasener HAL, Van Dalen R, van Lier HJJ, Vollaard EJ, Festen J. Prevention of bacterial colonisation of the respiratory tract and stomach of mechanically ventilated patients by a novel regimen of selective decontamination in combination with initial systemic cefotaxime. J Antimicrob Chemo 1990; 26sA:59-76.

270. Cockerill FR, Muller SR, Anhalt JP, et al. Prevention of Infection in Critically Ill Patients by Selective Decontamination of the Digestive Tract. Ann Intern Med 1992; 117:545-553.

271. Winter R, Humphreys H, Pick A, MacGowan AP, Willatts SM, Speller DCE. A controlled trial of selective decontamination of the digestive tract in intensive care and its effect on nosocomial infection. J Antimicrob Chemo 1992; 30:73-87.

272. Gastinne H, Wolff M, Lachatre G, Boiteau R, Savy FP. Antibiotic levels in bronchial tree and in serum during selective digestive decontamination. Intensive Care Med 1991; 17:215-218.

273. Zobel G, Kuttnig M, Grubbauer HM, Semmelrock HJ, Thiel W. Reduction of colonisation and infection rate during pediatric intensive care by selective decontamination of the digestive tract. Crit Care Med 1991; 19:1242-1246.

274. Stoutenbeek CP, Van Saene HKF, Miranda DR, Zandstra DF. A new technique of infection prevention in the intensive care unit by selective decontamination of the digestive tract. Acta Anaesthesiol Belg 1983; 3,September:209-221.

275. Stoutenbeek CP, Van Saene HKF, Zandstra DF. The effect of oral non-absorbable antibiotics on the emergence of resistant bacterial in patients in an intensive care unit. J Antimicrob Chemo 1987; 19:513-520.

276. Armstrong PJ, Barr JG, Webb CH, Blair PH, Rowlands BJ. Epidemiology of *Pseudomonas aeruginosa* in an intensive care unit using selective decontamination of the digestive tract. J Hosp Infect 1992; 20:199-208.

277. Nau R, Ruchel R, Mergerian H, Wegener U, Winkelman T, Prange HW. Emergence of antibiotic resistant bacteria during selective decontamination of the digestive tract. J Antimicrob Chemo 1990; 25:881-883.

278. Konrad F, Schwalbe B, Heiderich P, Schmitz JE, Ahnefeld FW. Bacterial colonisation and respiratory tract infections in long term ventilated patients under conventional antibiotic treatment and selective decontamination of the digestive tract (SDD). Intensive Care Med 1988; 14:abstract 3.

279. Vandenbroucke-Grauls CMJE, Vandenbroucke JP. Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit. Lancet 1991; 338:859-862.

280. Van Dalen R. Selective decontamination in ICU patients: benefits and doubts. In: Vincent JL, ed. Update in intensive care and emergency medicine. 14th ed. Berlin: Springer Verlag, 1991:379-386.

281. Weinstein RA. Selective intestinal decontamination - an infection control measure whose time has come? Ann Intern Med 1989; 110:853-854.

282. Ramsay G, Reidy JJ. Selective decontamination in intensive care practice: a review of clinical experience. Intensive Care Med 1990; 16s3:s217-s223.

283. Reidy JJ, Ramsay G. Clinical trials of selective decontamination of the digestive tract :review. Crit Care Med 1990; 18:1449-1456.

284. Deitch EA. Selective decontamination of the gut - is it enough? Crit Care Med 1990; 18:1043-1044.

285. Van Saene HKF, Stoutenbeek CP, Stoller JK. Selective decontamination of the digestive tract in the intensive care unit: current status and future prospects. Crit Care Med 1992; 20:691-703.

286. Van Saene HKF, Stoutenbeek CP, Hart CA. Selective decontamination of the digestive tract in intensive care patients: a critical evaluation of the clinical, bacteriological and epidemiological benefits. J Hosp Infect 1991; 18:261-277.

287. Fink MP. Selective digestive decontamination: A gut issue for the nineties. Crit Care Med 1992; 20:559-562.

288. Craven DE. Use of Selective Decontamination of the Digestive Tract - is the light at the end of the tunnel red or green? Ann Intern Med 1992; 117:609-611.

289. Moore RD, Smith CR, Lietman PS. Association of Aminoglycoside Plasma Levels with Therapeutic Outcome in Gram-Negative Pneumonia. Am J Med 1984; 77:657-661.

290. Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with Gram negative bacteraemia. J Infect Dis 1984; 149:443-448.

291. Moellering RC, Eliopoulos GM, Allan JD. Beta-Lactam/Aminoglycoside Combinations: Interactions and Their Mechanisms. Am J Med 1986; 80sC:30-34.

292. Klastersky J. Concept of empiric therapy with antibiotic combinations: indications and limits. Am J Med 1986; 80:2-12.

293. Potgieter PD. Pefloxacin therapy for nosocomial infections in the intensive care unit. J Antimicrob Chemo 1990; 26sB:83-89.

294. Klastersky J, Carpentier-Meunier F, Kahan-Coppens L, Thys JP. Endotracheally administered antibiotics for Gram negative bronchopneumonia. Chest 1979; 75:586-591.

295. Brown RB, Kruse JA, Counts GW, Russell JA, Christou NV, Sands ML. Double blind study of endotracheal tobramycin in the treatment of Gram negative bacterial pneumonia. Antimicrob Agents Chemother 1990; 34:269-272.

296. Stoutenbeek CP, Van Saene HKF, Miranda DR, Zandstra DF, Langehr D. Nosocomial Gram-negative pneumonia in critically ill patients: a 3 year experience with a novel therapeutic regimen. Intensive Care Med 1986; 12:419-423.

297. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification. Crit Care Med 1985; 13:818-829.

298. Knaus WA, Draper EA, Wagner DP. Prognosis in acute organ system failure. Ann Surg 1985; 202:685-690.

299. Baker SP, O'Neill B, Haddon W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974; 12:187-196.

300. Reusser P, Zimmerli W, Scheidegger D, Marbet GA, Buser M, Gyr K. Role of Gastric Colonisation in Nosocomial Infections and Endotoxaemia: A Prospective Study in Neurosurgical Patients on Mechanical Ventilation. J Infect Dis 1989; 160:414-421.

301. Martinez-Pellus AE, Ruiz J, Garcia J, SanMiguel MT, Seller G, Bru M. Role of Selective Digestive Tract Decontamination(SDD) in the Prevention of Nosocomial Pneumonia (NP): Is gastric decontamination necessary? Intensive Care Med 1992; 18:2218-221.

302. Cade JF, McOwat E, Siganporia R, Keighley C, Presneil J, Sinikas V. Uncertain relevance of gastric colonisation in the seriously ill. Intensive Care Med 1992; 18:210-217.

303. Rello J, Ausina V, Castella J, Net A, Prats G. Nosocomial Respiratory Tract Infections in Multiple Trauma Patients: Influence of level of consciousness with implications for therapy. Chest 1992; 102:525-529.

304. Hedlund JU, Ortqvist AB, Kalin M, Scalia-Tomba G, Giesecke J. Risk of pneumonia in patients previously treated in hospital for pneumonia. Lancet 1992; 340:396-397.

305. Hammond JMJ, Potgieter PD, Saunders GL, Forder AA. Double-blind study of selective decontamination of the digestive tract in intensive care. Lancet 1992; 340:5-9.

306. Cowan ST. Manual for the identification of medical bacteria. 2nd ed. Cambridge: Cambridge University Press, 1974:

307. Lorian V. Antibiotics in Laboratory Medicine 2nd edition pg 61, Williams and Wilkins, 1986

308. NCCLS Antimicrobial Susceptibility Testing, 3rd edition, Vol 10, no 7 American National Standards Institute, 1991.

309. Wiesner RH. The incidence of Gram negative bacterial and fungal infections in liver transplant patients treated with selective decontamination. Infection 1990; 18 suppl 1:s19-s21.