SEVERE COMMUNITY-ACQUIRED PNEUMONIA

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To Janet

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REVIEW OF COMMUNITY-ACQUIRED PNEUMONIA

CHAPTER 1

INTRODUCTION

Pneumonia, one of the earliest recognised diseases, still remains a medical enigma. The causative organism may remain unknown in up to 60% of cases of community-acquired pneumonia, with new organisms still being discovered, factors which aid in determining disease severity or influencing its prognosis are still poorly defined, the efficacy of many aspects of care remain anecdotal and unproved, and even the newer antibiotics have not been shown to be better than the old and tried regimens.

Its aetiological diagnosis is imprecise and the efficacy of aspects of treatment is still debatable, despite powerful antibiotics and modern intensive care.[1-3] Although agents like *Klebsiella pneumoniae* (Friedlander's Bacillus) and *Streptococcus pneumoniae* have been known to cause pneumonia since the last century, more recently discovered agents such as *Legionella pneumophila* (discovered in 1976), and *Chlamydia pneumoniae* (1986) are now recognised to be major causes of community-acquired pneumonia.[4-8] While the clinical diagnosis of pneumonia may be made with confidence in the majority of patients, and is likely to be incorrect in as few as 5% of cases, where another pulmonary disease such as pulmonary embolism, or less common diseases such as eosinophilic pneumonia, cryptogenic organising pneumonia (COP), may masquerade as pneumonia,[9,10] it is the diagnosis of the aetiological agent which is far more problematic, and the causative agent may remain unknown in up to 50% of all cases. With the increasing availability of newer invasive techniques for obtaining pulmonary specimens, improved culture and serological techniques, and techniques using the polymerase chain reactions and DNA probes, fewer cases will remain undiagnosed.[7,11-16]

Measures of the severity of illness in pneumonia, other than broad criteria for hospital admission, remain controversial and inaccurate, although it is now generally recognised that the elderly, patients with underlying disease, leukopenia, confusion, renal dysfunction and those with gram negative and staphylococcal infections require hospital admission.[17,18]

Criteria for determining the need for ICU admission, or intubation and ventilatory support, or prognostic indicators have not yet been clearly defined.[19-22] The role of modern intensive care with optimum antibiotic therapy, close monitoring and organ support, new ventilatory techniques utilising PEEP, inverse ratio ventilation, or CPAP. has also not yet been adequately determined. Unilateral lung ventilation and more radical forms of therapy such as surgery have also not been adequately evaluated and their use remains based on anecdotal reports.[1,23-28]

Many new antibiotics with improved pharmacokinetics, broader spectrum of activity, and fewer adverse effects have been developed, yet none has been shown to be more effective than the traditional historically proven agents.[29,30] No antibiotic studies however, have been designed to show improvement over the existing agents, but only equivalence in clinical and microbiological safety and efficacy.

Pneumonia is a disease with numerous aetiologies, and many diverse patterns of presentation, which may be influenced by numerous factors including seasonal influences, regional effects, the site of acquisition (e.g. hospital or community acquired), and host differences, including age, underlying disease, and most importantly immuno-compromised host defences. All these factors exert an influence on the spectrum of causative agents. As the initial treatment invariably requires empirical antibiotic therapy, before the results of microbiological investigations become available, the above variables which influence the aetiology of the pneumonia, need to be considered in order to make a logical selection of antibiotics. This makes a distinctive classification of pneumonia that defines the likely spectrum of pathogens, essential for describing the disease, planning treatment, and evaluating treatment and outcome.

In this thesis I will review the current knowledge of community-acquired pneumonia, including its classification, pathogenesis, pathology, aetiology, diagnosis, and antibiotic therapy and report my experience with severe community-acquired pneumonia in patients requiring admission to our respiratory intensive care unit. The original research in this thesis comprises a prospective, descriptive analysis of 196 cases of severe community-acquired pneumonia requiring admission to the Respiratory Intensive Unit at Groote Schuur Hospital from January, 1987 until December, 1992, with emphasis on the influence of aetiology on the severity of pneumonia, the aetiological diagnosis of pneumonia in severely ill patients, measures of severity of pneumonia, and an audit of ICU therapy and outcome. In addition, different aspects of novel therapies and specific aetiological varieties of pneumonia which have been investigated over the past ten years will be presented.

Classification of Pneumonia

A number of different classifications of pneumonia have been used in the past, including a widely accepted pathological classification. This divides pneumonia into lobar, bronchopneumonia or interstitial pneumonia, with further subdivisions according to the aetiological agent. This classification is however of little value in the clinical setting, where the determination of the aetiology of pneumonia using clinical features is of paramount importance in determining therapy. Furthermore, these classic, pathological features are altered following modern supportive therapy; and the histological appearance invariably demonstrates non-specific changes of diffuse alveolar damage, reflecting the effects of oxygen and ventilatory therapy, rather than the effects of the organism.

A radiological classification into lobar, bronchopneumonia and interstitial pneumonia, noting the presence or absence of an effusion, is another widely accepted means of classification, but its ability to assist in determining the aetiological diagnosis has recently been questioned.[9,31]

The most commonly used clinical classification divides pneumonia into broad, easily defined categories of community-acquired, nosocomial, aspiration and pneumonia in the immuno-compromised host. This classification may also incorporate both the pathological and radiological features described above, as the pathological and radiological descriptions are usually comparable.

In some recent studies of community-acquired pneumonia (CAP), the selection of the study patients by the addition of qualifying criteria such as lobar radiological abnormalities, may have introduced bias by pre selecting particular organisms [32]. In other studies, the inclusion of patients with pulmonary tuberculosis may have influenced the incidence of causative organisms and clinical features, as well as information on patient outcome.[33] Perhaps of even more concern with some studies is the inclusion of significantly immunocompromised patients, such as Human Immuno-deficiency Virus (HIV) infected patients, who are both at increased risk of developing pneumonia and have an increased mortality.[34,35] These potential problems with classification serve to emphasise the importance of standardising definitions of pneumonia, in order to achieve uniformity and avoid selection bias influencing subsequent results.

Whilst nosocomial pneumonia has recently been the subject of an international consensus meeting, and widely accepted definitions and a system of classification have been recommended [36,37], no definitions or classification of CAP are generally accepted at present, and a consensus on classification should be a priority in order to allow our understanding of CAP to advance. Following the initial submission of this thesis, a North American and Canadian consensus meeting on diagnosis, assessment of severity, and initial antimicrobial therapy has been held and guidelines published. The disease was still not clearly defined, and all cases of community-acquired pneumonia were considered in the broad definition of the disease. Subdivisions in terms of the severity of disease (into those patients requiring outpatient treatment, hospital treatment or those with severe pneumonia usually requiring ICU treatment), the presence of co-morbid illness, and or age (>59 years) have been recommended to

determine initial therapy.[38] Unfortunately, these guidelines were drawn up using only 9 recent prospective studies from North America and Western Europe and may thus lack general application.

Table 1: Classification of pneumonia.

1. **Primary community-acquired pneumonia.(CAP)**
1.1 CAP in the Elderly
1.2 CAP with underlying Chronic Obstructive Lung Disease
1.3 CAP with Diabetes
1.4 CAP with Neuromuscular disease
2.**Nosocomial pneumonia**.
1.1 Non-ventilator associated
1.2 Ventilator associated. (VAP)
1.2.1 Early onset
1.2.2 Late onset pneumonia
3. **Aspiration.**
3.1 Nosocomial.
3.2 Community acquired.
4. **Immuno-compromised hosts**.
4.1 Renal transplant.
4.2 Cardiac transplant.
4.3 Bone marrow transplants
4.4 Leukopenic patients(white cell count <1,000 cells/ml)
4.5 Systemic disease e.g. Systemic lupus erythematosis
4.6 AIDS.

Definitions

1. **Community-acquired pneumonia.** These are patients who develop a pneumonia in the community or within 48 hours of being admitted to hospital, and may thus be presumed to have been "incubating" their infection on admission.

2.**Nosocomial pneumonia.** Nosocomial pneumonia is a pneumonia developing in a patient at least 48 hours after hospital admission, or developing in a patient who has been hospitalised in the previous month. Nosocomial pneumonia can be further classified as non-ventilator or ventilator-associated pneumonia (VAP), and the latter may be divided into those occurring early within 5 days of admission (early onset pneumonia [EOP]) ,and those occurring after 5 days of admission.[36,39].

3. **Aspiration pneumonia.** Aspiration pneumonia is defined as a pneumonia occurring in a patient following a clear history of aspiration, or in a patient who has a depressed level of consciousness where the likelihood of aspiration is high. The aspiration may either have occurred in the community i.e. community-acquired or in the hospital i.e. nosocomial.

4. **Pneumonia in immuno-compromised hosts.** This includes patients whose immunity is significantly depressed as a result of either disease or drugs and in particular includes patients who have had transplants and patients with HIV infection.

5. **Non-responding pneumonia.** This is a term reserved for patients who have failed to improve after 5 to 7 days of antibiotic therapy. Whilst there is usually no worsening of the disease there is minimal or no response.

Patients with slowly responding pneumonia may also fall into this category as they would require a similar clinical approach but these patients would have a definite but slower than expected response.. The condition of non-responding pneumonia may

also be referred to as non resolving or slowly resolving pneumonia and, since the initial presentation of this thesis, three new reviews on the subject have been published.[40-42]

These patients form a specific group which requires specific diagnostic and therapeutic approaches.

CHAPTER 2

PATHOGENESIS

Introduction

Pneumonia occurs when the normal pulmonary defence mechanisms are unable to prevent the proliferation of micro-organisms which have gained access to the lung. These organisms multiply and cause pulmonary parenchymal inflammation, with an influx of inflammatory cells, interstitial fluid and alveolar exudate; this results in a systemic inflammatory response, and deterioration in pulmonary gas exchange. The development of pneumonia therefore depends on the balance between the numbers, virulence and pathogenicity of the micro-organisms, and the host immune-defence mechanisms.[43-45]

The organisms causing pneumonia may either originate from within the patient (endogenous) or from the environment or other carriers (exogenous). There are six main routes for entry, which are largely determined by the type of micro-organism, and include: inhalation, usually in droplet form, aspiration, micro-aspiration with subsequent colonisation of the respiratory tract, and haematogenous seeding, with inoculation and direct spread from contiguous sites being less common. More recently with recognition of bowel failure in critically ill patients, bacterial translocation from the gut as a source for pulmonary infection has been suggested, but this mechanism remains speculative, with recent literature refuting this entity.[46,47] Inoculation is only important in nosocomial infections or near drowning where non-respirable fluid from ventilatory apparatus may enter the lungs,[48] however it can be largely disregarded as a cause of community-acquired pneumonia, unless the patient is on some form of home inhalation therapy.

1. Routes of lung infection

1.1 Aspiration.

Aspiration, usually micro-aspiration of endogenous micro-flora from the oropharynx into the lungs is becoming recognised as one of the most important causes of both community-acquired and nosocomial pneumonia.[43,49,50] This is the most likely route of pneumonia caused by *S. pneumoniae* and *H. influenzae*, which are by far the most common causes of community-acquired pneumonia.[9,51,52]

It is evident that, even in normal people, small amounts of oropharyngeal secretions are aspirated during sleep.[53] Any decrease in the level of consciousness makes aspiration more likely. This mechanism is of particular importance in alcoholics where oropharyngeal reflexes are frequently more depressed, and in the elderly and those who are receiving hypnotics or nocturnal sedation. Aspiration is probably the major predisposing cause for the increased incidence of pneumonia in these patients. It may also account for the high incidence of *K. pneumoniae* pneumonia in alcoholics. Other patients at high risk of aspiration are those with bulbar dysfunction, especially those patients who are endotracheally intubated or have tracheostomies. Both these forms of intubation render the protective laryngeal reflexes incompetent, and in spite of appropriate cuff inflation, allow ongoing aspiration of supra cuff secretions. This is undoubtedly one of the most important mechanisms responsible for the high incidence of nosocomial pneumonia in patients who are intubated.[54-56]

The organisms which are aspirated in the normal individual comprise the normal flora of the oropharynx, including *S. pneumoniae*, *H. influenzae*, *S. aureus* and *Moraxella catarrhalis.* In the elderly and in patients who are ill, particularly those who are hospitalised, the flora of the oropharynx and upper

respiratory tract is recognised to change, with colonisation by Gram negative Enterobacteriaceae becoming common.[57,58]

While anaerobic microbial flora form the major component of normal flora they are seldom implicated as important pathogens in pneumonia except in cases of aspiration pneumonia or lung abscess.[59] The reason for this could be that anaerobic cultures are seldom performed in pneumonia unless special microbiological specimens are obtained. The host defences may also be capable of preventing proliferation of the usually less invasive anaerobic micro-organisms, unless there are additional anaerobic conditions such as would occur with a major aspiration.

1.2 Aerogenous inhalation.

The inhalation of micro-organisms is a far less common portal of entry, however, certain agents and in particular viruses (*Influenza A, Respiratory Syncytial Virus*, and *Para-influenza Viruses*), *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Mycobacterium tuberculosis,* are almost invariably transmitted via this route. These infections are usually transmitted in droplet form from other infected people, or from unaffected carriers.[43,60] *Legionella pneumophila*, an organism which is frequently found in water, is often transmitted from a water supply reservoir, and may gain entry to the patient from humidifiers, air-conditioners or showers.[5] This route of infection is the cause of epidemics of viral and *Mycoplasma pneumoniae* infections. Outbreaks of influenza in winter, and clusters of *Mycoplasma pneumoniae* infections occurring in young people who are confined together, such as in army barracks, occur by this mechanism.[61,62] A similar situation is seen in outbreaks of histoplasmosis in people who have been in infected caves, and who have inhaled the spores of *Histoplasma capsulatum*.

1.3 Colonisation.

Initial colonisation of the oropharynx or upper airways, followed by infection is an unusual mechanism for community-acquired pneumonia, except in those who have pre-existing disease, particularly broncho-pulmonary disease .This is an important consideration in patients who have an underlying bronchial abnormality, such as bronchiectasis or chronic bronchitis, which allows adherence and colonisation by such organisms as either *S. pneumoniae* or *H. influenzae* most commonly.[43,63] Such colonisation of the lower respiratory tract usually causes relatively minor inflammatory effects with increased mucus production. At times, when there is additional derangement of the natural barriers such as following influenzae, the colonisation by these organisms may proceed to active bronchial infection and even parenchymal invasion.[64] Thus in patients with chronic obstructive pulmonary disease infections with *H. influenzae* are far more common than in normal patients.

Patients with cystic fibrosis form a unique group as they are frequently colonised with either a mucoid form of *Pseudomonas aeruginosa* or *Staphylococcus aureus.* Pneumonia in these patients is often caused by these organisms.[65]

Any systemic disease which alters the immune defence to allow colonisation of the gastro-intestinal tract, and upper or lower respiratory tract with potentially pathogenic organisms, may predispose to pulmonary infection. This is particularly relevant in hospitalised patients who are commonly colonised with Gram negative bacteria. In the intubated patient, colonisation of the oropharynx is but a step away from tracheal colonisation, and invariably precedes infection in the majority of patients who develop nosocomial pneumonia.[49,66,67]

1.4. Haematogenous route.

This route of infection is relatively uncommon in community-acquired pneumonia, and when it occurs, is frequently caused by infections with *S aureus*, arising from either soft tissue, bone, or joint infections, which may not necessarily have been obvious on initial presentation.[68] Other haematogenous infections may be associated with septic venous thrombosis involving the internal jugular vein secondary to ear infections, intravenous lines, or septic pelvic thrombophlebitis associated with gynaecological sepsis. These infections are frequently poly-microbial, often involving anaerobic organisms.[68-70]

The haematogenous route of infection is also seen in immunocompromised patients with invasive aspergillosis.[71] This route of infection frequently has characteristic multi-lobular opacification on the chest radiograph, which may coalesce to diffuse opacification if the disease progresses.[69]

1.5. Spread from contiguous infection.

This route of infection is exceedingly uncommon, but may occasionally be seen secondary to a mediastinitis, pericarditis or rupture of a liver abscess through the diaphragm.

1.6 Inoculation.

Inoculation, as opposed to inhalation, is the direct introduction of droplets, too large to be normally respirable, which are not conventionally inhaled but rather mechanically sprayed directly into the lungs. This form of pneumonia is invariably associated with ventilatory or nebuliser apparatus, and as such is frequently nosocomial in origin. It may however occasionally be the route of infection with agents such as *Legionella pneumophila,* where inoculation may occur as droplets from humidifiers.[48]

2. Pathogenicity of micro-organisms.

The majority of pneumonias result from an underlying abnormality of the host defence mechanisms, leading to an inability to suppress the load of pathogenic organisms presented to them. Others are however related to the intrinsic pathogenicity of the particular agents, which allows them to cause a pneumonic process in spite of normal defence mechanisms.[72] Although these agents may be highly infectious, they are not necessarily particularly virulent and may cause only mild disease. They include the respiratory viruses, *Mycoplasma pneumoniae*, *Chlamydia spp.* and *Histoplasma capsulatum.* These organisms are easily transmitted between individuals and tend to spread by the aerogenous route. They frequently cause epidemics or clustering of infections where people are living in close proximity to one another.[44]

3. Host defence abnormalities.

Numerous respiratory tract defence mechanisms are active, and prevent damage and infection occurring to the delicate pulmonary tissues. These may be conveniently classified into physical, humoral and cellular mechanisms. (see table 2).

3.1. Physical barriers

3.1.1 Air conditioning effects

The upper airway including the nose and oropharynx presents a large surface area of moist, warm, mucosa to the inhaled air which provides an efficient air-conditioning effect. By the time air reaches the lobar bronchi it has already been warmed to body temperature and has been fully humidified. Low concentrations of soluble gases such as chlorine, ammonia and sulphur

dioxide may be completely removed. If the soluble gases are in high concentrations, or if insoluble gases such as ozone and oxides of nitrogen are present, they will reach the respiratory bronchioles, where damage leading to bronchiolitis may occur.

Although the air conditioning effect itself has little influence on destroying bacteria, it prevents damage to the respiratory bronchial mucosa and mucociliary escalator, which help to prevent any infection occurring secondary to physical damage.[45,60]

3.1.2 **Aerodynamic effects**

Particle deposition in the airway occurs by a number of mechanisms including inertial impaction, sedimentation and diffusion. The mechanism which results in the most deposition depends on the size, shape and density of particles, airflow velocities, respiratory frequency, and airway calibre.

a) Inertial impaction

Large particles are removed by the vibrissae filter at the nares, but those of 30 microns or less pass to the nasal cavity with its large surface area created by the septum and turbinates. Here 90% of particles of 10 microns and 75% of 5 micron particles are removed. The posterior nasopharynx and pharynx remove the remaining large particles. The tonsils and adenoids form a ring of immunologically active tissue in this area and this filters out impurities. The air entering the trachea has few particles larger than 5 - 10 microns because of the efficiency of inertial impaction. However only 20% of particles smaller than 5 microns are removed by impaction.[45,60]

Table 2: Pulmonary host defences

1. Physical barriers

1.1 Air-conditioning effect

1.2 Aerodynamic filter

- a) Inertial impaction
- b) Sedimentation
- c) Diffusion

1.3 Airway reflexes

- a) Cough
- b) Sneeze
- c) Bronchoconstriction
- d) Laryngospasm

1.4 Mucocilliary escalator

2. Humoral barriers

2.1 Non specific soluble factors

- a) Lysosome
- b) Lactoferrin
- c) Interferron

2.2 Immunologic barriers

- a) IgA
- b) IgM

3. Cellular barriers

- 3.1 Alveolar macrophages
- 3.2 Neutrophils
- 3.3 Lymphocytes

b) Sedimentation

This is the chief mechanism for removal of particles between 5 and 0.6 microns in size. Gravitational forces allow the particles to settle in the peripheral airways from the fifth bronchial division to the terminal lung units where the airflow velocity is less than 10 cm per second, which is necessary for sedimentation. This condition of low flow also exists adjacent to the airways higher up in the bronchial tree, however the main region for sedimentation is where the total airflow is low.

c) Diffusion

Particles of less than 0.01 microns in size are deposited by diffusion or Brownian movement in the peripheral portions of the lung. It is interesting to note that particles between .1 and .5 microns are virtually unaffected by the mechanisms of diffusion and sedimentation, and only 20% are retained. The aerodynamic diameter of viruses vary between .02 and .25 microns, whereas bacteria vary between .25 and 10 microns and, although many of these fall within the particle size that are hardly retained within the lungs, they usually form part of droplets of a greater size and are therefore deposited.[60]

3.1.3 **Airway reflexes**[45,60]

Cough, sneeze, gag, and bronchoconstrictor reflexes are all vital in preventing the inhalation of foreign agents, upper airway secretions, food particles, and gastric acid which has been refluxed. The lower oesophageal sphincter, which prevents reflux, may also be considered as an airway reflex. The lower oesophageal sphincter mechanism is particularly important in the critically ill or hospitalised patient, where the stomach may become colonised with potentially pathogenic micro-organisms.[43]

a) Cough

An effective cough can produce an explosive expiration with an airflow of 25,000 cm per second, and this blast of air removes secretions from the trachea

and major bronchi. It has little effect on the more peripheral airways other than acting as a gas liquid pump, which moves mucus to a proximal bronchus where it can be coughed up. The mechanism of cough is a deep inspiration often to total lung capacity followed by glottic closure for about .2 seconds with maximum chest wall, diaphragm and abdominal muscle contraction. Prior to glottic opening, the intra-thoracic pressure rises to as much as 50 to 100 mm Hg pressure; the glottis then opens and allows an explosive rush of air out through the mouth. Dynamic compression of the airways will increase the net velocity of airflow. The cough is the most important protective mechanism of the entire airway, and failure of this mechanism is a common cause of community-acquired or nosocomial pneumonia. Failure of the cough defence is a frequent cause of pneumonia associated with neuromuscular weakness and inco-ordination, severe chronic obstructive pulmonary disease, asthma and postoperative and post-traumatic pneumonia.

b) Sneeze

A sneeze is similar to a cough, but inspiration is usually limited, and forced exhalation occurs through the nose. This protective mechanism results from nasal stimuli.

c) Bronchoconstriction

This reflex of bronchoconstriction may result from any gaseous, physical, liquid or particulate stimulus. Bronchoconstriction acts a defence mechanism by limiting air entry into the peripheral distal air spaces and thereby reducing damage. It usually has little part to play in the prevention of pneumonia.[45]

d) Laryngospasm

This laryngeal reflex results in intense closure of the true and false vocal cords and prevents aspiration of secretions and other noxious substances. It is an important reflex which prevents macro-aspiration in all but deeply comatosed patients.

3.1.4 Mucociliary escalator

The mucus and mucociliary transport system of the upper and lower airway provide a physical, physiological and immunological barrier against the environment.[73] Particles of foreign material, including bacterial and other pathogenic agents, are trapped in the mucous blanket lying over the ciliated epithelium, and are moved up the mucociliary escalator to a point in the respiratory tree where the bronchial secretions can be expelled by coughing.[60] Failure of this defence mechanism may occur either due to an abnormality of mucous production, or ciliary function. In diseases such as chronic bronchitis, the number of mucus goblet cells increases, and excessive quantities of mucus are produced. This excessive mucous production, combined with pus cells from the chronic inflammation, lead to a loss of elasticity with the increased viscosity, resulting in a decreased efficiency of the mucociliary escalator with increased propensity to infection.

Ciliary action may be reduced by tobacco smoke, dry gases and other air pollutants, and a similar effect may be evident in diseases including asthma, bronchiectasis and recent viral and *Mycoplasma pneumoniae* infections. This ciliary dysfunction may require a month or more to return to normal. Other primary ultra structural defects of the cilia are seen in genetic disturbances such as the immotile cilia syndrome and Kartagener's syndrome. Abnormalities of these two components of the mucociliary escalator contribute significantly to inflammatory bronchial disease as well as predispose to pneumonia.[74-76]

Cystic fibrosis, an autosomal recessive genetic disorder which has recently been localised to an abnormality at the Cen-q22 region of chromosome 7, has a major influence on this barrier which leads to the clinical disease.[77,78] The pathogenesis is characterised by 2 general features: 1.) The affected cells are epithelia. 2.) The abnormality in the epithelial cells involve the regulation of ion transport: there is an abnormal regulation of the activation state of the

plasma membrane chloride channels, as well as an increased absorption of sodium ions in the airway epithelia. This results in decreased water content of secretions which changes the visco-elastic properties and linkage between the mucous component of secretions and cilia. This reduces both mucocilliary and cough clearance of secretions.

These initial defects resulting in reduced clearance of thickened secretions promote infections by *S. aureus* and *Ps. aeruginosa* The susceptibility to these infections may be increased by a change in the sulphate content of airway cell surface glycocalyx which facilitates bacterial adherence.[79] This persistent bacterial colonisation and infection, with the release of exotoxins, lead to airway destruction and bronchiectasis. Lipopolysaccharides, exotoxin A, and a cell wall associated rhamnolipid from *Ps. aeruginosa* have all been implicated. [80] The main cause of damage is an excessive inflammatory host response with inflammatory cell enzymes being the main players rather than any lack of immunological response.

3.2 Humoral barriers

3.2.1 Non specific soluble factors.

A number of non-specific circulating soluble factors provide a defence against infection and protect the integrity of the mucosal epithelial surface. These include lysosomes, lactoferrin, interferon, complement and numerous cytokines. When these cytokines, particularly tumour necrosis factor (TNF) are excessively activated, they appear to be the mechanism by which multiple system organ dysfunction occurs.

Lactoferrin is a molecule synthesised in glandular mucosal cells which has potent bacteriostatic activity, probably due to the binding of metallic ions. Lactoferrin together with IgA plays a leading role in preventing bacterial

invasion. The other circulating factors have less well defined effects in preventing infection, but all appear to have a role.

3.2.2 Immunologic defences

Antibodies are complex glycoproteins known as immunoglobulins. Both IgA and IgM are developed following exposure to an antigen, and they play a leading role in preventing infection.[81,82] The effectiveness of these antibodies in preventing infection usually correlates with their quantity in the bronchial secretions, rather than in the circulation. Dimeric IgA occurs predominantly on mucosal surfaces, whereas monomeric IgA occurs in the serum. The polymeric IgA and IgM are linked, via disulphide bonds, with a protein called J-chain. It is produced by B lymphocytes and is required to initiate secretion of IgM and dimeric IgA. Secretory component is another protein which is uniquely associated with mucosal IgA and IgM where it acts as a membrane receptor facilitating endocytosis, transport and secretion of the immunoglobulin onto the mucosal surface. Most important of these local secretory antibody defence mechanisms in the lung are secretory IgA antibodies, which form a primary defence mechanism. This mechanism is particularly active in viral infections, including *Rhinovirus*, *Adenovirus*, influenza viruses, para-influenza viruses and *Echo* viruses.

The role of antibodies in protection against infection requires enlisting host effector cells and activating the complement system to eradicate infecting organisms in a co-ordinated way. Antibodies and complement need to act against organisms in an extra-cellular site to minimise damage to host cells. Specific antibodies achieve this extra-cellular activity by:

i.) Opsonisation of organisms for ingestion and destruction by phagocyte cells

ii.) Cell-free lysis of susceptible organisms by the complement system

iii.) Neutralisation of toxins

iv.) Inhibition of attachment of organisms to host cells.

v.) Inhibition of the infectivity of extracellular viruses.

Organisms that are harboured in an intracellular situation are in a sanctuary where they are protected against antibodies or complement.

3.3 Cellular barriers

3.3.1 Alveolar Macrophages

The lung macrophage originates from blood monocytes and migrates out of the bloodstream across the pulmonary capillary endothelium.[83]. These cells may also proliferate after entering the alveoli. There are a number of different kinds of lung macrophages including bronchial, alveolar, and interstitial macrophages. The alveolar macrophage represents a population that is morphologically and functionally heterogeneous. It is characterised by a lobulated nucleus and vacuolated cytoplasm containing many mitochondria and lysosomes, and their size may vary from 12 to 40 m. They can be further divided into sub populations with different membrane-receptor expressions and cell function such as phagocytosis and mediator release.[84]

Macrophages interact with their environment by binding molecules to specific surface receptors. The alveolar macrophage is the resident phagocyte of the alveolar space and is one of the most important defence mechanisms against pulmonary infection. This function is facilitated by surface receptors for the Fc fragment of several immunoglobulins and for the complement fragment C3b which are essential for the phagocytosis of opsonised micro-organisms.[85] These cells phagocytose both organic and inorganic material deposited distal to the ciliated airways. The majority of these are subsequently carried upwards by the mucociliary escalator and expectorated or swallowed, but some enter the lymphatics, and drain to regional lymph nodes, or directly into the venous system. Occasionally macrophages may enter the bloodstream directly. These cells may also be stimulated to produce a number of soluble

substances necessary for lung defence. The macrophages may also be activated by interaction with lymphocytes to produce increased bacterial killing.[83]

3.3.2 Neutrophils

Neutrophils are not normally present in the lung but congregate in response to infection or other pulmonary insults, and they form the basis of the inflammatory response in pneumonia.[45] They produce soluble factors including tumour necrosis factor, interleukins, and platelet activating factor, all of which are bactericidal. They also phagocytose organisms directly. Over-production of the soluble factors due to marked aggregation of neutrophils in the lung, will lead to progressive capillary leak and the adult respiratory distress syndrome (ARDS) associated with sepsis. This mechanism rather than pneumonic inflammation may sometimes account for the rapid radiographic spread of pneumonia.

3.3.3 Lymphocytes

A local cell mediated immune response exists in the lung, which is similar to the humoral IgA type response. Both B and T cells are present in the lung, and these appear to produce antibodies when stimulated by direct intra-nasal or intra-tracheal antigen presentation. These cells may come from the blood, but are more likely to arise from bronchus-associated lymphoid tissue.[45] T cells obviously form a major barrier against infection, and when this defence is defective, such as in transplant, other immunosuppressed, or particularly in AIDS patients, pulmonary infections with opportunistic organisms, particularly *Pneumocystis carinii* and *Mycobacteria spp.*, occur frequently.

4. Specific host and micro-organism interactions.

4.1 *S. aureus.*

Invasive infection by *S. aureus* requires a series of interactions with the host including adhesion, invasion, chemotaxis of neutrophils, phagocytosis, and intracellular killing.

4.1.1 Adhesion

Colonisation by *S aureus* requires initial adhesion to host cells and this occurs in three situations.

i.) Adherence to nasal mucosa is mediated by the teichnoic acid component of *S. aureus* which is increased in carriers or following infection with *Influenzae A.*

ii.) Adherence to disrupted skin , endothelial surfaces and foreign surfaces requires interaction with fibrinogen, fibronectin, laminin and possibly collagen IV.

iii.) During septicaemia attachment of *S. aureus* involves both adherence and post adherence events, such as phagocytosis by endothelial cells. These provide a solid anchoring system to allow bacterial settling.

4.1.2 Invasion

After colonisation, the organism needs to penetrate through the defences provided by the epithelial or mucosal surfaces. Little is known about how invasion occurs.

4.1.3 Chemotaxis

Following invasion, ingestion and killing by both the neutrophil and macrophage systems become the major line of defence. Migration of these cells to the site of infection requires elaboration of microbial and host specific signals. Cell wall and extra cellular products of *S. aureus* such as peptidoglycan, teichoic acids and protein A are all involved. The major signal

results from activation of the complement system which is triggered by these products.

4.1.4 Opsonisation.

Recognition of the micro-organism by the phagocytes is mediated by:

i) their receptors for the Fc fragment of the IgG immunoglobulins;

ii) receptors for the activated subunit of C3b;

iii) and possibly other components of complement.

In some strains of *S. aureus* opsonisation may require highly specific antibodies; however, in most, complement opsonisation will override this specificity.[86] In serum from non-immune subjects complement activation via the classical or alternate pathway provides the major part of the opsonic activity.[87] In hyper-immune serum, opsonisation is largely a result of IgG activity.

The peptidoglycan matrix is also a major determinant of opsonisation and it can trigger opsonisation in the absence of immunoglobulin by activation of either the classical or alternate complement pathway.

Protein A plays a triple antiphagocytic role in the bacteria-cell opsonisation process by its binding to the Fc portion of IgG. Extracellular soluble protein A can react with the Fc terminals of the IgG molecules of human serum producing immune aggregates that consume complement. It may also bind to the Fc portion of specific anti staphylococcal antibodies coating the organism with their Fab fragment, thereby preventing any further interaction of the complex with the Fc receptor of phagocytes. Cell bound protein A binds to the Fc fragment of any IgG molecule eliminating both non-specific and specific antibodies. The capsule of *S. aureus* which may be present in as many as 50% of human isolates will also impair phagocytosis, probably by a mechanism of steric hindrance.[86]

4.1.5 Intracellular killing.

Once phagocytosed, the staphylococci are rapidly killed and degraded in the phagocytic vacuole. Prolonged survival may occur in some organisms and this may account for the high recurrence rate of *S aureus* infections.[88] Oxygen dependent bactericidal mechanisms including O^-_2. H_2O_2 and other free radicals are most important, although the low pH within the vacuole, lactoferrin and granular cationic proteins may also play a role.

4.2 *Ps. aeruginosa.*

Ps. aeruginosa rarely causes disease in healthy persons and usually behaves like an opportunistic pathogen, requiring a breach of host defences to cause infection. This usually involves disruption of the physical barriers such as skin or mucous membranes, or their circumvention by intravenous lines, urinary catheters or endotracheal tubes. They are therefore infrequent causes of community-acquired infection. Its adaptability to a wide range of physical conditions and its resistance to antibiotics allows it to exist in large numbers close to its prospective host, and this accounts for its pathogenicity. The fact that the pathogenicity of *Pseudomonas* is multifactorial is suggested by the number of potential virulence factors as well as the broad spectrum of disease that it causes. Of most relevance in pneumonia is its association with chronic lung disease, particularly cystic fibrosis.

Pseudomonas infections usually comprise three distinct, consecutive stages:

i) bacterial attachment and colonisation;

ii) local invasion;

iii) dissemination and systemic disease.

4.2.1 Colonisation

Bacterial adherence to epithelial cells is crucial for colonisation of the respiratory tract. Protein structures on the surface of the bacterium called pili are responsible for adherence on all epithelial cells.[89] Fibronectin in contrast

to *S. aureus* infections, usually protects against adherence by *Pseudomonas aeruginosa*. Sputa from patients with chronic lung disease or cystic fibrosis contain high levels of protease which breaks down the fibronectin coating leading to adherence. Cellular injury may also play a role as *Pseudomonas* like *S. aureus* also adheres to epithelia damaged by viral infection.

Pseudomonas pili are attachment organelles or adhesins as both purified pili and antibodies to these structures block bacterial adherence to epithelial cells. It is likely that specific molecular sequences on these structures act as ligands that react act with complimentary sequences or receptors on host cells. Galactose or mannose -bindings lectins of *Pseudomonas* may represent such ligands. The mucoid exopolysaccharide of mucoid strains and the pili of nonmucoid strains of *Pseudomonas* represent adhesins for tracheal epithelial cells.

4.2.2 Local invasion

Invasion follows colonisation and factors involved in this progression include cell wall associated structures that resist phagocytosis, or interactions with complement and antibodies, and also the ability of its extracellular enzymes or toxins to break down physical barriers.

Elastase and alkaline protease are the best characterised of the cellular proteases and both are clearly associated with virulence causing necrosis in the lung, skin, and other structures. These enzymes lead to disruption of connections between cells and specifically degrade basement membrane associated laminin leading to disruption of respiratory cilia as well as cleaving type III and IV collagen, and solubilising human lung elastin.[90] They may also make nutrients available for further bacterial growth thus further aiding invasion. *Pseudomonas* protease may also inactivate complement and the cleavage of IgG.

Cytotoxin another toxin widely produced by *Pseudomonas* is largely cytotoxic to neutrophils.

Haemolysins, one a heat labile protein phospholipase c , and another a heat stable glycolipid, act synergistically to break down lipids and lecithin leading to tissue necrosis. Phospholipase may also contribute to *Pseudomonas* pneumonia by degrading lung surfactants.[91]

4.2.3 Dissemination and systemic disease.

Dissemination from local sites of infection is aided by the same cell associated and extra cellular products responsible for invasion. *Pseudomonas* is inherently resistant to phagocytosis because of the mucoid exopolysaccharide, as well as by having direct bactericidal resistant mechanisms. *Pseudomonas* is however susceptible to natural antibodies or IgM, activation of classical and alternate complement pathways, and an adequate number of functioning neutrophils. These stringent criteria for adequate clearance by host defences are further tested by complement inactivation and immunoglobulin-cleaving by the organism itself, which may surpass the capacity of the host immune system.

Systemic illness or death, is most likely to result from excessive uncontrolled inflammatory mediator release largely caused by the lipid A moiety of the lipopolysaccharide endotoxin, and also exotoxin A. In addition to causing shock Exotoxin A also mediates local as well as metastatic disease by its ability to cause tissue necrosis, including dermonecrosis.

CHAPTER 3

PATHOLOGY OF PNEUMONIA

Introduction

Bacteria, viruses and other agents enter the lungs by various routes and, should the lung defences fail to clear the organisms, they will invade the lung tissue and cause inflammation. Differing forms of tissue damage and cellular responses are initiated by the different pathogens which results in distinctive pathological changes. These identifiable features led to the pathological classification of pneumonia, by causative organisms, first suggested by Cecil in 1922, and still in widespread use. The radiological classification into broncho or lobar pneumonia is also evident pathologically, and although also used, is of less value.

In bronchopneumonia the damage occurs primarily in the terminal and respiratory bronchioles. Here the walls are damaged to a variable extent with spread of inflammation into the surrounding peri-bronchiolar alveoli. In lobar pneumonia the organisms produce copious, watery, inflammatory exudate that spreads directly into the air passages and related alveoli. This spread extends to involve adjacent lobules and segments of lung. Although there is bronchial and bronchiolar wall involvement the spread is largely along the lumen of the air passages rather than through the walls of the terminal air passages.[92]

Interstitial pneumonia or pneumonitides in contrast to both lobar and bronchopneumonia which involve varying degrees of airspace consolidation , cause mostly interstitial inflammation confined to the alveolar walls and connective tissue around bronchovascular structures. There is little airspace exudation. Organisms that produce this type of inflammation include *M. pneumoniae*, viruses, *Chlamydia spp.*, *Coxiella burnettii* and *Pneumocystis carinii.* This pattern of inflammation may also however be seem with many noninfectious causes including drug reactions, radiation pneumonitis, hypersensitivity pneumonitis and collagen vascular diseases. Mixed

patterns of airspace consolidation with interstitial inflammation may also occur frequently. This can be due to superimposed bacterial and viral infections creating a fibropurulent airspace inflammatory reaction with mononuclear interstitial inflammation and bronchiolar epithelial necrosis. Viral cytopathic changes and identification of bacteria with Gram staining, may provide diagnostic clues.[93]

The development of abscesses, gangrene or haemorrhage in association with pneumonia is also dependent on the causative organism e.g. pneumolysin which is produced by pneumococci.[94-97]

It is also important to note that with modern day intensive care and antibiotic therapy, most of the classical pathological changes are seldom seen. Prolonged ventilatory support frequently precedes death. The pathological changes seen are modified by this ventilatory therapy and resemble non specific diffuse alveolar damage. The pathological process produced by certain organisms is relevant to the diagnosis and therapy, and a detailed description in certain pneumonias is warranted.

1. Pneumococcal pneumonia

Pneumococcal pneumonia, which is most frequently lobar in nature is caused by a number of different serotypes of pneumococci including, in order of decreasing frequency, type 1, 3, 2, 5, 7, 8 and 4.[72] The early spread of pneumonia is caused by the outpouring of serous oedema fluid usually far beyond the initial focus of infection.[92,98] This response is dependent on:

1) the size of inoculum of organisms;

2) excessive mucus production in airways;

3) presence of the inter-lobar septae which act as barriers to spread of infection;

4) virulence of the organism;

5) and the reaction of the host.[99]

The most important factor in determining spread appears to be the ability of the different pneumococci to produce cytoplasmic proteins such as nuraminidase and

pneumolysins which are released during autolysis. Pneumolysin has been shown to disrupt the integrity of human respiratory epithelium and cause slowing of the cilia.[72].

The distribution of the pneumococcal pneumonia usually favours the posterior basal segment of right upper lobe and the apical segment of right lower lobe, both dependent regions and this suggests that aspiration of organisms is the most likely route of infection, although aerogenous infection undoubtedly also takes place as evidenced by outbreaks of pneumococcal pneumonia in men's shelters.[100]

Classical sequential pathological changes are seen in the evolution of pneumococcal pneumonia in the absence of antibiotic therapy.

Macroscopically the pathology may be divided into three distinct phases: a) spreading inflammatory oedema - this resembles any form of ARDS but the oedema fluid contains numerous organisms. b) red hepatisation - the lung is firm, airless and brick red in colour with petechiae and fibrin casing the pleura. The cut surface is congested, airless, and the smaller bronchi are plugged with fibrin. c) Grey hepatisation - the lung is firm, non-crepitant and covered with a thick film of fibrin. The cut surface is greyish yellow. d) Resolution - this stage shows a return of the normal red colour, though aeration and re absorption of fibrin will still take a longer time.

Microscopically the lung progresses through the same four phases seen macroscopically. The early phase, though seldom seen as it progresses rapidly over a few hours, consists of oedema fluid, a few polymorphonuclear leukocytes and abundant pneumococci. This is followed by red hepatisation characterised by alveoli filled with red blood cells, fibrin and a few polymorphonuclear leukocytes. Alveolar capillaries are intensely congested and bronchial arteries may become obstructed proximal to the pneumonia. Grey hepatisation follows with the alveoli becoming choked with fibrin, large numbers of polymorphonuclear leukocytes and a few red blood cells. Pulmonary arterioles may become thrombosed and alveolar capillaries are inconspicuous. The thrombosis is probably caused by toxins produced by the pneumococci. This phase is followed by resolution which is characterised by

infiltration of macrophages with phagocytic leukocytes and their entrapped pneumococci.

Failure of the macrophages to function adequately causes persisting infection and incomplete resolution. Abscess formation, gangrene of the lung, and empyemata are well recognised late sequelae of incomplete resolution. Incomplete resolution with fibrosis is seen more commonly in the post antibiotic area and has been found to occur in 3.2% of 125 autopsies in patients with lobar pneumonia.[101] Radiological resolution may be delayed for weeks or months, but by six months the majority of cases have resolved.[9] More recently with effective mechanical ventilatory support, rapid spread of pulmonary infiltration is seen beyond the confines of the lung lobes on the radiograph. Histologically this is shown to be pulmonary oedema, typical of early ARDS, without the presence of numerous pneumococci.

2. Staphylococcal Pneumonia

Staphylococcus aureus is an uncommon cause of community-acquired pneumonia occurring in 3 to 8% of cases. It is nevertheless important as it has a high mortality particularly when associated with influenza infections; and its incidence has increased over the past few decades.[102-104] These organisms used to be invariably sensitive to penicillinase resistant antibiotics, however more recently a small number, particularly in the hospital environment, are sensitive only to vancomycin, fucidic acid and clindamycin. This change in sensitivity pattern has paralleled a significant increase in the number of these methicillin resistant *S. aureus* isolates in nosocomial infections, and these organisms have also gradually appeared in the community, but fortunately still remains uncommon (< 10%). The route of acquisition of *S. aureus* pneumonia may be either aerogenous, endogenous following micro-aspiration, or haematogenous; The different routes of infection tend to result in two distinctive patterns of infection.[68,103,105,106]

2.1. Aerogenous or micro-aspiration staphylococcal pneumonia.

This type of pneumonia usually occurs in adults and frequently follows viral infections. It may also be associated with other factors such as old age, bronchial neoplasms or immunosuppression with steroids or other drugs. It may present with either a fulminant acute, or sub acute illness, characterised by bloody sputum with numerous gram positive cocci in clusters present on Gram's stain. The chest radiograph has no typical features. Staphylococcal pneumonia complicating influenza has a mortality of over 40%.[105] A preceding viral infection favours growth conditions for bacteria and *S. pneumoniae*, *H. influenzae* and *S. aureus* are commonly involved in secondary infection.[107] *S. aureus* and viral co-infection however has the highest mortality, and this may be due to a protease secreted by some strains of *S. aureus* which can cause cleavage activation of the virus, and haemagglutination, resulting in rapidly increased viral proliferation and pathogenicity.[64]

Macroscopically the lungs are heavy, plum coloured, and the bronchi are filled with fluid that drains away leaving very inflamed bronchial mucosa. The larger bronchi often have a fibrinous pseudo-membrane that resembles a diptheretic membrane. Haemorrhages are widespread and parenchyma resembles haemorrhagic pulmonary oedema. The brunt of the disease is in the bronchi and bronchioles, but this spreads rapidly with necrotic bronchitis leading to thrombosis of adjacent lobular pulmonary arteries, with surrounding parenchymal oedema typical of ARDS. A less acute but more common form of the disease shows focal patches of peri-bronchial, greyish yellow areas of consolidation, which break down rapidly to form abscess cavities which are filled with sticky yellow pus, and are connected with small bronchi. These abscesses enlarge rapidly with pus spreading along the bronchi, demonstrating the tissue necrosing and pus promoting properties of *S. aureus*. These abscesses resolve slowly, becoming lined with granulation and fibrous tissue, and the adjacent parenchyma is extensively damaged and fibrosed, whilst the vessels may develop obliterative vasculitis. The cavities remained filled with pus with extensive

inflammatory cell reaction of the walls which gradually resolve. Staphylococcal infections of the lungs are frequently accompanied by a pleural reaction which may lead to an empyema in 7 to 27% of cases.[102,106,108]

2.2. Haematogenous staphylococcal pneumonia

Haematogenous staphylococcal pneumonia usually occurs less frequently than aerogenous or endogenous infection, however certain populations particularly young children in third world countries like South Africa, and drug addicts, have an equal or greater incidence of haematogenous staphylococcal infections.[68,69,109] These usually present with classical radiological features typical of septic emboli, which usually include a number of discrete pulmonary infiltrates varying from 3 to more than 5 cm in size, are lobular in distribution, and may progress to more confluent opacification , or even diffuse opacification typical of ARDS in severe cases. The initial infiltrate frequently cavitates with walls which are initially 2 to 4 cm thick and which resolve into thin walled (less than 2 mm) cavities, which resolve completely with time.[69,70,104]

Macroscopically the lungs appear similar to the previously described aerogenous pneumonia, however at a late stage there are characteristically multiple abscess cavities with almost complete destruction of lung parenchyma. Microscopically a pattern similar to endogenous infection is seen. Large pneumatocoeles are frequently seen in infants and young adults, and these may lead to pneumothoraces or empyemas. These occur more frequently with the haematogenous forms of the disease. They do occur in adults where they are seen less frequently than in the younger age group.

3. Klebsiella pneumonia (Friedlander pneumonia)

This disease was described in 1882 by Friedlander who recognised a characteristic lobar pneumonia caused by a gram negative encapsulated bacillus. It is now uncommon in developed countries occurring in less than 1% of community-acquired pneumonias. This organism has forty species plus serotypes, and includes *Klebsiella pneumoniae*, serotype 3; *Klebsiella ozaenae*, serotype 2,3 and 4; *Klebsiella atlantii*, serotype 1; *Klebsiella edwardsie*, serotype 1 and 2.[92] The majority of cases of pneumonia (more than 80%) are caused by serotype 1 whereas the remainder are caused by serotype 2. Serotypes 1,2 and 3 are frequent commensals in the mouth and oropharynx of patients with carious teeth; 5.8% of unselected people may however also be colonised.[110]

Primary *Klebsiella pneumoniae* pneumonia presents as an acute pneumonic illness, seen particularly in men over the age of 50 years, with poor dental hygiene or diabetes. 75% of cases are unilateral, occurring particularly in the posterior segment of the right upper lobe or the apex of the right lower lobe, which is a dependent area of lung and a characteristic site of inhalational infection. The disease usually starts in a lobular segment and spreads rapidly to involve the entire lobe.

Macroscopically the lung appears consolidated, is a greyish red colour, and has a characteristic sticky exudate. Smears show numerous large encapsulated Gram negative organisms, and abscess formation usually occurs within a few days. Outpouring of this oedema fluid, and mononuclear cells with organisms, is seen microscopically. Alveolar destruction follows with a polymorphonuclear cell reaction, and, later granulation and fibrous tissue formation occurs. During the early stages acute alveolar inflammatory oedema occurs in the perivascular region, and peribronchial lymphatic channels are distended, and there is severe oedema of the interlobular septae.

In the chronic stages, multiple abscess formation with granulation and fibrosis and secondary bacterial infection are seen. A quarter of these cases are associated with

empyema and again the posterior segment of the right upper lobe is commonly affected.

4. *Legionella* pneumonia.

All species of *Legionella* may produce a fibrinopurulent lobar or bronchopneumonia. Macrophages and neutrophils are the predominant inflammatory cell types within the alveoli and leucocytoclasis is a common feature. Organisms can often be found near areas of cell debris. Thrombosis of small vessels, septic arteritis, and alveolar wall necrosis occur and there is frequently a heavy mixed interstitial inflammatory pattern together with airspace inflammation.[111]

5. *Mycoplasma* pneumonias.

Pathologically these organisms all produce and interstitial pattern of pneumonia. *Mycoplasma* may produce a highly variable pattern ranging from lobar or lobular consolidation, to a diffuse interstitial pneumonitis. The microscopic picture is non-specific with a mixed interstitial inflammatory infiltrate including lymphocytes, plasma cells, and histiocytes. There may be an associated acute necrotising bronchiolitis and tracheobronchitis and microscopic peribronchiolar abscesses. Large collections of lymphocytes with or without follicle formation may be found around airways. The cytological atypia of viral interstitial pneumonitis is not a feature. Infrequently in severe disease diffuse alveolar damage with hyaline membrane formation may occur.

5. Viral pneumonias.

Viral agents produce an interstitial pattern of pneumonia similar to that of *Mycoplasma pneumoniae*. The lung responds in a similar way to the common viruses causing pneumonia, including *Influenza A* and *B*, *Respiratory syncytial virus* (RSV), *Adenovirus, Rubeola* and *Varicella*. The pneumonic disease may be patchy or diffuse. Macroscopically the lung appears congested and subcrepitant, without obvious consolidation. The pleura is smooth and pleuritis or effusions uncommon.

Microscopically the alveolar septa and interstitium is widened with mononuclear inflammatory cells and oedema. Neutrophils may be seen in very acute cases. The alveoli are frequently filled with proteinaceous acellular material, and hyaline membranes occur heralding diffuse alveolar damage or ARDS. Ulcerative bronchitis and bronchiolitis , haemorrhage, or a superimposed bacterial infection may also be present.

A few viral agents have specific cytopathic changes which may aid in diagnosis:-

i) *Adenovirus* produces amphophilic intranuclear inclusion bodies within bronchiolar epithelial cells. There is frequently bronchiolitis characterised by necrosis of bronchiolar epithelium and airway plugging with mucus, desquamated cells, fibrin and neutrophils. Pneumonitis, bronchiolitis or mixed patterns may occur.

ii) Measles virus pneumonitis is characterised by large multinucleated, syncytial epithelial cells within air spaces. These giant cells have up to 100 intact or pyknotic nuclei and eosinophilic cytoplasm.

iii) *Respiratory syncytial virus* infection results in necrosis of bronchiolar epithelium and cytopathic changes to infected parenchymal cells such as nuclear enlargement and chromatin dispersion. The regenerating reserve cells containing the virus form a syncytium for which the virus was named. It produces a necrotising bronchiolitis with mucopurulent plugging.

iv) *Cytomegalovirus* has characteristic cytopathic changes. The infected cells are large with abundant cytoplasm and megalic, pleomorphic nuclei harbouring

eosinophilic inclusion bodies surrounded by a clear halo. Smaller basophilic cytoplasmic inclusions are present and represent viral coat protein or complete viral units. These changes occur in bronchiolar epithelium, alveolar lining cells, intra-alveolar histiocytes and endothelial cells. [93]

CHAPTER 4

AETIOLOGY OF PNEUMONIA

Pneumonia is usually caused by a relatively small number of different bacterial and viral organisms, and less commonly it may even be caused by other types of organisms including spirochetes, nematodes or a variety of other potentially pathogenic species. The type of pathogenic organism will be influenced by a number of factors including regional, seasonal, exposure, and host differences. Using a classification which incorporates these factors, which is easily applicable, and which thus helps to define the spectrum of pathogenic organisms is important for clinical management decisions. The commonly used classification dividing pneumonia into community-acquired infection, nosocomial infection, post aspiration infection, and infection in immunocompromised patients is thus appropriate and useful. In community-acquired infections in particular, a number of additional factors may all influence the incidence of different pathogens, and these include age, the presence of underlying disease, domicile of patient and seasonal and regional differences. The nature of the disease itself in particular the tempo of onset, and the severity of the disease, may also be important in helping to determine the causative agent.[44]

Factors influencing aetiology in community-acquired pneumonia.

1. Age

Age is one of the most significant factors to influence the incidence of different aetiological agents, and both the paediatric age group, and the elderly, have a different pattern of agents causing infection.. Children under the age of 3 months are much more likely to be infected with *Respiratory syncytial virus*, whereas in those under the age of 5 years, bacterial infections are common, but a high incidence of viral infections still occur, . In non-immunised populations, measles may be a major cause

of morbidity and mortality. The elderly, particularly those over the age of 65 years not only have more severe disease, but are more likely to develop Gram negative infections.[112,113] A number of recent epidemiological studies have corroborated the higher incidence of Gram negative infections in the elderly.[58,114] There is also an increase in the incidence of *H. influenza*, *M. catarrhalis* and *S. aureus* pneumonia in the elderly, and this is thought to be due to an increased likelihood of micro-aspiration. In contrast however, in a recent carefully conducted study from Nottingham which included serological investigations, a spectrum of agents similar to a normal population was found in the elderly. It is noteworthy that even in this study, 40% of patients had no identifiable pathogens.[115]

Tuberculosis has also been noted to occur more frequently in the elderly population, however these infections may be more prevalent in patients living in old age homes.[114]

2. Pre-existing disease.

Patients with chronic obstructive pulmonary disease have been shown to have an increased incidence of pneumonia caused by *Haemophilus influenzae* or *Moraxella catarrhalis*, an agent which is increasingly being recognised as a cause of pneumonia. In these patients more than one pathogen is frequently isolated and with currently available techniques it is impossible to determine whether one or both organisms are causing the pneumonia.[44] One or other of these agents could be a coloniser but it would seem more likely that both are probably acting as true pathogens.[116]

Patients with cystic fibrosis are frequently colonised by *Ps. aeruginosa* or *S aureus* and either of these micro-organisms are likely causes of pneumonia in these patients.

Various abnormalities of host defence mechanisms may be associated with a higher incidence of specific infecting organisms. Complement deficient states which can occur in disease such as SLE will lead to an increased rate of infection with *S. pneumoniae* and *Meningococci.* Humoral defence abnormality such as

immunoglobulin deficiency will result in increased infection with *Pneumococci, Streptococci, H. influenzae* and *Meningococci* spp.

Other immunosuppressive diseases such as transplant patients, AIDS patients etc. will all have a major influence on the spectrum of pathogens causing pneumonia. These patients form a distinctive group who although likely to develop pneumonia with the usual spectrum of ordinary bacteria, will in addition be subject to developing opportunistic infections; each different type of immunocompromising disease will produce a specific pattern of infections.

Certain diseases or clinical situations by either altering host response, or facilitating colonisation are likely to predispose to infection with specific micro-organisms. These are illustrated in table 3.

Table 3: Conditions associated with an increased rate of infection with specific micro-organisms

Condition	Micro-organism
Elderly	Gram -ves, *H.influenzae, M. catarrhalis* and *M. tuberculosis*
Children <3 months	RSV
Children <5 yr.	viruses
COPD	*H. influenzae* and *M. catarrhalis*
Cystic Fibrosis	*Ps. aeruginosa* and *S. aureus*
Diabetes	*Candida spp., Cryptococcus neoformans* and *Nocardia spp.*
Sickle cell disease (C*)	*S. pneumoniae, Meningococcus spp.*, and *H. influenzae*
Splenectomy (C*)	*S. pneumoniae, Meningococcus spp.*, and *H. influenzae*
Renal disease (C*)	*S. pneumoniae, Meningococcus spp.*, and *H. influenzae*
Complement deficiency	*Meningococcusl spp.*

*C = predominantly complement deficiency.

3. Regional and seasonal factors.

Regional differences have only minor effects on the incidence of the most common pathogens including *S. pneumoniae* and *H. influenzae*, however marked differences may occur with organisms such as *Legionella pneumophila* and possibly *Mycoplasma pneumoniae*. The reported incidence of *Legionella pneumophila* varies from 15 to 20%, in series reported from France and the United Kingdom, whereas in a study of community-acquired pneumonia in Cape Town no cases were found in 80 patients with CAP [9], and subsequent surveillance, information at a time of a cluster of cases would suggest that the incidence is less than 10% (Goveia,C; The Incidence of Legionella pneumonia in Cape Town; Master of Medicine Thesis, University of Cape Town). An analysis of cases that occurred in Cape Town indicates a very low incidence in hospitalised patients and these cases have been shown to occur in unrelated clusters.[117] This almost certainly reflects a real difference in the incidence between the northern and southern hemisphere, although it may be possible that some of the reported series in the northern hemisphere may represent the effect of seasonal differences, or clustering of cases during a study period rather than the true incidence and this is supported by recent studies.[33,52,115].

Seasonal variations in the incidence of different organisms are also particularly important, and it is now well recognised that *Mycoplasma pneumoniae* frequently occurs in epidemics in a four year cycle.[118] Epidemiological studies which are performed during one of these episodes of increased infection rates may well over emphasise the importance of these agents as a cause of pneumonia.

The influence of aetiology on severity of illness

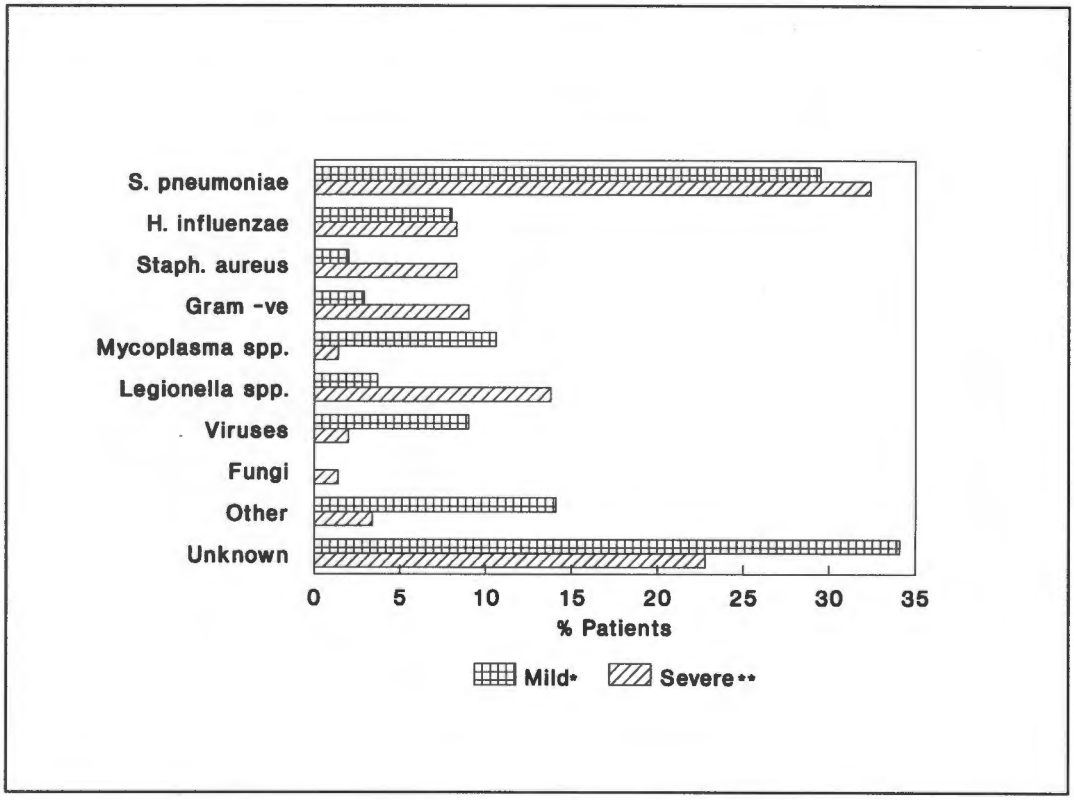
The infecting agent has a definite influence on the severity of the pneumonia, a factor which has not been previously adequately appreciated. A confounding factor is however that the severity of disease may be influenced by co-morbid disease or other

prognostic factors, and these factors may also have an effect on the incidence of different causative organisms. This influence may be relevant the elderly where Gram negative micro-organisms are more likely to cause pneumonia.

In pneumonias caused by *S. aureus* and *K. pneumoniae* the mortality is significantly higher. Although these pathogens are both uncommon causes of CAP, they are seen much more frequently in patients with more severe disease requiring ICU admission. Similarly the incidence of *Legionella* pneumonia is higher in these more severe cases.[1,3,32] The incidence of different pathogens in hospital based studies are compared with those from ICU patients which illustrates these differences. (figure 1).[1,9,33] These differences in the types of infecting organisms are not usually appreciated because of the small numbers of patients with these infections in most studies. We have recently shown that there is a fourfold increase in the incidence of infection by Gram negative micro-organism and a doubling of *S. aureus* infection in patients with severe pneumonia requiring ICU admission.[1] In the same survey we noted an incidence of *Legionella pneumophila* pneumonia of 5%, and an increased incidence of 9 to 15% was also noted in a study in the United Kingdom.[3,51] This incidence of *Legionella* pneumonia is considerably higher than that seen in general hospital based studies in both regions.

Mycoplasma pneumoniae, a common pathogen in general hospital based studies occurs in 2 to 15% of cases, whereas it is extremely uncommon for a patient with *Mycoplasma* pneumonia to require intensive care admission.[1,9,33,52,119]

Figure 1: Aetiology of mild verses severe pneumonia



Mild pneumonia.*[9,17,52] * Severe pneumonia.*[1,119]

It is important to recognise all the different factors which may influence the spectrum of pathogens causing pneumonia and when one analyses epidemiological data it is essential that one takes into account the type of patient, age, presence of underlying disease, immunocompromising factors, seasonal influences, site of acquisition, severity of illness, and the possibility of seasonal variations, minor epidemics, and clustering of certain infections which may influence the incidence of different agents.

CHAPTER 5

DIAGNOSIS OF PNEUMONIA

The diagnosis of pneumonia serves two purposes; firstly to identify patients with pneumonia, and secondly to determine the aetiological agent involved so that appropriate therapy can be instituted. The former is usually straightforward, however the latter presents more problems.

CLINICAL DIAGNOSIS OF PNEUMONIA.

The accurate clinical diagnosis of pneumonia is important, as early appropriate therapy has an important influence on successful outcome.[120] The diagnosis of the disease will be made in over 90% of cases using accepted clinical criteria, including signs of sepsis, purulent bronchial secretions, auscultatory signs of parenchymal consolidation, and standard radiological and haematological investigations. Acute bacterial pneumonia usually presents with an acute onset of fever, frequently with rigors and chills, a cough which may either be dry or productive of purulent sputum, with or without chest pain and shortness of breath. On examination the patient is usually pyrexial with a rapid respiratory rate and an area of crackles with bronchial breathing on auscultation of the chest. About 10% of cases have an associated pleural effusion, and the chest radiograph will usually show evidence of alveolar consolidation. The common radiological features may be either patchy consolidation i.e. bronchopneumonia, or lobar distribution i.e. lobar or segmental pneumonia, and occasionally in haematogenous infections, a lobular appearance may occur. In non-bacterial pneumonias or atypical pneumonias radiological features similar to bacterial pneumonias occur, although an interstitial pattern is more common, particularly early in the disease.

While incorrect diagnosis is uncommon, such conditions as pulmonary embolism, pulmonary tuberculosis, and rarer conditions such as an eosinophilic pneumonia or cryptogenic organising pneumonitis (COP) may occur with features clinically indistinguishable from pneumonia. The most frequent and difficult differential diagnosis is between that of pulmonary embolism and pneumonia, and it is important to remember that in pulmonary embolism the temperature can frequently be higher than 38°C, and the white blood cell count more than 12,000 cells/ml. The white blood cell count may even be as high as 20,000 cells/ml, however it seldom rises higher, and a left shift in the morphology of the leukocytes is unusual in pulmonary embolism.

Other conditions which occur in about 5 - 15% of patients also need to be considered in the differential diagnosis and include:

1) Pulmonary embolism/infarct

2) Pulmonary tuberculosis

3) Pulmonary vasculitides

4) Eosinophilic pneumonias

5) Cryptogenic organising pneumonia (COP), or bronchiolar obliteration and organising pneumonia (BOOP).

6) Sarcoidosis

7) Pneumonitis (chemical, inflammatory e.g. Leptospirosis, collagen-vascular disorders, or gas inhalation.)

8) Congestive cardiac failure

In a prospective study in our emergency unit designed to determine the aetiology of community-acquired pneumonia, initial misdiagnosis occurred in only 5% of cases and similarly in a study by Fang et al, in only 3% of cases, however in two other studies where this aspect was reported the diagnosis was incorrect in 17.4% in the one and the diagnosis was unproved in 47% of cases in the other.[7,9,52,121]

In most of these conditions the diagnosis usually only becomes evident with the full evolution of the disease, or when the patient fails to respond to treatment.

In cases of rapidly developing pneumonia, the chest radiograph may underestimate the extent of the pneumonic process, and early radiographs may even be interpreted as being completely normal, and only subsequent radiographs will show the presence of consolidation.

The white cell count may be either very low (less than 4,000 cells/ml), very high (more than 40,000 cells/ml), or within the normal range. It is perhaps of more value to look at the morphology of the white blood cells, where a left shifted pattern irrespective of absolute count invariably indicates acute infection.

Determining the Severity of Pneumonia.

The ability to determine the severity of pneumonia using readily available clinical criteria is of paramount importance when making early management decisions such as where the patient should be treated (either as an outpatient, or hospitalised in a general ward, or require intensive care unit admission); or will conservative treatment suffice or will supportive treatment including intubation be necessary.

While the question of which patients require ICU admission remains undefined, the clinical criteria determining the severity of pneumonia are well accepted. It is however important to note that severity of disease doesn't necessarily relate to an adverse outcome. Many patients with severe disease defined by pathophysiological abnormality will have a good outcome given appropriate therapy. This is seen in patients with *Varicella* or *Legionella* pneumonia where the ICU outcome is excellent.(see chapter 10) A study by Macfarlane and the report of the British Thoracic Society (BTS) delineating risk factors for severity of illness provide useful guidelines (see table 4).[17,122] The BTS study has shown that a combination of two of the following three criteria : respiratory rate = or > 30/min, renal failure (Urea > 7 mmol/l), and a diastolic blood pressure = or < 60 mm Hg predicted a twenty-one- fold increase in mortality. Two "rules" that predict a poor outcome, were also proposed as criteria for ICU admission. Rule 1 was the presence of two or more of: respiratory

rate of 30 breaths per minute or more, a diastolic blood pressure of 60 mm Hg or less, and a blood urea of >7 mmol/l. This rule had a 93% sensitivity and 94% specificity when used to identify which patients would die. Rule 2 substituted confusion for blood urea and it had a 93% accuracy and 94% specificity; however, it only identified 34% of patients who died. It can nevertheless be applied immediately on assessing a patient.[17]

In a subsequent retrospective study by the British Thoracic Society (BTS) group in 25 British general hospital ICUs, 60 patients were studied and rule 1 was found to identify 75% of the ICU cases, however its positive predictive value is only 19%. They were however unable to identify any individual clinical or laboratory features, duration of illness, prior disease, prior antibiotic therapy, early ICU transfer, or aetiological pathogen that was significantly associated with death.[3]

A number of studies have now been performed to attempt to validate the findings of the BTS. Farr et al in a study of 245 patients of whom 20 (8.2%) died found 8 of 42 previously identified factors to be predictive of death. In multivariate analysis only a respiratory rate of 30/min or more, a diastolic blood pressure of 60 mm Hg or less and a blood urea of > 7 mmol/L remained predictive. A discriminative rule of these factors was 70% sensitive and 84% specific in predicting mortality yielding an overall accuracy of 82%.[22] Karalus et al in a study of 92 patients including elderly patients, found a 16 fold increase in mortality if they had 2 or more of the following clinical criteria present on admission: a respiratory rate of 30/min or more, a diastolic blood pressure of 60 mm Hg or less and either confusion or a serum urea of > 7 mmol/L. There were only 6 deaths and the positive predictive value of death was only 22.7% which limits the value of these findings.[19]

Other studies from ICU populations including patients with pneumonia, suggest that the widely accepted APACHE II severity of illness scoring system, does not accurately predict outcome in individuals, however with appropriate adjustment for the disease, it can reasonably predict group mortality.[123]

Van Eeden et al compared ordinary ward admissions with patients requiring ICU admission in a retrospective study of only 34 patients and suggested that the APACHE II Score was an unreliable predictor, whereas a complicated scoring system including weighting (10 points) for a PaO_2 <7.5 on FiO_2 .4 , respiratory rate of >30 breaths/min, and bronchopneumonia with 2 or more lobes involved, and 5 points for abnormal liver function tests and low albumin, clinical septicaemia (3 of the following: SBP <75 mm Hg, confusion, serum HCO_3 <20 mmol/l, pre-renal uraemia, or a central venous pressure of <3 cm), and pre-existing factors for poor prognosis in pneumonia, was of value. This is an interesting concept , however the data that it is based on is totally inadequate to draw any conclusions.[20] A recent study from Baragwanath hospital (Soweto) evaluating the effect of steroid therapy on cytokine levels in severe pneumonia found no influence on cytokine levels, inflammatory response, or outcome; of interest there was no relation between cytokine levels and severity, however the APACHE II score accurately predicted severity.[65]

In a study from our own ICU, Hammond et al, demonstrated that an APACHE II score of more than 21, septic shock (SBP <80 mm Hg), a white cell count of less than 4,000 cells/ml, and a gram negative micro-organism (either *K. pneumoniae, E. coli, or Ps. aeruginosa*), or *S. aureus* causing the pneumonia, were all individually predictive of a poor outcome, and found no value in applying the previously described scoring system (South African Pulmonology Society Congress 1989). This increased mortality from pneumonia caused by Gram negative organisms, and also *S. aureus* , has been found in a number of studies in hospital and ICU patients.[52,124,125] Support for the importance of recognising "high risk" organisms was also demonstrated in a study designed to detect treatment failure in patients treated as outpatients, where infections with these organisms again predicted a high risk of treatment failure. Additional factors in this study designed particularly to define low risk patients, five factors predisposing to a complicated course were identified by logistic regression models, which included age >65 years (odds ratio 2.7), co-morbid illness (odds ratio 3.2), temperature >38.3°C (4.1), immunosuppression (12.0) and for

high risk organism an odds ratio of 23.3. The risk of a complicated course increased linearly with the number of risk factors from 12% with none to 100% with four.[18].

The clinical criteria used to define when a patient should be hospitalised, are now reasonably well defined, although not well scientifically proven, and the study by Macfarlane et al , the report of the British Thoracic Association study on pneumonia delineating risk factors, with the other papers discussed above provide acceptable guides (see table 4 risk factors).[3,17-19,22,52,124-126]

Table 4: Risk factors for a poor outcome.

AGE >60 - 65 years
CO-MORBID DISEASE
TEMPERATURE >38.3
CONFUSION
TACHYPNOEA >30 breaths/min.
PaO_2 <6.6 kPa
DIASTOLIC BP <60 mm Hg. (SBP<80 or 90)
UREA >7 mmol/l
WCC <4,000 cells/ml
MULTILOBE INVOLVEMENT
MICRO-ORGANISM - *Gm -ve*
- *S. aureus*
HYPO-ALBUMINAEMIA
BACTERAEMIA
IMMUNO-SUPPRESSION

Definitions of terms:

i) Sensitivity = true positive/true positive + false negatives.

ii) Specificity = true negatives/true negatives + false positives.

iii) Positive predictive risk = true positives/true positive + false positives.

iv) Overall accuracy = no of outcomes correctly identified/ no tested.

DETERMINATION OF THE AETIOLOGICAL AGENT.

Precise bacteriologic diagnosis of the infecting organism is difficult, and as a successful outcome depends on early effective antibiotic therapy, empiric therapy covering all the likely pathogens should be initiated immediately in severely ill patients. Pneumonia usually follows a benign course responding to the usual empiric antibiotic therapy, and extensive microbiological investigation to identify the pathogenic micro-organism in the majority of cases is unnecessary. Confirmation of the causative organism is however important, should the patient fail to respond appropriately, or in cases with severe pneumonia where very broad antimicrobial cover has been initiated. Once a causative agent has been identified, antimicrobial therapy should be tailored according to the antibiotic sensitivities of the micro-organism to avoid unnecessary side effects and cost. The accurate identification of the infecting agent is far more problematic than the clinical diagnosis of the disease, and the causative agent still remains undiagnosed in as many as 50% of cases in spite of modern microbiological techniques.[8,9,19,52,122]

The clinical features of pneumonia are of little value in determining aetiology, and can only be used as a broad guide as to the nature of the infecting organism, provided all clinical features are utilised. Previously, much reliance was placed on clinical features such as the age of patient, presenting symptoms, sputum, and chest radiograph in trying to predict the infecting agent. However recent studies negate this view, and one study showed that by using discriminant function analysis of age, duration of illness, bloody sputum, white blood cell count and lobar infiltration on the chest radiograph only 42% of infecting agents were correctly predicted[127], and in addition numerous individual clinical features and even radiographic features are unreliable in differentiating between atypical and typical pneumonia.[31,128] This still

remains controversial however, as there are still other studies being reported that indicate some value in clinical features, particularly the immediate Gram's stain and chest radiograph used in combination.[33,129]

Table 5: Clinical features of typical and atypical pneumonia.

	Typical	Atypical
Onset	Abrupt	Insidious
Respiratory symptoms	++++	+
Constitutional symptoms	+	++++
Extra pulmonary manifestations	+	++++
Fever	High	Low
Sputum	Purulent/Copious	Mucoid/Scanty
Radiograph	Lobar	Interstitial
Response	Good	Failure
Diagnosis	Easy	Difficult

Previously a lot of emphasis has been placed on the clinical features of so called "typical versus atypical pneumonia". Atypical pneumonia is defined as a pneumonia caused by viral, *Mycoplasma*, *Chlamydia* or *Legionella* organisms, which have been thought to have a presentation different to classical bacterial pneumonias. The clinical features distinguishing these two types of pneumonia are shown in table 5, however current opinion is that this classification is of little value as there is significant overlap in the clinical setting. Much of the criticism of this classification has been generated from studies of either *Mycoplasma pneumoniae* or *Legionella pneumophila* pneumonias, and the individual characteristics such as radiological changes and clinical features which were thought to differentiate them from other bacterial

pneumonias. These studies have shown poor correlation with these individual features and the aetiological agent involved.[31,128] Clearly considerable overlap does occur, however the original clinical features first recognised in the 1920's, and subsequently reported by Reimann in 1938, when taken in concert are probably still useful in alerting clinicians to the possibility of the infection being caused by either viruses, *Mycoplasma*, *Chlamydia* and similar organisms.[61,130] *Legionella* pneumonia should probably not be included in this category as the pathology, chest radiograph and clinical features resemble ordinary bacterial pneumonia more closely than the original atypical micro-organisms.[93]

Detection of the aetiological agent relies heavily on microbiological samples and techniques, and these include blood culture (the gold standard); Gram's stain, microscopy and culture of sputum, tracheal aspirate, transtracheal aspirate, lung aspirate and specimens obtained by fibreoptic bronchoscopy using a special sheathed brush, or broncho-alveolar protected catheter lavage; open lung biopsy; or serology.[11-15,131-139] The essential requirements for any microbiological test is that it should be reliable and sensitive, have few false positive or false negative results, be quick and cheap; and the specimens should be easily obtainable with little risk to the patient.

The value of microbiology is entirely dependent on the quality of specimen to be processed, and the following guides need to be adhered to:

1) the specimen should come from a normally sterile area

2) there should be no contamination by endogenous flora (not possible with sputum).

3) sufficient specimen should be obtained particularly in situations where the microbe load is small.

4) the specimen should be promptly and correctly transported

5) accompanied by relevant clinical information

6) promptly examined and cultured

7) preferably before antibiotic administration (NB therapy must not be delayed)

MICROBIOLOGICAL TECHNIQUES

1. Blood culture

This remains a most valuable technique and provides the gold standard for the determination of the causative agent. Unfortunately it is positive in less than 20% of cases although in severe pneumonia requiring ICU admission it can be positive in as many as 35% of cases[33,125]. Macfarlane and most other authors recommend that blood cultures should always be done even though the yield is only 30%.[11,122] Others have suggested that because the yield is so low, particularly in mild pneumonia, that blood cultures should be reserved for patients with severe pneumonia only.[33,116,139] Specificity is high, and a blood culture seldom gives false positive results, unless the technique of obtaining the specimen is poor. It may also be misleading in situations where dual pathogens are present, a situation which is now recognised more frequently. [8,33]. There is also some delay in the culture of organisms being detected, however by utilising the BACTEC system in which culture is detected by gas chromatography which identifies release of C14, 30% of positive results can be obtained within 24 hours, and 90% by 48 hours. (BACTEC Instruments, Johnson Laboratories). Other similar automated systems may also provide similar results however the BACTEC system is more widely used.

2. Sputum

Culture of sputum is generally unreliable as the specimen may be frequently contaminated by endogenous flora from the oropharynx. If the initial sample is of good quality, and the culture is of a predominant organism which was present in reasonable numbers on the Grams' stain its predictive value is high. Well obtained sputum samples where oropharangeal contamination is minimal, can provide a quick guide to the presence of gram negative bacilli and gram positive diplococci or cocci in clusters which are highly predictive of *Klebsiella pneumoniae, S. pneumoniae* and *S. aureus* pneumonia.[129,140-142] Rein in a study specifically designed to identify *S.*

pneumoniae by Gram's stain and microscopy, with >10 lancet shaped Gram positive cocci being considered diagnostic, defined 18 (62%) of 29 specimens containing pneumococci; only 2 false positive specimens were recorded; however there were 11 (38%) false negatives.[142] Gleckman, in a study of 59 bacteraemic patients showed that a physician could correctly determine monotherapy in 94% of cases using clinical criteria and morphology of Gram stained sputa. In 3 of 5 patients with *H. influenzae* pneumonia however, alternative pathogens were suggested.[131] In the majority of patients with pneumonia suitable sputum is unobtainable, or even with careful collection falls far short of the standard generally considered adequate for examination and further processing. Two studies found that samples collected by nurses were better than those collected by house staff in 38 to 42% of cases[33,143]

No uniform criteria for culture of sputum exist however the majority agree that a specimen containing more than 25 WBCs per low power field (LPF) and less than 10 squamous epithelial cells (SECs) /LPF is good ; a specimen with <10 SECs and 10-25 WBCs /LPF is satisfactory and should be cultured; >10 SECs and >10 WBCs poor; >10 SECS <10 WBCs unsatisfactory. Specimens with >10 SECS are heavily contaminated by oropharyngeal secretions and not considered to be representative of lower respiratory secretions as judged by transtracheal aspirate.[12,138,140]. Applying the above criteria for suitability for processing resulted in 75% of samples being discarded in a study from the Mayo Clinic.[12]

Quantitative culture of sputum has proved little better than routine culture in predicting true pathogens, and washing of the specimen is time consuming and has likewise proved of little value.[135,139]

Prior antibiotic therapy will significantly influence the results of sputum examination with both fewer positive findings and an increased number of false positive results.[134] Spencer in a study of community-acquired pneumonia found a 29% incidence of *S. pneumoniae* and *H. influenzae* infection ,and only 8% with no pathogen in patients who had received no antibiotics. Of 52 patients who had

received antibiotics coliforms were found in 29% and no micro-organisms in 69% suggesting a major antibiotic influence.[144]

3. Transtracheal aspirate

A transtracheal aspirate first described in 1959, where a catheter is passed via a needle introduced through the cricothyroid membrane into the trachea, is suggested as an ideal way of obtaining uncontaminated lower airway secretions, which allow culture results to be more easily evaluated.[145] Although it is a technique said to have few side effects, it remains widely recommended but seldom used.[12,135,138] Bartlett in a study of 488 procedures found a positive culture in 369 procedures and negative results in 119 patients. Of these negative procedures 71 were considered to have no infection on subsequent clinical grounds, and 48 parenchymal infection and were considered false negatives. Of these 44 had received prior antibiotic therapy. In 23 cases of bacteraemic pneumonia the companion transtracheal specimen yielded the same pathogen.[134] In this study only one patient developed a side effect which was severe self limiting haemoptysis, however there have been reports of fatal complications.[146,147]

It is however an uncomfortable procedure, even if carefully performed using local analgesic techniques. The instillation of local analgesic solution into the trachea, as well as the introduction of the catheter produces excessive coughing, which in a critically ill patient can lead to significant hypoxaemia. The position of the catheter is also uncontrolled and it may even be coughed into the oropharynx rather than going down into the trachea and bronchus. Aspirated specimens are usually scanty, and frequently have to be collected following a small saline installation, which may further dilute the specimen. Although it has a low incidence of bleeding and surgical emphysema, it is not a technique that should be routinely recommended as the complications are uncontrolled, and can lead to significant hypoxaemia. It has also been superseded by newer fibreoptic bronchoscopic techniques, which are safer and of particular value in patients with non-responding pneumonia.[148]

4. Tracheal aspirate

A tracheal aspirate taken immediately on intubation of the trachea is extremely valuable and should be regarded as an essential requirement following every intubation for severe pneumonia. In a recent report on 18 patients with severe *Klebsiella* pneumonia, 16 out of 17 had numerous Gram negative organisms present on the Gram's stain of the specimen obtained immediately after intubation, and the aetiological diagnosis was confirmed on culture of the tracheal aspirate or blood.[129] A tracheal aspirate may however be contaminated by oropharyngeal secretions before, or immediately after intubation, as many of these patients already have an incompetent larynx immediately preceding intubation because of the associated severity of illness. The presence of the endotracheal tube allows rapid colonisation of the lower airways following intubation, emphasising the need for early collection of specimens. Tracheal aspirates taken even hours later, are only of value in detecting infections by organisms unlikely to be colonising the oropharynx, e.g. *Mycobacterium tuberculosis*, or should be regarded as surveillance cultures which may be of value in detecting new nosocomial colonisation.

5. Lung aspirate

Percutaneous lung aspirate with an ultra fine needle (23 to 25 gauge)(FNAB) clearly provides an uncontaminated specimen. The yield is excellent in spite of the small inoculum and Zavala in a group of immunocompromised patients reported a 100% positive yield with only an 8% incidence of pneumothoraces.[149] The incidence of pneumothorax varies from 3 - 10% in other series, and the risk of empyema is as yet undetermined in community-acquired pneumonia. The risks of this technique would be considered too high for routine use in pneumonia, particularly in severe pneumonia, however it is justified in those cases who fail to respond, or who show progressive deterioration, or who are likely to have an unusual organism. This technique has also been used successfully in epidemiological studies.[8] In a study of 18 cases of pneumonia who failed to respond FNAB under ultrasonic guidance

yielded positive results in 72.2% on culture and 50% by direct microscopy.[150] A recent study tested the efficacy of pneumococcal and *Haemophilus influenzae* type B latex agglutination testing as well as pneumococcal antigen detection in the urine identified a causative organism in 88% of cases, the needle aspirate antigen test increasing the yield from 50 to 78%.[151]

6. Fibreoptic bronchoscopy.

Fibreoptic bronchoscopy has become widely used for the diagnosis of many pulmonary diseases.[152] It is an extremely valuable tool for diagnosing pulmonary tuberculosis, and other opportunistic infections particularly where the presence of the micro-organisms in the specimen invariably mean infection.[153,154]. Its routine use in the diagnosis of community-acquired pneumonia is however limited, both because of cost, and because the suction channel of the flexible bronchoscope becomes contaminated with endogenous organisms from the nose and oropharynx, resulting in difficulty with interpretation of the results.[155] Various techniques have been developed to limit the effects of oropharyngeal contamination of specimens, initially by quantitative culture of specimens obtained by FOB through the suction channel, and subsequently by using protected specimen brushes (PSB), or protected lavage with quantitative culture.[14,19,156,157] Bronchoalveolar lavage using 100 to 240 ml of saline and a quantitative culture where 10^4 cfu/ml which represents 10^5 or 10^6 organisms/ml is considered diagnostic, has been suggested as a better way of obtaining a more representative sample than either PSB or small sample protected lavage techniques;. The same oropharyngeal contamination may occur as in ordinary bronchoscopic samples however.[13,14,132,133] BAL using the presence of intracellular organisms to define the presence of infection may however prove a more valuable means of differentiating pneumonia from contamination, and an advantage is that it gives a more rapid result.[158-160] BAL in the presence of hypoxaemia is potentially hazardous as it invariably results in hypoxaemia, and it has also been shown to produce sepsis-like systemic effects in patients with pneumonia.[161]

The use of a special sheathed brush (PSB)[130] and also a protected wedge catheter lavage[14,162] with quantitative culture, which avoids the problems of oropharyngeal contamination, provides valuable microbiological specimens, and may be regarded as a "gold standard " in the setting of ventilator-associated pneumonia.[157] Their use in community-acquired pneumonia has been inadequately investigated and in one prospective study of severe community-acquired pneumonia, in which an attempt was made to improve and speed up the diagnosis by using a comprehensive protocol, an etiologic diagnosis was obtained in 81% of patients, in 53% within 72 hours. Bronchoscopy was performed in 29 of these patients, all of whom were receiving antibiotics, and using BAL and PSB specimens, cultures were positive in 48%. compared with 42% with sputum, suggesting that it played a useful role.[163] In another recent study where 40 patients with moderately severe CAP underwent bronchoscopy prior to antibiotic therapy, and comparing BAL (180 ml) with PSB specimens, a positive diagnosis defined as 10^3 cfu/ml was made in over 70% of patients with both techniques performing equally well.[164] In a recent study of patients with community-acquired pneumonia, limited to those patients who failed to respond to treatment, we made a positive diagnosis in only 3 of 35 patients.[1] Ortqvist in a study of FOB in 24 patients with CAP showed that in the setting of early antibiotic failure (<72 hours) PSB would seem to be of limited value as it gave a positive diagnosis in only 1 patient (16.6%), although a true negative may be considered useful. The value of PSB in the late failure group was also disappointingly low, with only 1 positive diagnoses in 11 procedures. The yield in patients not receiving antibiotics with 4 of 6 positive was much more rewarding.[156]

In cases of truly non-responding pneumonia (i.e. no response after 5 days of therapy) where the organism is commonly an unusual pathogen, or another pathology is present FOB is of undoubted value.[156,165]

The failure of this technique to diagnose ordinary bacteria may be due to antibiotic therapy as is seen in ventilator-associated pneumonia where the use of these techniques following antibiotic therapy has been shown to be of little value.[162].

Ortqvist showed that the yield from PSB specimens in patients with CAP admitted to ICU the was reduced from 80 to 12% following the administration of antibiotics [156] The side effects of FOB are minimal unless transbronchial biopsy is used, when the incidence of pneumothorax and haemorrhage is around 5%.[166] The cost of this procedure, particularly if a PSB is used (more than US $150) , needs to be considered and weighed up against benefits.

Protected specimen brush or BAL specimens are essential if direct fluorescent antibody techniques for the detection of *L pneumophila.* are to be used. This investigation may have a sensitivity of 70% and specificity of as high as 99%.[167,168] Fibreoptic bronchoscopy is therefore a useful tool in patients with community-acquired pneumonia in whom no diagnosis has been made, and where *L. pneumophila* or opportunistic infection is suspected. It is also valuable where additional pathology needs to be excluded, but it should not be regarded as a routine investigation.

7. Open lung biopsy

This technique should not be considered routinely in any case of community-acquired pneumonia except those who have failed to respond, and in whom other tests have failed.[14,169] It may also be considered where the diagnosis of pneumonia is in question, and where the progression of the illness will not allow time for a second investigation. It does however produce the largest specimen and the area of lung for biopsy can be selected. An area of lung with clear involvement and an adjacent piece of relatively normal lung should be selected, as grossly abnormal lung may show only non-specific end stage disease.[43]

8. Serological techniques

Serological bloods tests are of most value in the atypical pneumonias including *Mycoplasma*, *Legionella* and *Chlamydia*, where other microbiological techniques have a low yield.[14] In *Mycoplasma pneumoniae* pneumonia the rapid specific IgM test is most useful and is positive in 86% of patients on admission. Cold agglutinins

occur in 57% and a fourfold rise in the complement fixation titre occurs in 26% of patients.[31] In *Legionella pneumophila* pneumonia a fourfold rise in antibody titre is also considered diagnostic, however it may be necessary to repeat the test six weeks after the initial sample to confidently exclude an infection.[5], The use of immediate immunofluorescent staining and microscopy of bronchoscopically obtained PSB specimens is of value in obtaining an early diagnosis.[5,14]

Antigen detection is recognised as a possible way in which a rapid diagnosis may be made in community-acquired pneumonia, and may be of particular value in patients receiving antibiotics.[15] Polysaccharide antigens to the cell walls of micro-organisms are specific and may be identified as being potential markers of a recent infection by the organism, and the identification of the infecting organisms is therefore possible by identifying these antigens in various body fluids by either counterimmunoelectrophoresis (CIE), coagglutination, or enzyme linked immunosorbent assays (ELISA).[16] Guzzetta et al investigated 101 patients with community-acquired pneumonia in an attempt to detect *S. pneumoniae, H. influenzae, K. pneumoniae* or *Ps. aeruginosa* antigens in sputum, using both CIE and coagglutination techniques to diagnose the causative pathogen. Coagglutination detected the appropriate bacterial pathogen in 16 of 17 patients (94%) with a definite aetiological diagnosis whereas CIE identified only 11 (64%). Only one pathogen was identified in 19 control patients indicating a high specificity for both tests.[170] Detection of pneumococcal antigens in blood, urine, pleural fluid, and sputum, has been used and in some studies, have increased the yield of identified pneumococcal disease. In a recent study using detailed microbiological investigations including CIE for antigen detection with pneumococcal omniserum and 19 mono-specific antiserum, Macfarlane found *S. pneumoniae* in 76% of patients with community-acquired pneumonia.[51] These pneumococcal antigens are distributed widely in many body fluids including sputum, pleural fluid, serum and urine during acute pneumococcal infections, and usually the more antigenic the sicker the patient, but they may persist for a prolonged period of months. Not all patients are antigenemic and the exact

specificity and sensitivity are not known, but are not absolute. Oropharyngeal colonisation by *S. pneumoniae* will influence sputum and positive antigenemia has been found in 20% of healthy volunteers. Detection of antibodies to pneumolysin which is more specific of infection but the results are not immediate and are therefore only of value in epidemiological studies.[16] These techniques are not freely available and have a significant false positive rate however they show promise for the rapid diagnosis of pneumococcal pneumonia and further studies on the sensitivities and specificity's are necessary.

PRACTICAL APPROACH TO DIAGNOSIS.

In practice the conventional clinical method of determining the likely causative agent in pneumonia requires a knowledge of the incidence of pathogens in different clinical settings, and interpretation of the Gram's stain of bronchial secretions. This is correlated with clinical features and a best "guess" empiric therapy to cover likely pathogens is selected. Both accurate cultures, and serological investigations take days or weeks. A number of studies have pointed out the unreliability in predicting causative agents by using clinical features such as history, radiological changes, nature of sputum, temperature and other signs in isolation.[127,128] In a recent study of critically ill patients in the ICU, and a number of studies in less severe disease, moderately accurate prediction of the causative agent has been possible using all available clinical features, including a gram stain of well collected bronchial secretions, and severity of illness estimation.[1,11,33,129,142]

In spite of extensive investigations the causative agent still remains undiagnosed in 30% or more patients with pneumonia, and the role of prior antibiotic administration, and as yet undetected pathogens may play an important role.

The practicality of management and expense of medical care, particularly in economically depressed regions, has determined that we should develop a cost effective approach to treatment. The clinical and bacteriological diagnosis of

pneumonia and its severity needs to be accurately defined to provide specific therapy, or appropriate cost effective empirical antibiotic therapy. To extend this philosophy, it is essential that we develop a protocol for immediate empirical antibiotic therapy, and the clinical and biochemical investigation that will provide minimal, essential information, without adding any risk to the patient.

A recent paper by Levy et al reporting the practical approach to diagnosis in a cohort of patients with community-acquired pneumonia, has added significantly to our understanding of the value of different diagnostic procedures in modern practice. The results of the different tests are shown in the following table.[33]

Table 6: Diagnostic procedures for pneumonia.(adapted from Levy et al)[33].

	+ve	-ve	Total	Poor quality**
Sputum*	44	12	90	34**
PSB	1	6	7	0
Protected catheter	12	6	20	2***
Blood culture	14	102	110	-
Pleural asp.	4	29	33	-

** Gram stain and quantitative culture*

*** Poor quality = >10 squames or <20 leukocytes/LPF; ***contaminated specimen.*

Critical to the decision about what investigations and treatment are necessary, is the determination of the severity of the pneumonia; this will impact both on the selection of empirical antibiotics as well as the necessary investigations. The severity of disease will reflect the spectrum of pathogenic organisms, with an increased number of Gram negative and *S. aureus* infections in more severe disease. In fulminant

disease where there will be no time to institute second line antibiotic therapy should the patient fail to respond all potential pathogens need to be covered by the initial therapy.

The Gram's stain and culture of sputum has long been regarded as an essential initial investigation, however its positive contribution in mild pneumonia is of questionable value. Numerous studies evaluating Gram's stain and culture of sputum have shown that 50% or more specimens are so contaminated by oropharyngeal secretions that they are of no value.[12,141] Using specific criteria for evaluation of specimens such as the number of squamous cells and pus cells on microscopic examination, they suggest that if more than 10 SECs are present, the specimen should not be processed further. Even in those specimens that warrant further evaluation, particularly in mild pneumonia, the yield lacks specificity, and is so low that the overall influence on antibiotic selection is minimal. In the study by Levy where 35% of samples were unsuitable, concordance between the Gram's stain and quantitative culture was found in 86% of cases.[33] This has led to the somewhat heretical recommendation that sputum should not be a routine investigation in patients with mild pneumonia.

The value of sputum or tracheal aspiration may also depend on the type of pathogen identified. In the case of *S. aureus* and *K. pneumoniae* the results are likely to be more sensitive and specific than *S. pneumoniae or H. influenzae*.

Blood culture has also come under similar scrutiny in the group with mild pneumonia, because of the low positive yield of between 12 to 14%[33,51], and the fact that the positive blood culture which is usually, *S. pneumoniae*, seldom leads to a change in antibiotics. This has led to the suggestion that blood cultures should also be reserved for patients with severe disease only, where the culture may be positive in as many as 35%, as a cost saving exercise even though the result is 100% specific. In patients with severe disease the yield with both tests is much increased, and a positive test is of great value in determining therapy, both antibiotic and supportive measures. It is however important that in this setting the specificity of a positive blood culture may be lower than expected. Fagon has recently suggested that 58% of positive blood

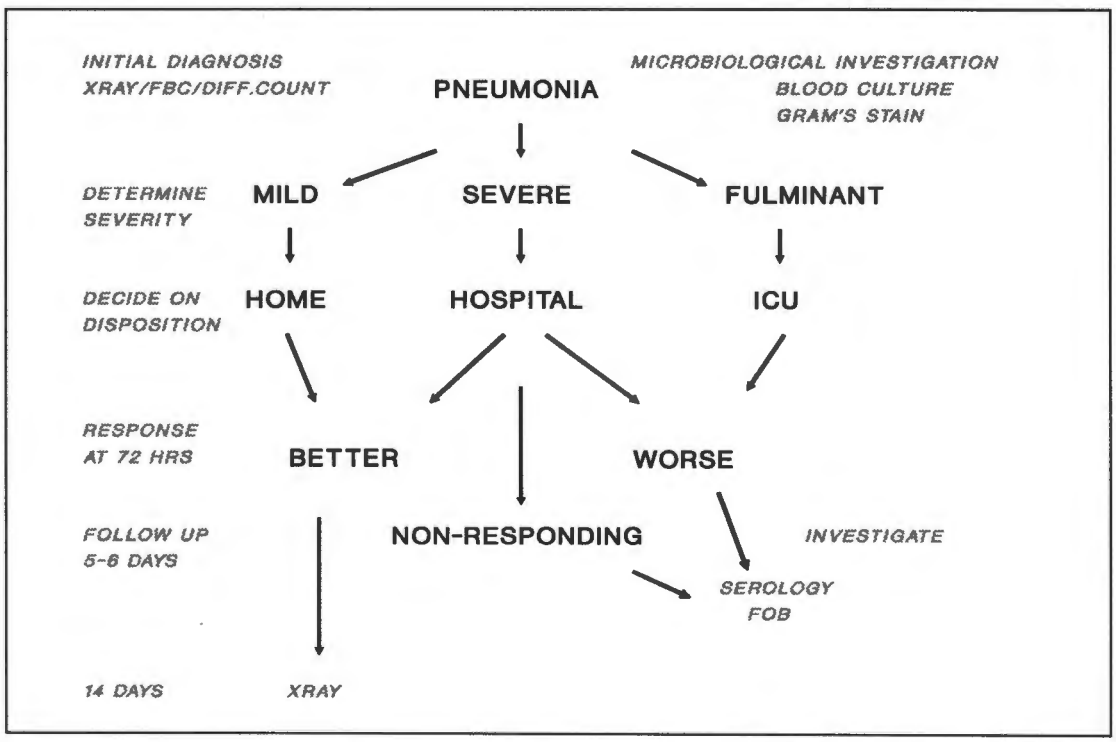
cultures, particularly in patients with nosocomial pneumonia, may arise from non-pulmonary sources and not be representative of the pulmonary infection.[171]

In any patient following intubation an immediate tracheal aspirate sample, before any contamination from the oropharynx has occurred, is of great value for immediate Gram's stain and culture. Hammond, in a study of 18 cases of *K pneumoniae* pneumonia requiring intubation, found numerous Gram negative bacilli on microscopy of tracheal aspirates taken on intubation in 16 patients, and a positive correlation between tracheal aspirate and blood culture in all 6 bacteraemic patients.[129]

Pleural fluid which is often considered to be useful hasn't been adequately evaluated, however in the study by Levy, pleural fluid was found to be positive on culture in only 4 of 33 pleural specimens.

A practical algorithm for a diagnostic approach to pneumonia is given in the following flow diagram.(see Figure 2)

Figure 2: Diagnostic approach in community-acquired pneumonia.



The investigation and therapeutic path taken initially is determined by the severity of the pneumonia, and subsequent decisions by the response to therapy, decided after 48 hours and subsequently at 5 days.

Mild pneumonia is considered to be disease without any of features that would suggest a poor prognosis including:- age >60 - 65 years, co-morbid disease, Temperature > 38.3, confusion , tachypnoea >30 breaths/min. PaO_2 <6.6 kPa, Systolic <90 mm Hg., urea >7 mmol/l, WCC <4,000 cells/ml, multilobe involvement, Gm -ve or *S. aureus,* hypo-albuminaemia, bacteraemia, and immunosuppression.

Severe pneumonia would include patients with any of the above features which suggest a poor prognosis as well as one of the following: confusion and/or inability to cough, inability to oxygenate on mask oxygen and inability to maintain alveolar ventilation, or shock (SBP <90 mm Hg) i.e. those requiring immediate intubation. . Fulminant disease would be severe cases where there is an inability to oxygenate on FiO2 <0.5 or with unresponsive shock.

The patients who fail to respond after 5 days particularly those patients with less severe disease form a distinctive subgroup, the "non-responding" pneumonias and are considered in chapter seven.

In patients who show progressive deterioration or no improvement within 48 to 72 hours, more invasive investigation is warranted. Although fibreoptic bronchoscopy has a low positive yield, the detection of *Mycobacterium tuberculosis*, fungi or *Legionella spp.* is of critical importance for antibiotic management, and a true negative, the most likely result, will avoid unnecessary expensive antibiotic changes, and focus therapy on supportive measures such as fluid and ventilatory therapy, and host factors.

CHAPTER 6

TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Introduction

Pneumonia may vary from a very mild illness to a fulminating life threatening disease The treatment should therefore be tailored to the severity of the disease; this may vary from home therapy in mild cases, to hospitalisation in general wards or an ICU in more severe or fulminating life threatening disease. Determination of the severity of illness is therefore once again of paramount importance in determining if and where the patient should be admitted, and what therapy should be given. The widely accepted criteria from the BTS study group used to determine the severity of pneumonia are useful in determining therapy, and when used in conjunction with other studies of severity including a recent study that showed which factors were likely to be associated with failure of home therapy, can successfully predict which patients may be treated as outpatients.[17,18,122](see table 4, chapter 5)

Criteria for ICU admission still need further validation, however if the accepted features of severe pneumonia including any of the following : significant confusion, septic shock, unresponsive hypoxaemia, a low WCC <4,000 cells/ml, inability to clear secretions, or an extending pneumonia despite treatment are present, ICU admission is mandatory. Additional factors such as Gram negative or *S. aureus* infection and co-morbid disease must also need to be considered.

Thus using these criteria we are thus able to divide pneumonia into those who can be treated at home (mild disease), those requiring hospitalisation (moderate disease), and those requiring ICU admission (severe/fulminant disease).

ANTIBIOTIC THERAPY

1. Selection of Antibiotic.

a) Empiric antibiotic therapy.

Initial selection of antibiotic therapy will depend on the severity of the pneumonia. In **mild disease** oral agents with a spectrum of activity that includes *S. pneumoniae* are indicated. In certain instances in young people from communal living environment e.g. army barracks, during known epidemics of *Mycoplasma* or in similar situations, an agent that includes activity against both *S. pneumoniae* and *M. pneumoniae* may be more appropriate, however these antibiotics are invariably more expensive and could be reserved for cases that fail to respond within 48 hours.[118] Optimal oral agents would include amoxicillin, erythromycin or the newer macrolide antibiotics such as clarithromycin. In the latter the cost is considerable, and no additional benefit in efficacy has been shown although side effects may be reduced.[172] A practical approach in the hospital outpatient setting is the combination of initial parenteral administration, followed by oral antibiotics; a combination of penicillin G intramuscularly, followed by oral amoxicillin has proved highly effective in our emergency unit. (Dr A. Aboo, personal communication). Many of these patients would remain overnight because of inadequate transport or home settings and as compliance may be suspect intramuscular agents may be preferable.

The concern of emerging penicillin resistance in *S. pneumoniae* may influence initial empirical antibiotic selection, however this problem appears exceedingly rare in adult pneumonia in Cape Town. In other areas such as Johannesburg, Israel, Spain and southern Europe, this may be more of a problem.[98,173] The incidence of pneumococcal resistance in patients with pneumonia however requires further accurate epidemiological evaluation before major antibiotic policy changes are recommended.

The empirical antibiotic selection for **severe** pneumonia should again include agents effective against *S. pneumoniae* but parenteral administration is the route of choice. Intravenous penicillin 1-2 million units six hourly is likely to be effective against the vast majority of infections, however if the Gram's stain of the sputum suggests *S. aureus*, intravenous cloxacillin 2 grams six hourly should be used instead, and if a Gram negative micro-organism morphologically resembling enterobacteriaciae is seen, an aminoglycoside (initial starting dose twice the standard dose calculated by weight) should be added.[44,174,175]

In a **severe** infection when time will not allow for additional antibiotics to be added following initial failure, intravenous penicillin, cloxacillin, and an aminoglycoside, should all be commenced immediately. In view of our low incidence of *Legionella* in Cape Town and the high cost, intravenous erythromycin is not recommended unless the clinical picture is suggestive of *Legionella* infection.

A number of special circumstances may dictate a somewhat different approach. In patients with COPD, *H. influenzae* is a more common pathogen and although high dose intravenous penicillin appears to be effective, amoxicillin either oral or intravenous is a better choice.[9,175] Beta-lactamase producing *Haemophilus spp.* is relatively uncommon in our region and again because of cost, a cephalosporin would only be recommended in cases where there is failure to respond. In known epidemics of *M. pneumoniae* or in young army recruits or similar situations oral erythromycin is more appropriate as empirical therapy.[118] In the presence of renal dysfunction a third generation cephalosporin should be substituted for the aminoglycoside.[29,30]

b) Specific Antibiotic therapy.

Once the causative micro-organism has been identified the antibiotic therapy should be tailored appropriately. In cases of *K. pneumoniae* infection, a combination of an aminoglycoside and third generation cephalosporin may be more effective than monotherapy, and has been recommended.[129,176] *Ps aeruginosa* infections similarly

should also be treated with a combination of an aminoglycoside and anti-pseudomonal penicillin or ceftazidime.[177,178]

The role of dual or multiple pathogens causing pneumonia has been recognised more frequently with the use of more discriminatory invasive and serological microbiological tests. With only 50% or fewer cases of pneumonia having definite pathogens identified it is not surprising, given the difficulty with diagnosis, that multiple pathogens have not previously been recognised. Once an agent has been identified, no further search for additional pathogens is usually attempted, and both the identification of further pathogens, and the determination of significance is extremely difficult. The significance of infection with multiple pathogens has only recently been fully appreciated.[9,116] It may therefore be prudent to broaden antibiotic cover, and intensify the search for an additional pathogenic organism in a situation with a "known" pathogen where there is failure to respond to appropriate antibiotic therapy.

In our region as with Singapore, Hong Kong, and even France, a high incidence of *Mycobacterium tuberculosis* is found and this pathogen should always be considered.[9,33,179,180]

c) Failure to respond within 48 hours.

In any patient who has failed to respond within 48 hours, additional antibiotic or supportive therapy should be considered. If no pathogen has been identified, the initial penicillin therapy should be changed to an agent that includes the atypical pneumonias in its spectrum of activity. In cases of severe pneumonia, an antimicrobial agent that covers Gram negative micro-organism should be added in addition to cover for atypical micro-organism. Further microbiological investigations including serology are mandatory in these cases.

The following algorithm (figure 3) is a useful guide for antibiotic therapy in community-acquired pneumonia.

Figure 3: Antibiotic Therapy.

SEVERITY OF PNEUMONIA	**MILD**	**MODERATE/ SEVERE**	**FULMINANT**
INITIAL PRESENTATION	*Penicillin G or Amoxicillin or Erythromycin*	*Penicillin G and Aminoglycoside or Cephalosporin.*	*Penicillin G, Aminoglycoside and Cloxacillin*
Investigation	*Gram's stain sputum*	*Blood culture, Gram's stain and sputum culture*	*Ditto*
48-96 HOURS NO RESPONSE	*Change to Erythromycin*	*Exchange Erythromycin for Penicillin*	*Erythromycin in place of Penicillin.*
Investigation	*Serology*	*FOB* with PSB**Serology*	*FOB* with PSB**Serology*
		Serum antibiotic levels	*Serum antibiotic levels*
		Are antibiotics appropriate?	*Are antibiotics appropriate?*
Worsening	*Consider as ---> severe*	*Consider as fulminant ----------> Cloxacillin, Quinolone or 3rd Generation Cephalosporin*	*Cover all potential pathogens*
Investigation			*FOB with PSB and Lavage*
			Serology

**FOB = fibreoptic bronchoscopy.*

***PSB = protected specimen brush for Gram's staining and immunoflurescent staining for Legionella spp.*

SUPPORTIVE TREATMENT

In cases of mild pneumonia patients may be treated at home as outpatients . It is however important to ensure compliance with antibiotic medication, and there should be no factors present which may adversely influence absorption of the drugs. Long acting parenteral penicillin or cephalosporins may overcome these problems, however close supervision is necessary. Supervised care is essential, and time should be taken to instruct the supervisor in detail as to when the patient should seek further medical care. Deterioration of the patients condition will present with increasing dyspnoea, confusion, or failure of the febrile illness to defervess and any of these features must be considered serious, and an absolute indication for the patient to return for further medical evaluation.

Similarly, in severe disease close monitoring for features indicative of deterioration is essential. The respiratory rate, pulse rate and blood pressure, level of consciousness, and fluid balance should all be monitored regularly. Oxygen therapy is frequently necessary and in cases of deteriorating clinical features, pulse oximetry or regular blood gas analysis may be indicated. In this situation frequent radiological monitoring is necessary to detect spread of disease with increasing consolidation which is indicative of a need for increasing respiratory support. Careful fluid balance will be essential to avoid aggravating renal dysfunction with too little fluid, or worsening hypoxaemia with excessive fluid administration.

Features such as unresponsive hypoxaemia, confusion, renal dysfunction, a high risk micro-organism, failure to respond, and an inability to clear secretions are all indicators that ICU admission and intubation may be necessary. Septic shock (Systolic Blood Pressure < 90 mm Hg despite adequate fluid resuscitation) even in the presence of acceptable blood gases requires urgent intubation and cardio-respiratory support.

1. Ventilatory Support

The extent of the ventilatory support required will depend on the severity of the pneumonia, and invariably if hospitalisation is needed, some form of oxygen therapy is usually indicated. This may vary from face mask oxygen only, in severe cases, to constant positive pressure ventilation in patients with refractory hypoxaemia. The goals of ventilatory support are to maintain a PaO of > 8 kPa, and a $PaCO_2$ of < 5.3 kPa.

Ventilatory support may be :

1. Oxygen by face mask.

This is usually indicated where the patient is fully conscious, capable of clearing secretions, maintaining alveolar ventilation, and where adequate oxygenation is achieved with an inspired oxygen (FiO_2) of 40%.

2. Continuos Positive Airway Pressure (CPAP.)

If adequate oxygenation cannot be maintained by face mask oxygen, CPAP by face mask provides more efficient and controlled oxygenation. It is however essential that upper airway reflexes are intact and that the patient can protect his own airway, is co-operative, and clear secretions.[24,181] Patients treated by face mask CPAP require particularly close monitoring and the use of pulse oximetry is mandatory as dangerous hypoxaemia may occur very rapidly. These patients should never be off oxygen, and if eating or drinking, should be on oxygen by nasal prongs.

3. Mechanical Ventilation.

Indications for constant positive pressure ventilation (CPPV) in severe pneumonia include unresponsive hypoxaemia, confusion, inability to clear secretions, septic shock, exhaustion, and inadequate alveolar ventilation. The nasotracheal route of intubation is preferred in many hands as it is recognised to have a number of advantages in this situation including:

1. Ease of intubation without sedation or muscle relaxants using a blind nasal technique and topical analgesia.

2. More secure fixation than the oral route.
3. Better patient comfort than oral tubes.
4. Size of tube limited by size of nostril.

Disadvantages include an increased risk of sinusitis, and potential compression of tube by turbinates that may make suctioning difficult. An early tracheostomy is indicated when copious thick secretions make suctioning difficult, or when a prolonged ICU course is predicted.

IPPV with positive end expiratory pressure (PEEP) is invariably indicated, except when active air trapping with airflow obstruction is present.[182,183] Occasionally with unilateral disease PEEP needs to be carefully tailored, or independent lung ventilation with the level of PEEP determined for each lung may be necessary. The ventilator should be set to approximate the ventilatory pattern of the patient prior to intubation. This will avoid the necessity for heavy sedation and paralysis in most cases, but will mean a respiratory rate in the region of 18 to 25 breaths per minute, with a reasonably fast inspiratory flow rate of around 50 l/min. The tidal volume should be adjusted to provide 10-12 ml/Kg body weight, but should the inspiratory pressure be too high, the volume may be reduced to maintain the pressure below 50 cm H_20. The PEEP should be adjusted to allow an inspired oxygen (FiO_2) of 50% or less. It is however essential that the SaO_2 is > 90 % at all times, and it may therefore be necessary to maintain a higher FiO_2 for a period of time.[184] If adequate oxygenation is not achieved, sedation with muscle relaxation may be necessary, and an even higher respiratory rate, with ventilation using an inverse inspiratory to expiratory ratio (inverse ratio ventilation) may improve the situation.[185]

Regular suctioning and position changes are necessary to prevent postural atelectasis, and where this may cause desaturation a special sheathed suction catheter (Steri Cath, Portex Ltd., U.K.) which reduces suction hypoxaemia should be used.

2. Circulatory Support.

a) Fluid therapy.

In cases of severe pneumonia, pre-existing dehydration may be present, and in addition distributive circulatory changes secondary to sepsis will further aggravate this situation, creating an increased need for intravenous fluid therapy. The adequacy of fluid therapy can be assessed by ensuring an adequate urine output of .5 cc/ kg /hour, however it should be remembered that excessive fluids will aggravate lung oedema and gas exchange.

b) Inotrope therapy.

A small number of patients with fulminant pneumonia will develop septic shock and require inotropic support. Dopamine in a "renal" dose (<10 micrograms/min) is usually commenced when urine flow falls, and should the systolic blood pressure fall below 90 mm Hg, it is necessary to commence additional inotropic support. Either adrenaline (4 ampoules/200 ml saline) or Dobutamine (10 - 30 micrograms/min) an expensive alternative, may be used in a dose sufficient to achieve an adequate systolic blood pressure. Excessive fluid therapy and inotropes used in an attempt to achieve "optimum goals" (O_2 delivery >600 ml/min -m^2 or O_2 consumption >170 ml/min-m^2) suggested by Shoemaker[186], have yet to be shown to improve outcome in this setting, and may even cause harm. A pulmonary artery catheter is however indicated for ventilatory and fluid management in patients requiring PEEP of 15 cm H_2O or more, or where urine output is compromised.

PREVENTION OF SECONDARY INFECTION

These patients with pneumonia are at particular risk of developing secondary infection because of the additional immunosuppressive effects of the illness, as well as the effects of the antibiotic therapy. All the usual methods for reducing exogenous infection should be implemented, but in addition methods of selective gastro-intestinal decontamination should be considered. A subgroup analysis of patients with

community-acquired pneumonia determined "a priori" were shown to have a significantly reduced incidence of secondary infection, and although no deaths occurred in this group the numbers were too small to show a significant reduction in mortality.(Potgieter,P.D, Hammond,J.M.J Abstract 18th ICC, Stockholm, 1993) This is very suggestive that SDD may be of benefit in these patients, and if not all the components are used, at least oral topical anti fungal therapy should be used.

IMMUNOTHERAPY.

Immunotherapy has long been considered for the treatment of severe sepsis including pneumonia, and early attempts at using corticosteroids have failed to show any improved outcome.[187,188] Our understanding of the cascade from sepsis to multiple organ dysfunction and death, has however greatly increased over the past few years. With this increased knowledge a number of exciting new therapeutic options, particularly monoclonal antibodies against the various mediators of sepsis, or their receptors have been developed.

There have been a number of clinical studies evaluating the use of different forms of immunoglobulin preparations in the prevention of the spiral from the systemic inflammatory response syndrome to multiple organ failure. One of the more recent advances was the development of mouse and then human monoclonal antibodies directed at Gram negative sepsis and in particular endotoxins.

Initial use of pooled human anti-endotoxin immunoglobulin or J-5 antibodies had to be abandoned because of the fear of associated transmission of blood-borne diseases [189]. This line of intervention has been followed by the development of the E-5 murine monoclonal anti-endotoxin antibody and the human monoclonal HA-1A antibody. Such forms of therapy are directed at the lipid A component of the wall of Gram negative bacteria which limits their spectrum of efficacy. Reports of the administration of the E-5 monoclonal antibody to 486 patients with suspected Gram

negative sepsis in a double blind randomised study have been published [190]. The 30 day survival in those who received E-5 was 60% compared with a non-significantly different 59% in those who received placebo. In 316 patients, the presence of Gram negative sepsis was confirmed, 54% (179 patients) of this subgroup with the presence Gram negative bacteraemia; in these patients the 30 day survival in those who received E-5 was 55% compared with 60% in those who received placebo. The 137 non-shocked patients showed an apparently significant benefit from the administration of E-5 and in those who received the active drug the 30 day survival was 70% compared with 57% in those who received placebo.

The 28-day survival in the widely publicised HA-1A multi-centre study conducted by Ziegler [191], in which this immunoglobulin or placebo were administered to patients, has earned this drug acceptance as first line therapy for presumed Gram negative sepsis. The mortality of the initial 543 patients enrolled in this study was not different between the two groups (39% in those who received HA-1A vs. 43% in the placebo group), 200 were confirmed to have Gram negative bacteraemia, and 70% of those who received HA-1A survived to day 21 compared with a statistically significant fewer 51% of those who received placebo. However, the 28 day survival was not significantly different between the groups, being 60% in those who received placebo compared with 55% in those who received the drug; the lack of efficacy in the patients with Gram negative infection, but without bacteraemia is difficult to explain, as endotoxaemia may often occur without bacteraemia. This observation also contrasts with the experience with the administration of E-5 where the outcome was improved in both bacteraemic and non-bacteraemic patients, but while HA-1A was apparently effective in both shocked and non-shocked patients, E-5 was ineffective in those who were shocked.

Since the publication of this study, there have been numerous criticisms of the methodology and the conclusions reached. The patients in the placebo group were sicker, older and more received inadequate antibiotic therapy than those in the active

group. While individually such factors may not have been significant, the combination surely did not favour as good an outcome and probably means that the groups were not entirely comparable. Recent evaluation of the studies has shown that the empirical administration of HA-1A to patients with Gram positive sepsis may actually worsen their outcome, and this prompted further trials to be initiated by the American Federal Drug Administration (FDA), to establish the role of this substance. The recently completed multi-centre CHESS study which evaluated the efficacy of HA-1A has confirmed these earlier suspicions and the drug has been withdrawn.[192]

Tumour necrosis factor and related cytokines have been identified as playing a central role in all forms of the systemic inflammatory response (SIRS) which leads to the development of multiple organ failure, and agents which are able to block the cascade at this point may prove still more useful, as they are less specific [193,194]. Since the anti-endotoxin studies, antibodies directed at anti-tumour necrosis factor, and interleukin receptor antagonists, both of which have been developed. These new drugs have an increased spectrum of activity and theoretically block both Gram negative, Gram positive, fungal, and viral mediators of sepsis. A number of large multi-centre studies have been initiated in patients who have severe sepsis, and while some results are equivocal although a recent European multi-centre study (Intersept Study Group; Lancet 1996. in print) shows a 17% reduction of mortality.

Other modalities, still largely in the experimental phase at present, include inhibitors of thromboxane A_2, leukotrienes, and prostaglandins [14]. Part of the difficulty in developing this type of therapy, is the extreme complexity of the inflammatory cascade which is subject to numerous positive and negative regulatory feedback controls, and numerous alternative pathways may trigger the final insult. Not only are there receptors for many of the cytokines, but there are also naturally occurring antibodies to these receptors, and until greater understanding has been achieved in this field, more harm than good may be done by disturbing the balance between these factors.

The role of these agents in specific infections such as pneumonia will have to be evaluated independently.

VACCINATION.

Vaccination against bacterial pneumonia was first described by Sir Almroth E. Wright in a seminal paper published in the Lancet on January 3, 1914.[195] In the introductory paragraph in reference to the treatment of pneumococcal pneumonia he states: *"-our task is to supply to the organism substances which are specifically bacteriotrophic- that is substances which make chemical attack specifically on the microbes of disease. We saw that in connexion with each saveral disease two paths of research open out before us. On the one hand there is the path of pharmacotherapy. Following this we may come to an effective and non-poisonous specifically bacteriotrophic drug. There is, on the other hand, the path of immuno-therapy. Following this, we may come to a effective vaccine- i.e. to a vaccine which will, when administered in a proper dose, stimulate the chemical machinery of the patient to elaborate the required specifically bacteriotrophic substances."* In this paper he firstly defines that in newly recruited South African gold miners, *S. pneumoniae* was the cause of pneumoniae in 25% of cases, using blood culture, and in 70% of cases, using lung puncture. He then described the preparation, standardisation, and final testing of this vaccine. Results of this vaccine showed a reduction of episodes of pneumonia. These studies were started in 1912 and he used whole bacteria cultured on newly devised culture media which were then killed and purified. These vaccines were developed before the knowledge of the different pneumococcal types. In 1930 the immunogenicity of pneumococcal capsular polysaccharides was discovered, and since then monovalent and polyvalent vaccines have been successively developed from capsular polysaccharides to provide the widest possible cover for most common pneumococcal infections. There are 82 capsular types of *Pneumococci* known, however 84% of bacteraemic infections and 77% of deaths associated with bacteraemia, are caused by 12 serotypes (types

1,2,3,4,5,6,7,8,12,14,18,19) in adults, and, in children, eight serotypes (1,3,6,7,14,18,19,23) account for 70% of infections.[196]

The first, a 6 valent vaccine was investigated in gold miners. In this selected group who are at increased risk because of "recruit disease" (with an incidence of 200 per 1000 per annum) the vaccine was found to be 78.5% effective in preventing radiological proved pneumococcal pneumonia (76% by 6-valent and later 92% by 12-valent) and 82.3% effective in preventing bacteraemia caused by the types in the vaccine. An increase in antibody levels of between 6 and 25-fold occurred, and minimal side effects were shown.[197] Subsequent studies with 8-valent vaccines in sickle cell disease and asplenic patients have also shown a reduction of pneumococcal infections.[198]

The vaccine is prepared from purified capsular antigens and the currently available preparation consists of 14 common individual types of pneumococci. (PNEUMOVAX, MSD) The protective effect of vaccination may last for up to 5 years and immunisation should not be repeated more frequently than every 3 years. Current recommendations for immunisation are patients over the age of 2 years with sickle cell disease, and individuals who have had a splenectomy or who have impaired splenic function; the use in the elderly and patients with chronic heart, renal or lung disease, and diabetes or other metabolic disorders is not as clearly defined as yet.

A recent report of the utilisation of pneumococcal vaccine in elderly medicare beneficiaries found that it had been administered to over 1.4 million beneficiaries at a cost of 14.3 million $. The level of administration peaked in 1985 and by year 2000 an estimated goal of 60% of the elderly will be immunised. Unfortunately no efficacy was measured but Medicare believes that it is cost effective and encourages vaccination as no copayment is necessary and the deductible limit is not affected.[199]

23-valent pneumococcal vaccine is now in widespread use in the USA.

Influenzae vaccine is used widely but probably has little effect on community-acquired pneumonia per se, although it is very effective in preventing influenzae epidemics.

Other bacterial vaccines can easily be prepared but the incidence and significance of these microbes in community-acquired pneumonia do not warrant their development.

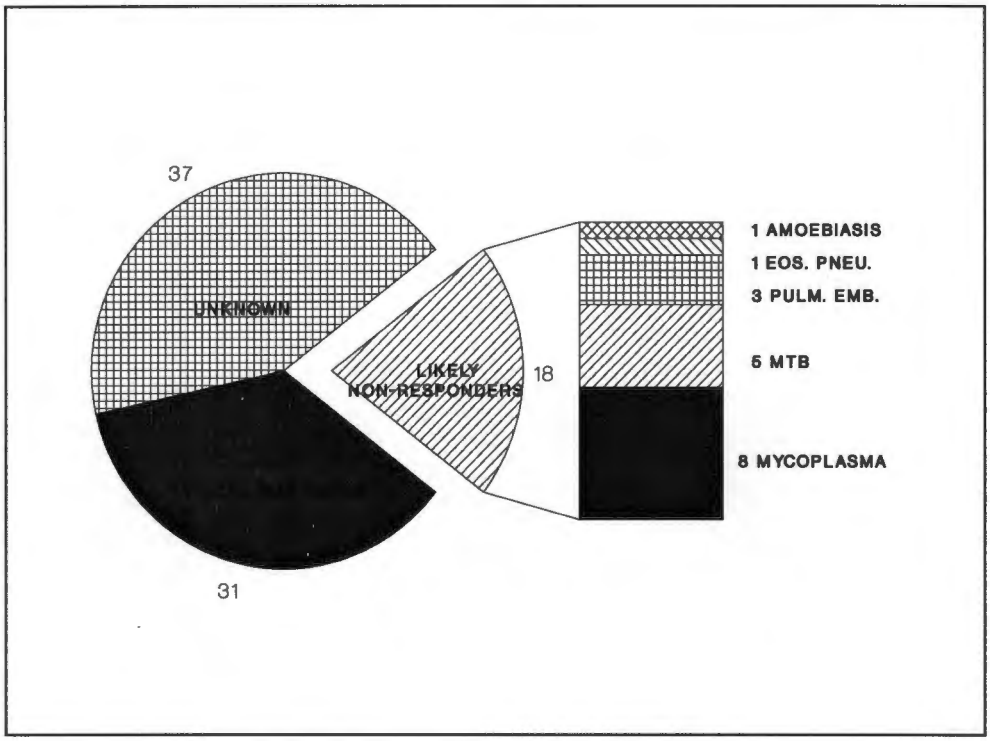
CHAPTER 7

NON-RESPONDING PNEUMONIA

Pneumonia is a common infection in adults affecting approximately 1.5/100 of the population annually.[200] Although community-acquired pneumonia may lead to death in 1 to 5% of patients, it usually responds well to antibiotic therapy with defervescense of the acute febrile symptoms within a few days, and complete resolution within a week or two. Those who die usually run a fulminant course and the pneumonia is caused by the common community-acquired pathogens including *S. pneumoniae*, *Staph.aureus* and *K. pneumoniae*.[9,43,52,122,200] A small number of patients fail to respond within 5 to 7 days of initiating therapy, and these cases usually form a distinct group which are considered **non-responding** pneumonia. More recently this group has been subdivided into slow-resolving and non-resolving; this distinction may be of value although there are only subtle differences. Outcome is similar but aetiology may vary with the non-resolving group more likely to result from an incorrect diagnosis of pneumonia, whereas slowly resolving disease more likely to be due to pre-existing disease including anatomical abnormalities of the lung parenchyma or airways, other host defence deficiencies, unusual organisms resistant to the antibiotics, necrotising pneumonia or development of an empyema or lung abscess.

The incidence of non-responding pneumonia in an outpatient-based population is unknown, but re-analysis of the data from Prout et al[9], suggests that the incidence may be in the region of 15%. In this study a clinical diagnosis of pneumonia was made in 86 patients attending the emergency room. Those patients who may have responded slowly, or in whom the initial diagnosis was incorrect are illustrated in figure 4.[9]

Figure 4: Potential non-responding pneumonia group



CAUSES OF NON-RESPONDING PNEUMONIA

Unusual micro-organism

These organisms usually form a distinct subgroup of community-acquired pneumonia, the "atypical pneumonias". While some may be slow resolves or fail to resolve, others will behave in a manner identical to other bacterial pneumonias. The most frequent causes of an atypical pneumonia are *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis* (MTB).[43,179,180,201] Epidemiological surveys in the United Kingdom and United States have shown that *Chlamydia*, particularly *Chlamydia pneumoniae* (TWAR agent) is becoming prominent, and although usually causing a mild acute illness, may cause an indolent pneumonia[52,202-204]; in our region we have yet to identify this pathogen as a cause non-responding pneumonia, however it has been reported to have been responsible for 6% of community-acquired pneumonias in a recent survey (Gary Maartens, South African Society of Infectious

diseases Conference 1993) The full spectrum of agents causing atypical pneumonia are shown in table 7.

Table 7: Causes of atypical pneumonia

Bacteria	*M. pneumoniae*
	Chlamydia spp.
	Coxiella burnetti
	Bacillus anthracis
	Leptospirosis
Fungi	Histoplasmosis
	Coccidiomycosis
	Cryptococcus
Viruses	Influenzae
	Para-influenzae
Mycobacterium	*Mycobacterium tuberculosis*
	Others (MOT)

Atypical pneumonia is characterised by an unusual clinical presentation. These agents may produce a relatively low-grade infective pneumonia which resolves slowly, or not at all, even if appropriate antibiotics are given. Multi-organ involvement is common and diagnosis is difficult. They are fastidious and difficult to culture requiring special media. Diagnosis is usually dependent on the detection of antigen or antibody response and this may take weeks or even months before the diagnosis can be adequately confirmed. The clinical features differentiating atypical from typical

pneumonia are shown in table 5, chapter 5. However, it must be noted that in a large proportion of cases the clinical presentation is identical to other bacterial pneumonias as is the time course of the disease.. A recent study indicates that no features are classical of these organisms and suggests that the classification "atypical pneumonia" be abandoned and this may not be unreasonable as the term "atypical pneumonia" was coined in 1938, a time when *Mycoplasma pneumoniae* was the only atypical pathogen that had thus far been identified and the original clinical descriptions don't necessarily fit the clinical features caused by the newly described micro-organisms particularly *Legionella spp.*[52]

Mycoplasma pneumoniae is the most common cause of an atypical pneumonia in our population (see figure 4).[9] *Mycoplasma pneumoniae* pneumonia produces no diagnostic clinical or radiological features. Duration of symptoms vary from 1 day to more than a month, and although younger patients are predominantly affected, the elderly are not spared. The disease is often subclinical or self limiting and passed off as influenza, and a large number of infections probably remain undiagnosed.. Extra pulmonary manifestations including haemolytic anaemia (17%), Steven's Johnson syndrome (4%), neurological abnormalities (4%), arthritis, hepatitis and pericarditis are common. Diagnosis relies on serological tests and the most useful is the rapid, specific IgM test which is positive on admission in 86% of patients. Cold agglutinins are present in 57% and a fourfold rise in complement fixation titre occurs in 26%.[31]
The clinical features of *Legionella pneumophila* pneumonia, an agent discovered 40 years after the first description of atypical pneumonia, was initially thought to mirror the criteria for atypical pneumonia. Recent experience, however, suggests that the pathological and radiological changes resemble other bacterial pneumonias more than the atypical pneumonias.[93] There are some distinctive features and it frequently has a fever higher than pneumonia from other aetiologies, and is often associated with haematuria, renal and hepatic dysfunction, confusion, diarrhoea and hyponatraemia[52]
It occurs infrequently in our region, but has been noted to occur in small unrelated

clusters.[117] The incidence is increased in patients requiring ICU admission (5% to 30% of community-acquired pneumonia) but the mortality remains relatively low.[1,52,205] Extra pulmonary manifestations are again common and response is usually slow and diagnosis difficult. Characteristically no pathogens are found in the sputum and blood culture is negative and the diagnosis depends on a four fold rise in antibody titre. Direct imunoflurescent antibody staining of protected brush or lavage specimens have recently been introduced and are highly sensitive and specific if uncontaminated specimens are examined.

Mycobacterium Tuberculosis (MTB) occurs frequently in our community and although it usually presents with characteristic clinical and radiological features, it may mimic acute community-acquired pneumonia in up to 5% of patients diagnosed as having community-acquired pneumonia.[9] Recent studies from Hong Kong and Singapore have reported an incidence in similar circumstances as high as 12% and 21% respectively [179,180] Pulmonary tuberculosis not infrequently presents with a short history and radiological opacification of the lungs involving regions other than the classical upper zone infiltrates, particularly in patients with underlying immunocompromising conditions such as immunosuppression or AIDS. It is also important to consider the role of dual aetiology which is becoming increasingly recognised with the use of more discriminative diagnostic tests.[116,206] In our survey of community-acquired pneumonia one patient presented with a viral pneumonia and associated pulmonary tuberculosis.[9]

Necrotising Pneumonia (Chronic destructive pneumonia)

Aspiration pneumonia is a distinct entity resulting from inhalation of large quantities of oropharyngeal or gastric contents. It usually occurs in patients with an underlying predisposition to aspiration including dysphagia or unconsciousness, and results in either a chemical pneumonitis or bacterial infection. Bacterial infection may either present early, with features indistinguishable from other forms of acute pneumonia,

which may or may not resolve, or one to two weeks later with suppurative complications including necrotising pneumonia, lung abscess or empyema.[59] Necrotising pneumonia itself may present with an acute suppurative illness, or a more indolent protracted course, with chronic symptoms of low grade fever and copious foul smelling purulent secretions. The chest radiograph may show a single lung abscess, but more typically multiple pulmonary cavities less than 2 to 3 cm in diameter, usually in dependent regions of the lung. The bacteriology of this disease consists of multiple pathogens particularly the anaerobic bacteria, *Peptostreptococcus*, *Fusobacterium spp.*, and *Bacteriodes spp.* commonly, and less frequently, the aerobic bacteria *S. pneumoniae*, *H. influenzae*, *Staph.aureus* and Gram negative bacilli.[6,59] The diagnosis is usually confirmed by exclusion of other indolent pneumonias such as MTB or *Nocardia asteroides*, and pulmonary neoplasms. These necrotising pneumonias respond slowly to antibiotic therapy and 30% may require surgical treatment.[6]

Empyema or Abscess Formation

Although the majority of lung abscesses follow an aspiration pneumonia, a number of common pathogens including *S. pneumoniae*, *S. aureus* and *K. pneumoniae* have a predilection to cause necrosis, with abscess formation or empyema. This complication must be considered in any patient who fails to respond, as tube thoracostomy or surgical drainage of the pus may be necessary.[207] Computerised tomograph (CT) scanning of the thorax is a very useful way of differentiating between pleural and intrapulmonary disease and is valuable in planning surgery.[26] Most empyemas can however be diagnosed clinically, and on the plain chest radiograph, and pleural drainage should never be delayed.

Table 8: Host defence abnormalities

Mechanical	Aspiration
	Cilia abnormality
Humoral	Systemic disease (diabetes or collagen vascular disease)
	Transplant patients
	Immunosuppressive drugs
	AIDS
Non-specific	Advanced age
	Smoking
	Malnutrition

Host Defence Abnormalities

These may either be due to mechanical or humoral factors (see table 8).[60] The usual spectrum of pathogens seen in community-acquired pneumonia occur in the same frequency in these patients, but opportunistic infections are much more common, and their incidence depends on the type of concomitant disease and regional differences. In our region diabetics and transplant recipients frequently develop *Nocardia asteroides* pulmonary infections and transplant recipients have a high incidence of *Mycobacterium tuberculosis* and fungal infections, particularly invasive aspergillosis.[154]. Although *Pneumocystis carinii* is common in patients with AIDS in Europe and the United States, in endemic areas for MTB many of these patients present with *Mycobacterium tuberculosis* infections.

Anatomical Abnormalities

Anatomical abnormalities may lead to non-response or slow-response particularly where normal bronchial clearance of secretions is obstructed. These anatomical defects may also lead to repeated infections with the usual spectrum of agents, or by the micro-organisms which have colonised the anatomical deformity.

Response in these cases is either slow, or there may be complete failure to respond. These abnormalities may be broadly categorised into parenchymal, or bronchial lesions, but in both inadequate drainage is the main cause of infection (see table 9).

Table 9: Anatomical abnormalities leading to slow response

1.Parenchymal	COPD
	Lung cysts
	Interstitial Lung disease
	Hydatid disease
	Tumours
	Sequestrated Lung
2.Bronchial	Bronchiectasis
	Foreign body
	Tumours (benign and malignant)
	Stenosis
	Compression (nodes, etc.)

Incorrect Diagnosis

A number of pulmonary diseases, which will require specific therapy for resolution, may present with clinical and radiological features indistinguishable from acute pneumonia. Whilst the majority are uncommon, some such as pulmonary infarct or embolism, occur frequently, and occasionally closely mimic pneumonia. Clinical features of infection such as a pyrexia, increased white cell count and sputum production occur with either disease, and although a white cell count of more than 20

000 cells/ml is uncommon in pulmonary embolism, it can frequently be elevated to levels between 10 000 to 20 000 cells/ml, and special investigations including venography, lung scanning and pulmonary angiography may be necessary to differentiate. Another less common but otherwise indistinguishable condition, is a pulmonary infiltrate with eosinophilia (PIE) where a differential white cell count should usually clinch the diagnosis. Other diseases including the pulmonary vasculitides such as Wegener's granulomatosis may need lung biopsy to confirm the diagnosis, however serum antineutrophil cytoplasm antibodies (ANCA) measurements may be helpful. Table 10 lists conditions which may be misdiagnosed as an acute pneumonia.

Table 10: Diseases mimicking pneumonia

1. Pulmonary embolism/infarct
2. Pulmonary neoplasm
3. Cryptogenic organising pneumonia or bronchiolitis obliterans and organising pneumonia
4. Pulmonary Infiltrate with Eosinophilia (PIE) - Eosinophilic pneumonia, etc.
5. Lipoid pneumonia
6. Collagen vascular diseases - Systemic lupus erythematosis, Rheumatoid arthritis
7. Alveolar haemorrhage syndromes
8. Pulmonary vasculitides
9. Necrotising sarcoidosis
10. Drug reactions - Amiodarone, Furadantin, Bleomycin, etc.
11. Neighbourhood pathology-Amoebiasis, Mediastinitis

MANAGEMENT OF NON-RESPONDING PNEUMONIAS

Diagnosis

An accurate diagnosis is paramount for the correct management of a pneumonia that fails to respond.

The following diagnostic approach should be followed in all patients who fail to respond to therapy after 5 to seven days of antibiotic therapy. (Figure 5)

Figure 5: Diagnostic approach in a pneumonia failing to respond after 5 to 7 days of therapy

Likely diagnosis	Incidence	Investigations
MTB	++++	FOB* with PSB**,
Atypical pneumonia	+++	Lavage,Transbronchial biopsy
CA Bronchus	++	and cytology.
Anatomical abnormality	++	CT scan
Empyema	++	~
Abscess	+	~
Foreign body	+	Rigid bronchoscopy

* *FOB = Fibreoptic bronchoscopy*

** *PSB = Protected specimen brush for ZN staining, direct immunofluorecent staining and fungal stains.*

Antibiotic therapy

If after 5 to 7 days of conventional antibiotic therapy no response has occurred atypical pneumonia should be considered, and appropriate treatment instituted if this has not already been started. Antibiotic therapy should be organism specific and care should be taken to give adequate doses. The antibiotic should be continued for 48 to 72 hours after resolution of all clinical features of infection.

Mycoplasma pneumoniae should be treated with erythromycin in an oral dose of 250 mg, 6 hourly . *Legionella pneumophila* should be treated with erythromycin 1g, 6 hourly intravenously, however if no response occurs rifampicin or ciprofloxacin, which have been shown to improve cure rate, may be added.

PART 2

SEVERE COMMUNITY ACQUIRED PNEUMONIA REQUIRING INTENSIVE CARE

CHAPTER 8

RESEARCH PROTOCOL

INTRODUCTION

Although community-acquired pneumonia is a common disease which leads to death in 13.1 per 100,000 of the American population, and has the highest age adjusted death rate of any infectious disease, little has been described about the aetiology, severity of illness, or critical care management of severe pneumonia admitted to an ICU. A number of different aspects have previously been addressed in these patients and guides for determination of the severity of illness, indication for admission, and use of fibreoptic bronchoscopy in the diagnosis, have been suggested. These recommendations are however based on small numbers of patients, and these findings require further validation. This descriptive prospective study of all patients with community-acquired pneumonia admitted to a teaching hospital, respiratory intensive care unit over a six year period reviews aetiology, clinical features, complications and therapy in an attempt to define current practices in caring for severe pneumonia requiring ICU admission. Included are also longer studies of less common specific etiologic pneumonias as well as specific therapeutic studies within this cohort of patients.

OBJECTIVE

1. To define the population of patients with different types of severe pneumonia requiring ICU admission.

2. To determine the aetiology of severe community-acquired pneumonia (CAP).

3. To evaluate different diagnostic techniques in severe community-acquired pneumonia.

4. To determine factors that might predict increased mortality in severe community-acquired pneumonia.

5. To evaluate ICU complications and causes of death in severe community-acquired pneumonia in an attempt to determine ways in which these may be reduced.

6. To characterise severe community-acquired pneumonia of specific aetiology including *Klebsiella* pneumonia, *Staphylococcal* pneumonia, *Varicella* pneumonia and *Pneumococcal* pneumonia..

PATIENTS

All patients with a clinical diagnosis of acute pneumonia defined on admission, and with ultimate evolution of the disease confirming this diagnosis are included in the study. The criteria for the diagnosis included a clinical history of an infective illness suggestive of pneumonia; pyrexia or hypothermia; clinical signs of lung consolidation including crackles or bronchial breathing; an elevated white cell count or a left shift in the morphology of the neutrophils, and evidence of an infiltrate on the chest radiograph. Patients with pulmonary or disseminated tuberculosis were excluded. Patients admitted with pneumonia but only after a cardiac arrest resulting in irreversible neurological damage were also excluded.

No specific criteria for admission to the ICU existed and all patients who were considered likely to benefit, were admitted depending on bed availability. Patients were usually seen in the medical wards prior to admission, and therapy instituted immediately and transferred to the ICU when a bed became available. No patients

were excluded because of old age or any other clinical features suggesting a poor outcome.

METHODS

Clinical Diagnosis

The diagnosis of pneumonia was determined on admission by the attendant physician and confirmed with subsequent evolution of the illness in problematic cases. All associated diseases present on admission were recorded. The pneumonia was classified as :

Community-acquired pneumonia (CAP):-

Pneumonia that occurred in the community without any major comprising factors. Patients with COPD, diabetes, and similar underlying diseases were included.

Nosocomial pneumonia:-

Pneumonia acquired after 48 hours of hospital admission or in a patient who has been in hospital within the previous month.

Aspiration pneumonia:-

Pneumonia following observed aspiration or a very likely clinical setting e.g. after a fit; and further classified as either community-acquired or nosocomial.

Pneumonia in an immunocompromised patient:-

Pneumonia in a transplant patient; patients on immunosuppressive drug therapy e.g. azathioprin, methotrexate, cyclophosphamide, steroids > 30 mg/day, and cancer chemotherapy; diseases including haematological malignancies, lymphomas, collagen vascular diseases and HIV infections.

The data on community-acquired pneumonia only is reported, other than in chapter 9 where an overview of all admissions to the ICU are presented, and those with all types of pneumonia are further described in terms of aetiology, treatment and outcome to give an overall perspective.

Demographics and Severity of Illness.

Patient demographics were recorded and the severity of illness was calculated using the APACHE II scoring system with the worst physiological parameters in the first 24 hours being used. (See appendix 2)[208] The organ failure score was assessed daily for the first 5 days following admission using the following criteria for defining organ failure :

Respiratory -

Respiratory rate <6 breaths/minute or >49 /minute or

$PaCO_2$ >5.9 kPa or

$AaDO_2$ >46 kPa (PiO_2 - PaO_2 - $PaCO_2$) or

Dependent on ventilator for >3 days.

Renal -

Urine output <480 ml/24 hours or <160 ml/12 hr or

Serum creatinine >300 micro mol/l or

Serum urea >20 mmol/l.

CVS -

Mean blood pressure <50 mm Hg or

Heart rate <55 beats/minute or

pH <7.25 with $PaCO_2$ <6 kPa.

Haematological -

WCC <1000 cells/ml or

Platelets <20,000 cells/ml or

Haematocrit <21%

Neurologic

Unconscious Glasgow Coma Score <7 (no sedatives for 24 hr)

Diagnosis

The diagnostic procedures used were those that were considered to be good clinical practise and the following approach was used for community-acquired pneumonia.

1. On admission:

    Blood culture plus sputum Gram's stain and culture

2. Immediately on intubation:

    Sputum Gram's and Ziehl-Neelsen stain and culture

3. Gram's stain unhelpful and clinical features suggestive of an atypical pneumonia:

    Serology for *Legionella* and *Mycoplasma.*

4. At 48 hours:

    Clinical response - no further investigation.

    No response - Empiric antibiotic change and PSB (including immunoflurescent staining and microscopy for *L. pneumophila*), if additional factors suggested the possibility of an unusual organism or another diagnosis. Serology for *Legionella* and *Mycoplasma* was performed

5. No response at 5 days:

    Fibreoptic bronchoscopy with PSB and transbronchial biopsy if indicated.

In patients with nosocomial pneumonia a similar approach was used except that in fulminant disease fibreoptic bronchoscopy and a PSB were used on admission .

In the immunocompromised group of patients invasive methods of diagnosis were performed on admission.

Microbiological Methods.

Microbiology was performed in the routine laboratory using standard laboratory methods.

Blood cultures were processed by the Bactec system using both aerobic and anaerobic bottles

Sputum specimens.

1. Specimens were examined macroscopically, and if unsuitable (e.g. salivary), were discarded except in the case of neutropenic patients. Sputum was described macroscopically as salivary, mucoid or purulent, and the presence of blood noted.

2. A Gram's and Ziehl-Neelsen (ZN) stain was prepared using a sterile swab. The Gram's stain was evaluated for pus cells (graded 1+,2+ or 3+); epithelial cells (graded as >1+ to signify salivary specimens.); and predominant organism (i.e.> 1+), mixed organisms, or a pure single organism.

3. The specimen was inoculated onto Boiled Blood Agar and Columbia Gentamicin Agar, both inoculated at 37° C overnight under CO_2 conditions and McConkey agar incubated at 37° C overnight.

4. Pathogens were identified according to standard laboratory protocols. Disc sensitivity testing was done using NCCLS specifications for all organisms with the exception of cloxacillin. Cloxacillin was initially tested by the disc method and subsequently the cut off method was adopted.[209]

During the time of this study however a number of specific studies were conducted including selective decontamination of the digestive tract, and evaluation of cefpirome and perfloxacin where additional microbiology was performed.

Bronchoscopy Specimens.

Bronchoscopic specimens were taken during fibreoptic bronchoscopy. Minimal local anaesthetic (lignocaine 2%) was used to anaesthetise the airways, and the bronchoscope was introduced through a special swivel adapter that permitted uninterrupted IPPV. The FiO_2 was increased to 1.0 during the procedure, and the EKG, pulse, and oxygen saturation, was monitored continuously. Specimens were taken either by a bronchial brush, or a PSB if indicated, or a lavage trap specimen, and transported to the laboratory immediately. PSB specimens were agitated on a rotator to release material adhering to the brush, and then handled in a similar way to trap and other brush specimens. These were centrifuged at 4000 r.p.m for 15 minutes, and the supernatant then carefully removed and retained in a sterile tube, using a sterile

Pasteur pipette. A Gram's and ZN stain of the deposit were prepared and evaluated for micro-organisms and pus cells. Ziehl-Neelsen stains were done for all specimens, and direct immunoflourescence staining for *Legionella spp.* when this became available, The specimen was inoculated onto Boiled Blood Agar and Columbia Gentamicin agar, and both were incubated overnight at 37°C under CO_2 conditions; and a McConkey agar was incubated at 37°C overnight. Additional anaerobic culture was performed using a Vancomycin/Neomycin agar plate and a Nalidixic acid agar plate which were incubated anaerobically at 37°C for 48 hours. Further identification was done by standard laboratory methods as for sputum. All remaining deposit and supernatant fluid was forwarded for further processing for fungi and for Kirschner to exclude *Mycobacterium spp.* These organisms were identified according to standard laboratory protocols. In certain cases for study purposes quantitative culture of PSB specimens was performed however the results reported here consider all growth from the PSB to be significant.

Definitions of Pathogenic Micro-organisms.

Causative organisms were defined as those that were cultured from blood; those that were seen on the Gram's from sputum or tracheal secretions and cultured in pure growth; a predominant heavy growth of a pathogen, and all micro-organisms cultured from the PSB (quantitative culture was not used routinely). Mixed flora on the Gram's stain and mixed growth were considered as contaminants. Serology showing a fourfold rise in antibody titre was considered positive.

MONITORING

Continuous EKG and oxygen saturation monitoring using a pulse oximeter and intra-arterial blood pressure monitoring was used for the first few days until stable, and thereafter routine two hourly nursing monitoring of pulse, respiratory rate, blood pressure and temperature recordings were done. Urine output was measured hourly initially and subsequently two hourly. Routine monitoring of ventilatory variables was performed as indicated, and all ventilator alarms and EKG monitor alarms were appropriately adjusted. The duration of ventilation and different ventilatory modalities were documented.

The patients were under the direct care of a registrar in training (either anaesthetics or internal medicine), and the management was supervised by a specialist intensivist or pulmonary physician on routine twice daily rounds, or more frequently if necessary. Regular clinical monitoring and daily chest radiographs were performed. A special note of all procedures and their complications, and all other complications was recorded. Drug therapy was also documented.

Microbiological surveillance of tracheal aspirates, and urine if catheterised, was done routinely twice weekly; and all IV catheters were cultured on removal. Other specimens were obtained when clinically indicated.

In cases who died the cause of death and particularly the relationship to the pneumonia was documented. The relationship to secondary infection was determined clinically as far as possible. An autopsy was performed in all cases in whom consent was available, and an attempt was made to determine the causative organism and factors leading to death.

THERAPY.

Antimicrobiol Therapy

The antibiotic protocol used for the duration of the study was as follows:

Empirical therapy in severe fulminant disease was commenced with intravenous Penicillin 5 million units 6 hourly, amikacin 15 mg/kg body weight 12 hourly (or gentamicin 1.5 to 2 mg/kg, 8 hourly), and cloxacillin 2 g, 6 hourly, until a pathogen was isolated. In less severe disease cloxacillin was omitted. In patients with renal dysfunction a third generation cephalosporin was substituted for the aminoglycoside.

In cases where a causative organism was isolated, organism specific therapy was instituted. For *S. pneumoniae*, penicillin only; for *H. influenzae* if no response had occurred, intravenous ampicillin only; for *S. aureus*, cloxacillin and the aminoglycoside or in the case of cloxacillin resistance, vancomycin was given alone; for *K. pneumoniae*, a combination of aminoglycoside and third generation cephalosporin; and for *Ps. aeruginosa* a combination of an aminoglycoside and anti-pseudomonal penicillin or ceftazidime. If the organism was resistant to any of the usual antibiotics an agent to which the organism was sensitive was substituted. All patients with *Varicella zoster* pneumonia (chickenpox pneumonia) received acyclovir in addition to broad spectrum antibiotics. In cases with aspiration pneumonia, and occasionally in primary community-acquired pneumonia, metronidazole was added.

In the immunocompromised group of patients invasive diagnostic procedures were performed whenever possible to define the causative organism and allow specific antimicrobial therapy.

Ventilatory Therapy.

The majority of patients needed intubation and mechanical ventilation however a few were treated with continuos positive airway pressure (CPAP) by face mask.

CPAP by face mask.

Indication for this form of therapy was persisting hypoxaemia (PaO_2 <8 kPa), despite 40% oxygen by mask, adequate alveolar ventilation ($PaCO_2$ <5.5 kPa), with an effective cough, and fully co-operative and capable of protecting the airway.

A free-flow design CPAP apparatus with an oxygen blender and heated humidification designed in the respiratory ICU was used. (Cape CPAP system.).

Intubation and IPPV with PEEP.

Failure to meet the above criteria for adequate respiratory function, and also any evidence of septic shock (Systolic Blood Pressure <90 mm Hg in spite of adequate volume replacement), were both individually, indicators for immediate intubation. High volume low pressure cuffed endotracheal tubes were used exclusively (Portex profile, Portex LTD. Hythe, Kent, England.), and these were usually introduced transnasally using a blind nasal technique. In cases where suctioning was difficult, or where ventilation and oxygenation were difficult, or where a prolonged course was anticipated a tracheostomy was performed using a cuffed tube (Portex LTD, Hythe, Kent, England). Cuffs were all inflated to minimal occlusion pressure, adjusted two hourly, and monitored on an air pressure manometer.

Patients were ventilated using constant volume ventilators (Bear 2 or 2e or CPU 1) with heated humidifiers (Fisher-Paykel), at an inhaled temperature of 32-35^{o}C incorporated into a standard circle circuit. The respiratory rate was set between 15 to 25 breaths /minute, a tidal volume of 10 to 15 ml/kg body weight, a flow rate of 40 to 50 l/min, and a positive end expiratory pressure (PEEP) level of 5 or more cm H_2O as dictated by oxygenation.

Goals of ventilation were:

1. PaO_2	>8 kPa
2. $PaCO_2$	<6 kPa
3. Peak Inspiratory Pressure (PIP)	< 50 cm H_2O
4. FiO_2	<.50

The aim was to maintain oxygenation above 8 kPa at all times, and if it were necessary the goal limits particularly FiO_2, were exceeded for as long as was necessary. If the PIP was exceeded, the tidal volume was reduced, and if the problem persisted, the patient was sedated and paralysed. If in spite of appropriate ventilator adjustment, hypoxaemia persisted, and the patient failed to adjust to ventilation, heavy sedation and paralysis was used.

In cases of refractory hypoxaemia, PEEP levels of >15 cm or inverse ratio ventilation at a rate of 20 to 30 breaths/minute were used. The rate was increased to meet the patients respiratory demands using minimal sedation if possible. In these difficult cases pulmonary artery catheters were inserted to monitor oxygen delivery and optimise fluid balance.

Standard weaning criteria were used to decide when to initiate weaning: these included an adequate PaO_2, Vital Capacity >12-15 ml/Kg body weight, and reversal of the pneumonic process. The patients were weaned using techniques of Intermittent Mandatory Ventilation (IMV) or increasing time on CPAP.

Respiratory circuits including the humidifier bowel were changed twice weekly.

Standard nursing procedure was carried out in all these patients, which included routine monitoring and charting of blood pressure, pulse, respiratory rate; intake-output fluid and urine charting including 1-2 hourly urine volumes plus S.G. and glucose estimations; ventilatory pressures, tidal volumes, suctioning and tracheostomy care; mouth care; positioning, and turning, and pressure care; feeding and all other personal hygiene. Care of the endotracheal and tracheostomy tubes, cuffs and endotracheal suctioning was shared by the nurses and physiotherapy teams, and

ventilator aspects with the ICU/Respiratory technologists. There was an ICU trained intensive care nurse responsible for this care whenever possible.

Physiotherapy was performed by two physiotherapists (on a 6 monthly to a year rotation), usually with one experienced in ICU care. Their responsibility was largely chest physiotherapy, respiratory care, and mobilisation of patients, which was usually done twice daily. Their role was also supervisory and teaching to enable the nursing staff to continue the physiotherapy programme more frequently.

All these procedures in particular suctioning, was carried out with EKG and pulse oximetry monitoring to avoid causing hypoxaemia. If necessary the FiO_2 was increased before suctioning, and if still inadequate, a special sheathed suction catheter which allows uninterrupted ventilation was used.(Steri-Cath, Portex LTD, Hythe, England)

Supportive Therapy.

Patients were given full circulatory support with intravenous fluids and inotropic support where indicated. Dopamine was used in a dose of <10 micro-grams/kg/minute in cases of decreased urine output, and if further inotropy was necessary an adrenaline infusion was used in a dose of 10 to 100 micro-grams/hour.

Patients were fed as soon as possible, by balanced enteral tube feeds with the majority receiving 1000 to 1,500 kcals/day (Ensure), or where diarrhoea was a problem, Osmolite (Abbott/Ross Laboratories, South Africa). Supplementary vitamins were given to all patients.

No routine prophylaxis was used for stress ulceration.

DATA COLLECTION.

All data was collected by the registrars in training during the patients stay in the ICU, and this was recorded on a data collection form which was reviewed at a weekly clinical meeting convened by PDP or a deputy, to ensure the correctness of the data. The data collection forms and Apache II forms are in appendix 1 and 2. Data was

stored on a DBase 4 programme (Ashton-Tate) specifically designed for this ICU information (developed by PDP), and further analysis was performed using the DBase program, Epi Info Program and Epistat (Centres for Disease Control,USA).

STATISTICAL METHODS.

Numerical data is reported as mean and standard deviation. Comparison between data was done by Students t for nominal data, and Chi square testing for categorical variables where appropriate using the Epi-Info and Epistat statistical packages.

CHAPTER 9

PNEUMONIA REQUIRING ICU ADMISSION - AN OVERVIEW.

INTRODUCTION.

This chapter reviews all patients admitted to the ICU in whom a diagnosis of pneumonia was the primary indication for admission. These patients with pneumonia are classified according to the pathogenesis in immunocompetent patients, or as a specific group in those who are severely immunocompromised. This classification can be determined on admission and may be useful to provide a guide for further antibiotic management in pneumonia requiring ICU admission.[210] The total number of ICU admissions are presented according to the primary admission diagnosis to give some perspective of the relative importance of pneumonia in the overall ICU case mix.

PATIENTS.

A total of 2385 patients that included 1436 patients with medical diseases (60.2%), 218 with general surgical disease (9%), 11 cardiac (.5%), 75 thoracic (3.1%), 87 orthopaedic (3.6%), 69 (2.9%) other surgical, 160 (6.7%) obstetrical and gynaecological, and 326 (13.7%) following trauma were admitted during the study period . The disease profile of all admissions and mortality are shown in table 11.

The mean age of admissions was 41.7 years (range 11-87 years); 319 (13.4%) were black male, 278 (11.7%) black female; 248 (10.4%) white male, 192 (8.1%) white female; 641 (26.9%) male, and 707 (29.6%) female of mixed race.

413 (17.3%) patients were admitted to the ICU with pneumonia during the six year study period from January 1987 to December 1992. This included 196 patients with community-acquired pneumonia, 75 nosocomial, 101 following aspiration and 41 immunocompromised patients. 35 patients with pulmonary tuberculosis and 15 with disseminated tuberculosis were not included in the patients with community-acquired

pneumonia for analysis. One patient with dual infection with pulmonary tuberculosis and a bacterial pathogen was included in the analysis.

Table 11: Different diseases with APACHE II and mortality.

	No.	APACHE II	MORT.%
ASTHMA	223	11.2	0.45
ARDS	192	14.8	23.4
COPD	89	17.5	4.5
PNEUMONIA	413	16.2	24*
OTHER LD**	192	13	18.2
POISONING	172	12	5.8
NEUROLOGICAL	204	14.7	22.1
SURGICAL	235	10.1	6.8
TRAUMA	534	9.33	5.4
OTHER DISEASE	131	28.2	52.7
TOTAL	**2385**	**13.5**	**14.8**

*X^2 $p = .000001$; ***includes interstitial lung disease, carcinoma and bronchiectasis.*

The classification of the pneumonia; age, severity of illness, and outcome is shown in table 12.

Table 12: Classification of pneumonia with severity and outcome.

	No	AGE	APACHE II	MORT.%
CAP	196	44.9+-17.09	16.9+-7.95	25.5%
Nosocomial*	75	46.3+-16.85	14.6+-7.77	20%
Aspiration**	101	40.4+-16.29	15.3+-8.55	15.8%
Immunocomp.	41	41+-14.89	17.5+-6.75	45%

*Non ventilator associated pneumonia only. **Includes both community-acquired and hospital acquired aspiration.

AETIOLOGY.

The aetiology of the different types of pneumonia is shown in Table 13.

Table 13: Micro-organisms causing severe pneumonia

	CAP	NOSOC*.	ASPIR.**	IMMUNO.***
	%	%	%	%
S. pneumoniae	32.1	16	20	17.1
S. aureus	8.7	16	11.9	17.1
S. epid.	0.5	2.7	1	0
Other Gm +ve	0.5	1.3	0	2.4
H. influenzae	11.2	14.7	18.8	7.3
Br. catarrhalis	0.5	0	0	0
K. pneumonia	8.2	20	8.9	4.9
E. coli	3.1	4	7.9	0
Ps. aeruginosa	1	6.7	3	2.4
Acinetobacter spp	1	1.3	2	0
Enterobacter spp	0	2.6	2	0
Other Gm -ve	1	0	2	0
Anaerobes	1	1.3	2	0
Candida spp	1	0	0	9.8
Legionella spp	3.1	0	0	1
Mycoplasma	0.5	0	0	0
Viruses	3.6	0	0	9.8
Others	1.5	1.3	4	9.8
P. carinii	0	0	0	14.6
Unknown	29.6	33.3	42.6	26.8

** Nosocomial pneumonia; ** Aspiration pneumonia; *** Immunocompromised patients.*

There was only one HIV positive patient admitted to the ICU with a pneumonia during this time period, and this patient was one of 5 patients with *P. carinii* infection; the others with *P. carinii* infections included 2 renal transplant patients, and 2 with haematological malignancies.

SPECIAL INVESTIGATIONS

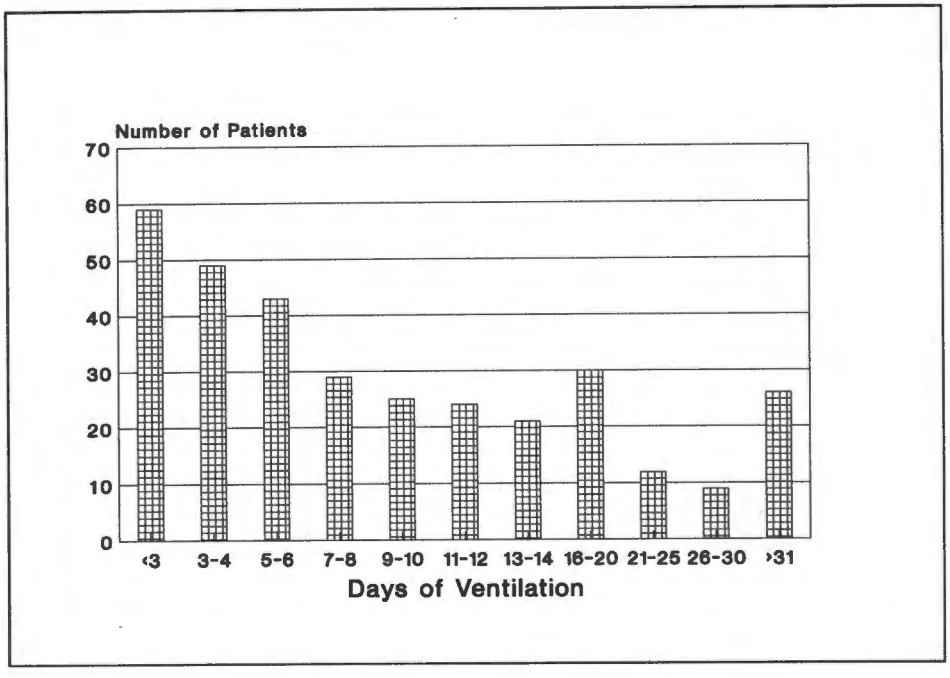
A number of special investigations were performed which included fibreoptic bronchoscopy (73), transbronchial biopsy (9), open lung biopsy (5), lumbar puncture (23), bone marrow (15), lung or body scan (11), ECHO or MUGA scan of heart (43), angiography (6), and computerised tomography or ultrasound of the abdomen (79). Pulmonary artery catheterisation was used in 96 patients with 138 procedures being performed. The right internal jugular was used in 109 procedures, left in 16 , left subclavian 3, and right subclavian 1. Complications were largely technical, with 4 patients requiring multiple attempts to find the vein, 3 attempts failed, 4 arterial punctures occurred, 5 balloon ruptures and in 1 it was impossible to obtain an adequate wedge, 3 patients developed arrhythmias that required treatment and in one a pneumothorax occurred.

TREATMENT

The majority of patients were in hypoxaemic respiratory failure and 215 patients were managed with endotracheal intubation, and 129 required tracheostomy. The indications for initial intubation were considered to be respiratory failure in 301, secretion retention in 19, and miscellaneous causes in 19 patients, whereas for tracheostomy 114 were for respiratory failure and prolonged intubation, 7 to assist weaning, 5 secretion retention, and 3 for upper airway obstruction following extubation. 316 patients were treated with CPPV, 31 with IPPV, 39 CPAP by face mask, and 27 oxygen by face mask only. The mean level of PEEP was 7.48 and 26 patients required 15 cm H_2O, or more. 6 patients were treated with double-lumen

endotracheal intubation and independent lung ventilation. The duration of ventilation is shown in figure 6.

Figure 6: Duration of ventilation



Additional supportive treatment included haemodialysis (73 patients), peritoneal dialysis (35), and total parenteral nutrition (70). All patients received enteral nasogastric tube feeding as soon as they could tolerate it (177 patients), starting with 500 kcals and building up to a maximum of 1000 to 1500 kcals.(Ensure or Osmolite; Abbotts/Ross Laboratories)

The antibiotics used in these patients are shown in table 14. 5 patients received one antibiotic only, 17 two antibiotics and the remainder more than two antibiotics.

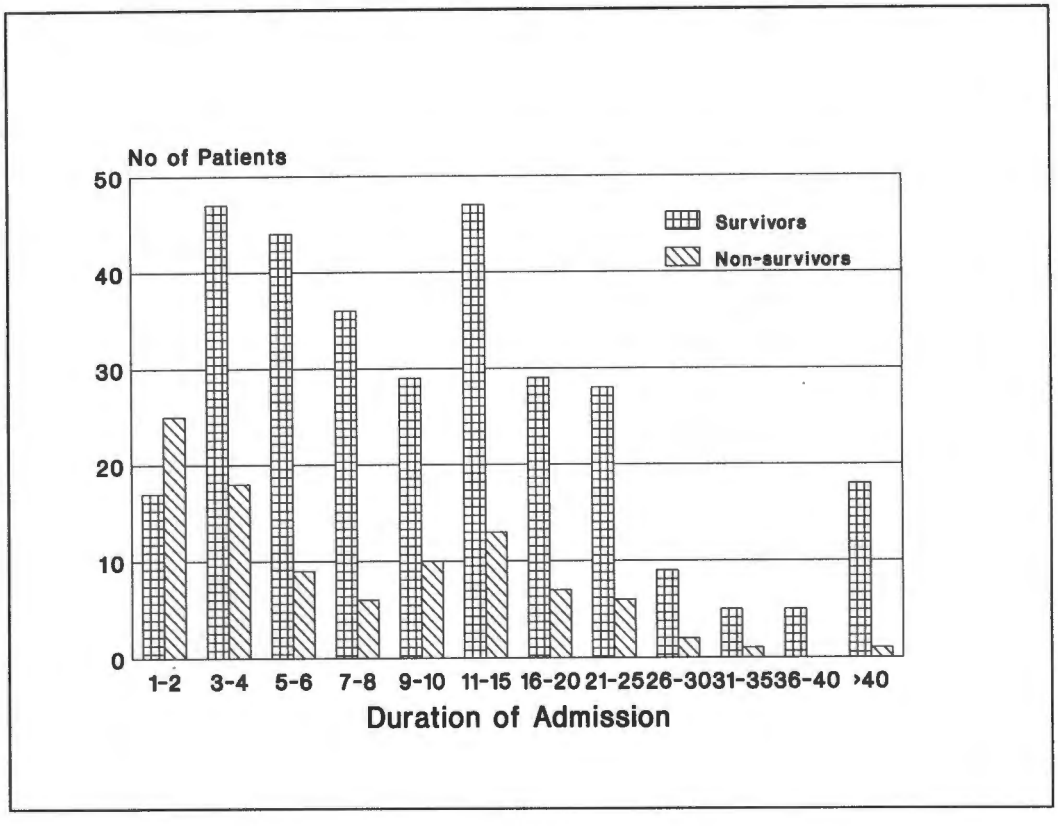
Table 14: Antibiotic therapy that was prescribed.

Antibiotic	No of Patients n = 413
Penicillin G	228
Amikacin	201
Gentamicin	75
Tobramycin	3
Cloxacillin	68
Erythromycin	65
Cefotaxime	64
Ceftriaxone	63
Ceftazidime	28
Cotrimoxazole	69
Amoxicillin	39
Piperacillin	18
Clindamycin	27
Amphotericin B	21
Metronidazole	165
Vancomycin	33
Fucidin	7
Quinolone	17
Chloromycetin	5
Tetracycline	2

The duration of admission to ICU ranged from <1 day to 165 days (a patient with Guillain Barre' admitted with severe pneumonia), with a mean duration of 13.01 days (S.D. 14.69). The mean duration of admission in the 314 survivors was 14.29 +-15.93

days, and 8.92 +- 8.57 days; in the 99 non-survivors (p = 0.00002). The duration of admission is shown graphically in figure 7.

Figure 7: Duration of ICU admission of survivors and non-survivors



COMPLICATIONS OCCURRING IN THE ICU

Complications occurred in 210 patients and these were usually related to the severity of the disease, and included secondary infections, gastro-intestinal haemorrhage and diarrhoea. A number of complications of ventilation occurred and included 27 pneumothoraces, 6 blocked endotracheal tubes, 7 accidental extubations and 3 tracheostomy bleeds. There were no cases of tracheal stenoses, even with long-term follow up. The frequency of different complications is shown in shown in table 15.

Table 15: Incidence of complications in the ICU.

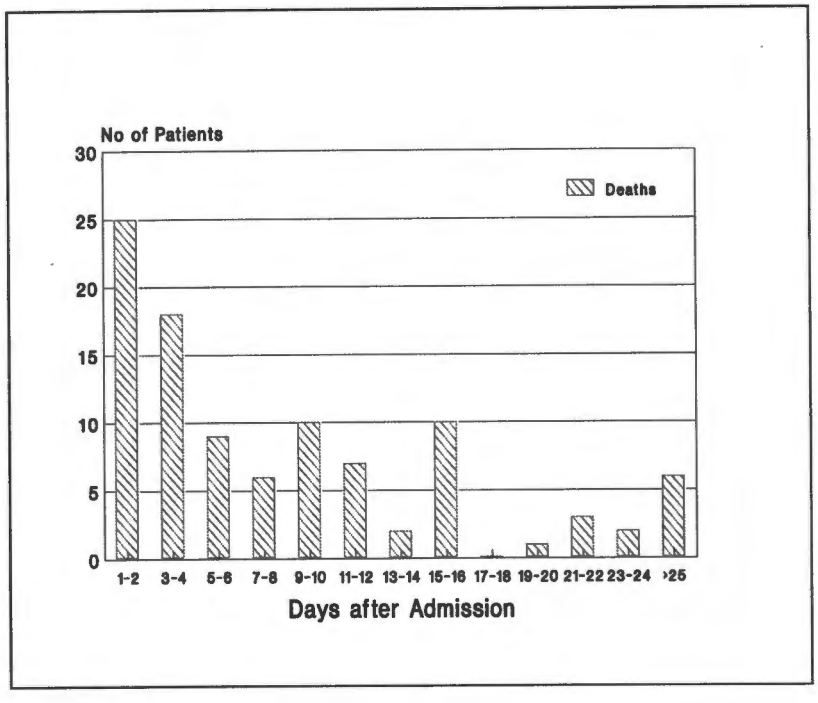
	No of complications
Gastrointestinal bleeding	32
Pulmonary embolism	1
DVT*	3
Haemoptysis	7
Pneumothorax	27
Ventilatory complications	24
Respiratory infection	47
Septicaemia	11
IV line sepsis	22
Diarrhoea	23
IV line complications	23
Drug complications	25

* *Deep venous thrombosis*

MORTALITY

The overall mortality was 24% (99 patients), with 25% of deaths occurring within 48 hours. The time of death is illustrated in figure 8.

Figure 8: Time to death following admission



Deaths were considered clinically to be due to septicaemia and multiple organ failure in 53 patients, respiratory failure in 27, hypoxic brain damage 9, pulmonary embolus 1, and cardiac in 9. In 2 of these patients death occurred following withdrawal of active therapy because of no chance of meaningful recovery. The outcome of the different pneumonias are shown in table 12.

DISCUSSION

Patients admitted with pneumonia contribute significantly to the patient load in our multidiciplinary ICU. The mortality varies considerably depending on the type of pneumonia. This classification seems useful in clinical decision making and epidemiological studies of ICU admissions, as both mortality, and aetiology, are different in the different categories which allows planning of appropriate therapeutic strategies. Many previous ICU studies have combined pneumonia with other causes of ARDS which tends to lose these clinical distinctions, and will make evaluation of these studies and new therapeutic strategies difficult to interpret.[211]

In this study the aetiology of the pneumonia was determined using routine clinical methods, but because of the severity of the disease most patients had tracheal secretions sampled immediately on intubation, and other special procedures such as fibreoptic bronchocscopy were used more frequently. Not surprisingly because of the physiological decompensation prior to intubation with acidosis, shock and a depressed level of conciousness, the larynx was usually incompetent on intubation. Many of the secretions that the patients were unable to expel because of a weak cough appeared to be of oropharyngeal origin. This may also explain the many cases of unknown aetiology as these specimens would have been discarded as unsuitable for microbiological processing. The diagnostic approach that was used was also pragmatic and not all patients were subjected to all the tests particularly FOB and serology. This may have influenced the results and underestimated pathogens such as *Legionella spp.*, or *Mycoplasma pneumoniae,* where the diagnosis is only possible using these techniques. The number of *S. Pneumoniae* infections may also have been increased had we used specific antigen detection, however this would have been unlikely to have influenced the incidence of Gram negative infections to any extent. The aetiology of infections in the immunocompromised group may also be altered by having other ICU's in the hospital where these patients are initially treated and only the worst often non responding cases are admitted to the RICU often after prolonged antibiotic therapy.

This classification which can be applied on admission to the ICU proved to be as useful in patients with severe pneumonia as it is in patients with less severe disease, as each different category appears to have a characteristic spectrum of causative micro-organisms.[210] This helped in empirical antibiotic and other therapeutic decisions such as what further diagnostic procedures were necessary. Whilst the general pattern was similar with *S. pneumoniae* remaining the most common organism, an increased number of Gram negative micro-organisms were seen in the nosocomial group, and more opportunistic infections occurred in the immunocompromised patients. There was a high incidence of *S. aureus* infections in all the categories, and interesting *H. influenzae* was also common in all groups; this agent was frequently identified as a second pathogen, and whether it truly contributed to infection was difficult to determine, however appropriate clinical response often only occurred after specific therapy for *H. influenzae* was instituted. There were no episodes of *L. pneumophila* other than in the patients with CAP.

The nature of pathogens in these patients with severe CAP differ from those seen in less severe cases with an increased number of Gram negative infections, particularly *K. pneumoniae,* as well as an increase in *S. aureus* infections.[17,125]

Pulmonary artery catheterisation had a low complication rate and in the majority of patients catheterised, the information from the procedure was considered most valuable, and contributed to decision making particularly with regard to fluid, and ventilatory therapy when high levels of PEEP were necessary. It was also helpful diagnostically in a small number of patients in whom a pulmonary embolism or cardiac failure was diagnosed vis a vie pneumonia.

The mortality for the different diseases varied considerably, and the relationship between mortality and the APACHE II score is well illustrated showing how pneumonia has a high mortality relative to the APACHE II score. The mortality in pneumonia compared to all other admissions was significantly increased. ($p = .000001$) (see table 11.)

CHAPTER 10

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

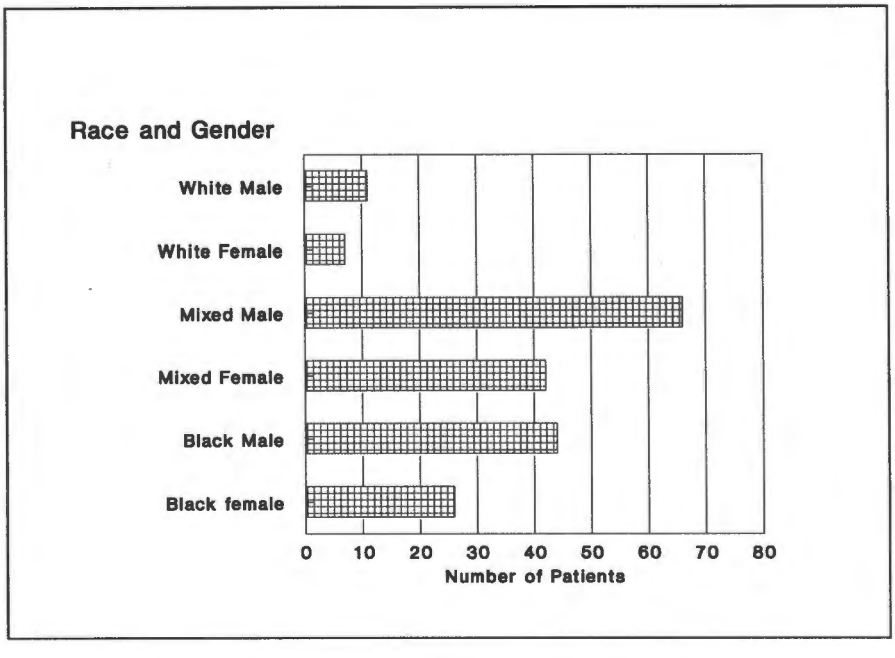
INTRODUCTION

Severe community-acquired pneumonia forms a clearly distinct category that accounts for the majority of patients with pneumonia who require ICU admission. This group includes all patients with community-acquired pneumonia, other than those who have had a clear episode of aspiration, or who are severely immunocompromised. It includes those with underlying diseases such as COPD, diabetes and neurological abnormalities. These patients with severe CAP differ significantly from those with milder forms of CAP, and also other types of pneumonia. As such these patients warrant separate analysis and in particular clinical features including aetiology, diagnosis, and determinants of severity require documentation to contribute further to our understanding of the clinical features and management of these patients.

RESULTS

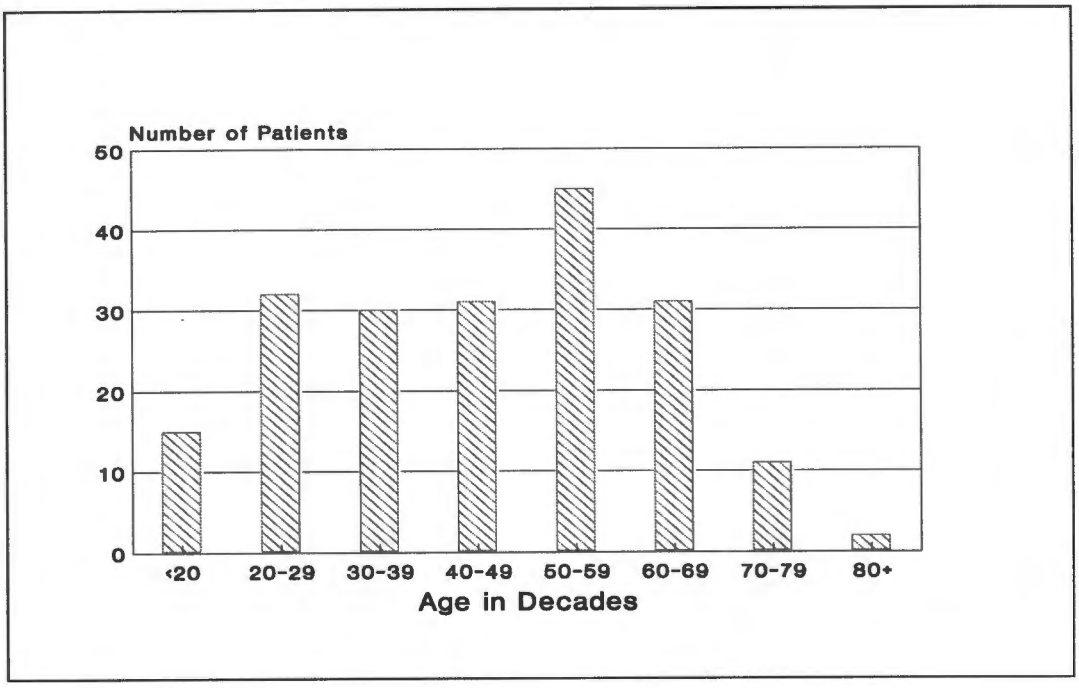
There were 196 patients with CAP including 121 males, and 75 females. There were 70 blacks, 18 whites, and 108 of mixed race (see figure 9).

Figure 9: Race and gender of patients with CAP.



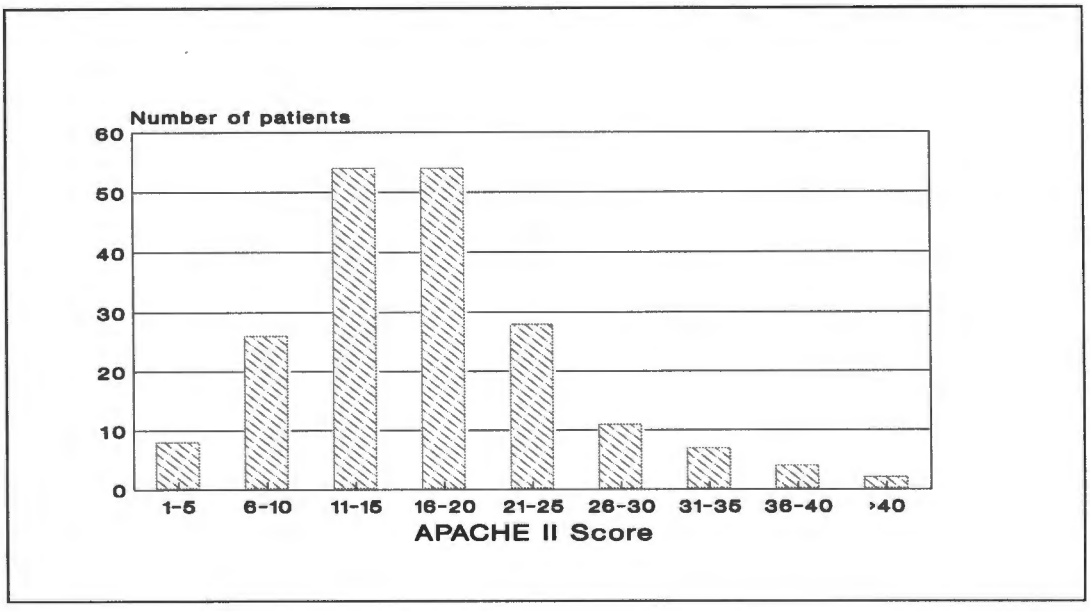
The mean age was 44.9 (S.D.±17.09) years, and the distribution of age is shown in figure 10.

Figure 10: Age distribution of patients with CAP



The APACHE II score was 16.9 (S.D.±7.95) and distribution of scores is shown in figure 11.

Figure 11: APACHE II scores (Worst in first 24 hours of admission)



The organ failure scored on day 1 showed that 88 patients had one organ failure, and 57 with more than 1 organ failure (mean of 1.47, S.D.±1.04). 21 patients were admitted with septic shock (Systolic blood pressure [SBP] <80 mm Hg); 24 patients had renal failure (Creatinine >300 micro mol/l, or urea >20 mmol/l) on admission and a further 8 developed renal failure.

Associated disease occurred in 100 patients and the relationship of this disease to age, severity of illness, and outcome is shown in table 16.

Table 16: Concomitant disease related to age, APACHE II, and mortality.

	n	AGE	APACHE 2	MORT.%
COPD	42	54.15±15.12	18.95±9.22	11 (27%)
Asthma	13	36.15±15.52	15.54±6.09	0
Old PTB	18	43.06±16.02	16.06±5.76	4 (22%)
Lung disease*	8	41.88±16.13	19.5±7.11	3 (38%)
Diabetes	21	54.57±13.64	17.81±6.65	6 (29%)
Cardiac	16	58.94±16.74	18.69±5.28	3 (19%)
Neurological**	8	36.63±15.52	14.63±5.73	1 (13%)

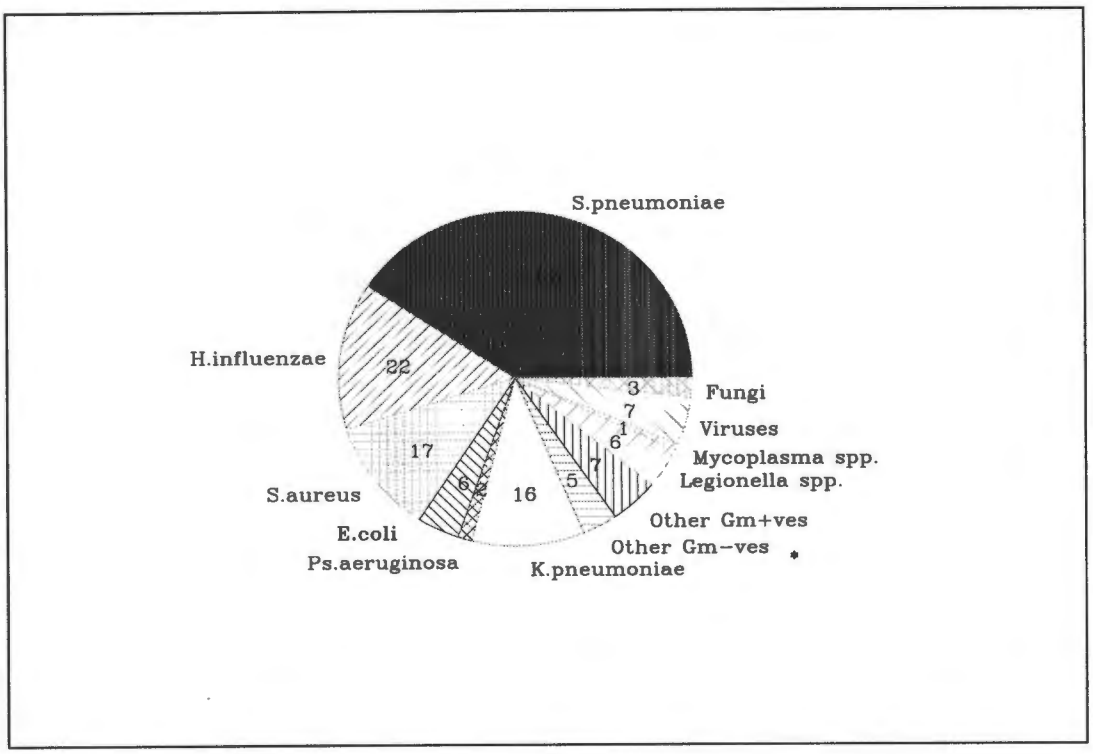
** Bronchiectasis (3 patients), Interstitial fibrosis (4), Kyphoscoliosis (1).*

*** Myasthenia Gravis (4 patients), Myopathy (3),Tetanus (1).*

AETIOLOGY.

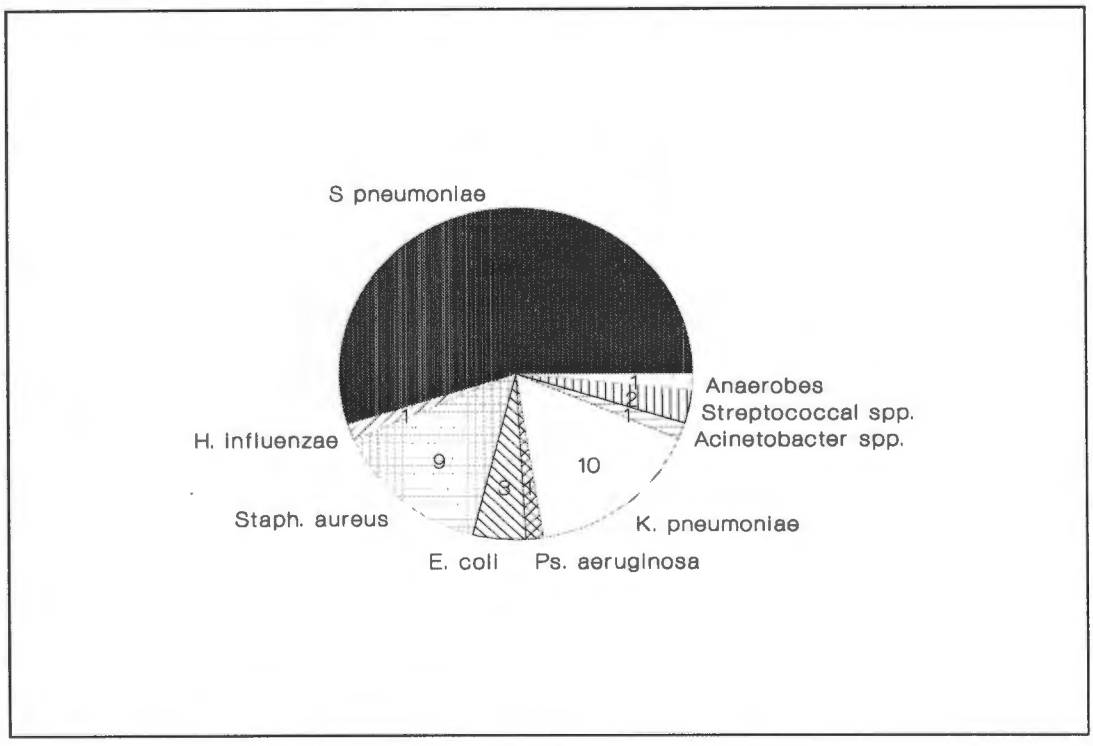
The aetiology of the pneumonia was determined by blood and bronchial secretion cultures, and serology. The spectrum of aetiological agents is shown in figure 12, and the aetiology determined by blood culture only (58 patients) in figure 13.

Figure 12: Aetiology of severe community-acquired pneumonia.



** Br. catarrhalis (2), N. meningitides (1),), Acinetobacter spp. (1), Proteus spp. (1).*

Figure 13: Aetiology of severe CAP determined by blood culture.



Blood culture was positive in approximately 50% of cases where causative organisms were identified. In *H influenzae* pneumonia it was significantly lower. (1 in 22 cases; X^2 p = .039)

The aetiology related to underlying COPD, diabetes and in the elderly (> 60 years of age) are compared to the aetiology in all patients in figures 14,15,16.

Figure 14: Aetiology of severe CAP in COPD

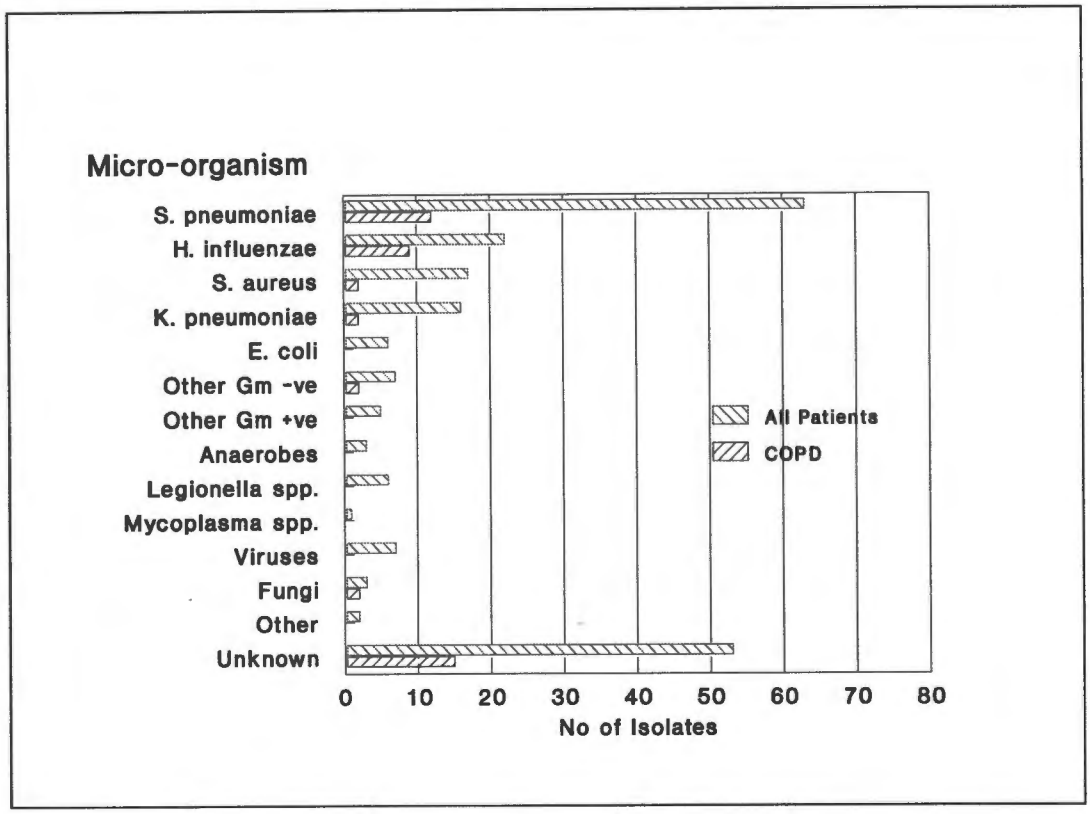


Figure 15: Aetiology of severe CAP in diabetics

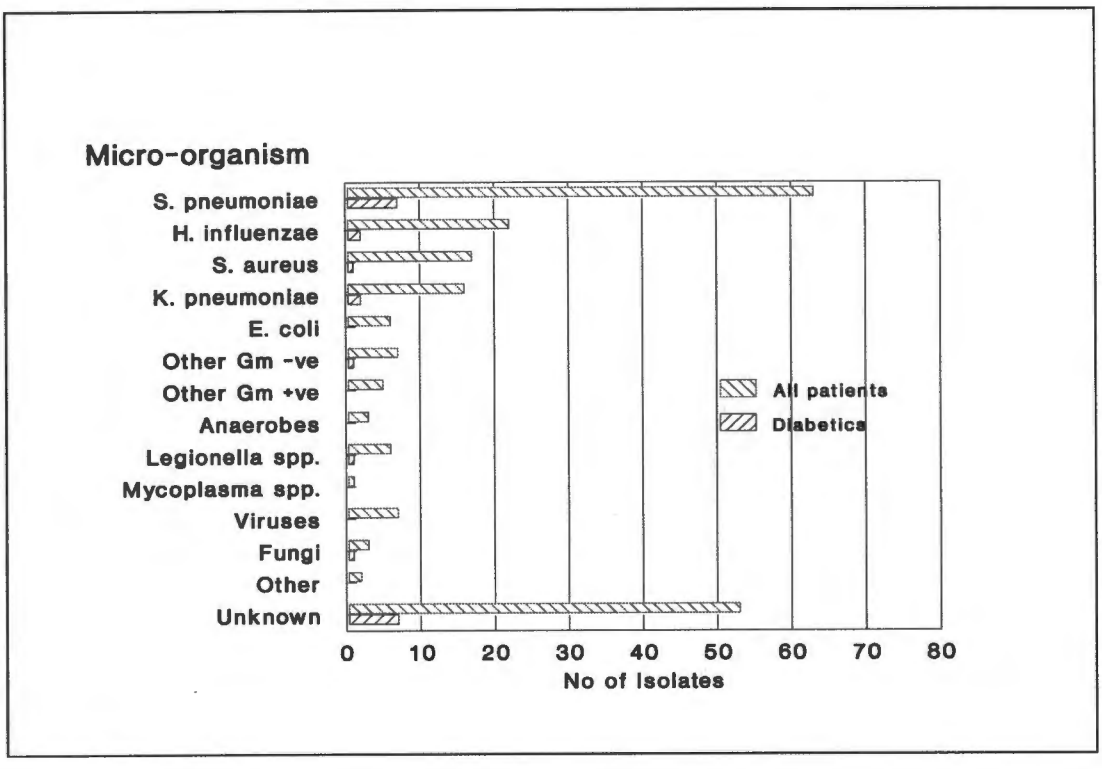
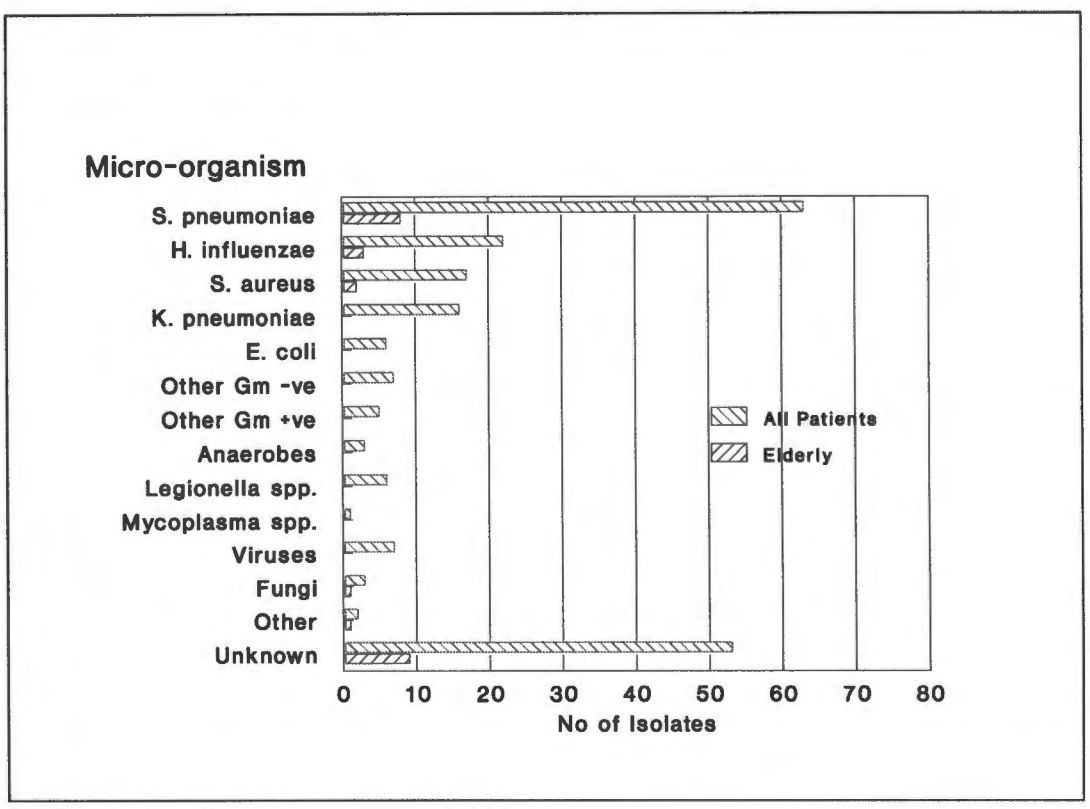


Figure 16: Aetiology of severe CAP in the elderly



There were 23 patients who were considered to have pneumonia caused by dual infections; 1 by three pathogens, and one patient had active pulmonary tuberculosis and a blood culture positive bacterial pneumonia. The most common multiply occurring pathogen was *H. influenzae* in 11 cases, and anaerobes in 2.

The severity of illness, duration of therapy and mortality in relation to pneumonia of different aetiologies is shown in table 17.

Table 17: Relationship between micro-organism, severity of disease, and outcome. *{All values given as mean and (S.D.)}.*

	No	AGE (years)	APACHE II	ORGAN FAILURE	DURATION ICU (days)	MORT
S. pneumoniae	63	44.7	18.4	1.56	9.09	13
		(16.88)	(8.7)	(1.06)	(7.07)	20.6%
H. influenzae	22	41.6	18.5	1.33	10.6	7
		(18.49)	(18.5)	(0.97)	(8.68)	31.8%
S. aureus	17	37.1	13.5	1.27	11.59	6
		(20.93)	(7)	(0.88)	(7.95)	35.3%
K. pneumoniae	16	45.3	19.2	2.06	9	7
		(11.25)	(7.77)	(1.34)	(9)	43.8%
E. coli	6	45	15.7	2.0	16.4	2
		(8.25)	(5.28)	(1.0)	(30.16)	33%
Varicella	7	28.7	6.43	0	0	0
		(12.19)	(5.09)			
L. pneumophila	6	47	16.67	1.33	13.5	0
		(13.3)	(6.98)	(1.03)	(16.67)	
Unknown	54	47.8	16.12	1.34	8.63	15
		(16.8)	(7.06)	(0.96)	(7.74)	27.8%
Total	**196**	**44.8**	**16.89**	**1.47**	**9.5**	**50**
		(17.09)	**(7.95)**	**(1.04)**	**(9.8)**	**25.5%**

CLINICAL FEATURES.

The earliest clinical features documented on admission to hospital were recorded where possible prior to instituting therapy.

Table 18: Clinical features on admission

Clinical Feature	No. of Patients	Mean	S.D.
Confused n=	150	27/150	
Temperature ^{o}C	191	37.48	1.41
Resp. Rate	183	30.99	12.36
WCC ml/l	185	17430	29612
Polymorphs %	185	68.28	
Platelets ml/l	185	219753	134254
Na^+ m mol/l	191	136.46	6.88
K^+ m mol/l	187	3.95	0.85
PO_4^- m mol/l	158	1.14	0.85
Urea m mol/l	191	12.15	13.51
Cr^- micro mol/l	190	199	481.4
ALT units/l	165	48.5	65.2
AST units/l	165	80.52	87.8
LDH units/l	156	590.9	774.9
Alk. Phos. I U/l	166	116.3	84.7
Bilirubin (Conj.) micro mol/l	170	9.8	13.6
Bilirubin (Total)micro mol/l	175	17.7	16.2
Protein (Total) g/l	169	58.6	9.7
Albumin g/l	175	28.22	6.43
pH	190	7.39	0.15
PaO_2 kPa	190	12.87	7.62
$PaCO_2$ kPa	190	4.48	1.54
PaO_2/FiO_2	190	200.7	101.5

The level of oxygenation is also shown in the table above as the PaO2/FiO2 ratio to eliminate the influence of supplementary oxygen therapy.

Radiological Features.

The chest radiographs were classified on admission as either lobar or segmental, bronchopneumonia, interstitial, or lobular; the presence of an effusion; diffuse changes of rapid onset suggesting that there was ARDS were also noted. These features related to the different aetiologies of the pneumonia are shown in table 19. The radiographs were all viewed blindly by the author without any clinical history, and an aetiological diagnosis was attempted in 132 patients. The correct diagnosis was made in only 34% of cases. Whilst the patients with Chicken pox pneumonia, and those with haematogenous *S aureus* infection were all correctly identified there were many false positive diagnoses even in these groups. Only 11 patients had evidence of an effusion but most radiographs were taken in the supine or semi-erect anterior posterior projection. Those with effusions included *S. pneumoniae* 3, *S. aureus* 3, unknown aetiology 3 and 1 each for *E. coli* and *H. influenzae*.

Table 19: Radiological features of pneumonia of different aetiologies

	n.	Bilat.	Lobar	Broncho.	Lobular	Interstitial	ARDS
S. pneumoniae	37	26	28	3	2	4	7
H. influenzae	12	11	5	5	2	0	3
K. pneumoniae	10	5	9	0	1	0	3
S. aureus	13	11	4	3	5	1	6
Legionella spp.	5	3	4	0	0	1	3
Unknown	43	36	23	7	6	7	13
Total	**120**	**92**	**73**	**18**	**16**	**13**	**35**

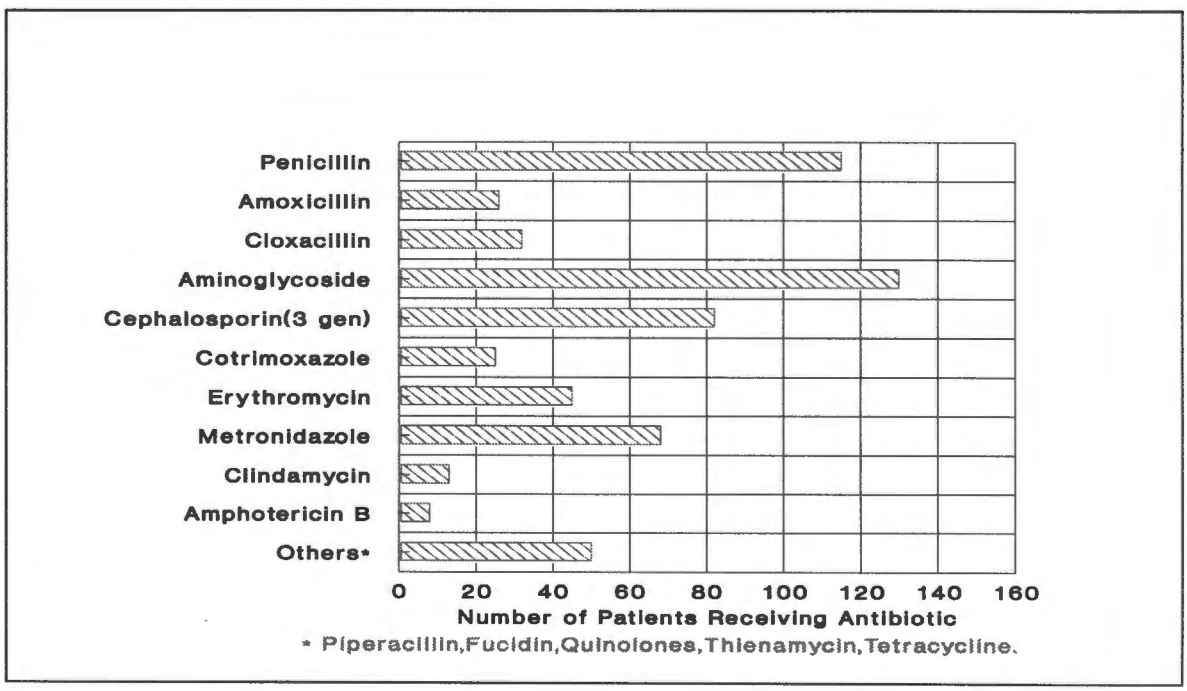
SPECIAL INVESTIGATIONS.

A number of special investigations were performed including fibreoptic bronchoscopy with bronchial brushing in 41 patients, transbronchial biopsy in 4 and open lung biopsy in one; 4 patients underwent blind bronchial brushing. Echo-cardiography was performed in 10, ERNA scanning in 6, abdominal ultrasound in 10, radio isotope body scan in 7, lumbar puncture in 5, and computerised tomographic scanning both chest or abdomen in 16.

THERAPY

Antibiotic therapy was instituted as soon as possible usually starting in the emergency unit and if the selection was considered suitable it was continued in the ICU, and antibiotics were changed when so directed by microbiology, or if the patient was considered to have failed to respond within 48 hours. Antibiotics were discontinued after 24 hours of resolution of the signs of infection. The antibiotics used in this group of patients are shown in figure 17.

Figure 17: Antibiotic prescription in severe CAP



All patients required ventilatory support with 160 patients requiring intubation and mechanical ventilation, 22 CPAP by face mask, and 14 oxygen only. The indications for intubation were for respiratory failure in 155 patients and retention of secretions in 5, and tracheostomy was done for prolonged ventilation in 50 patients, secretion retention in 4 and to assist weaning in 3.

Different methods of ventilatory support, severity of illness, duration of support, complications, and mortality, are shown in table 20. Continuous positive pressure ventilation was used in 140 patients, and in 16 patients more than 15 cm H_2O PEEP was required. 20 patients were ventilated without PEEP because of associated air trapping due to obstructive lung disease. Four patients three of whom survived were intubated with double lumen endotracheal tubes (Broncho-Cath, National Catheter Corp., Mallinkrodt, Argyle, New York.), and ventilated using independent lung ventilation. Two of the survivors required pulmonary surgery.

Table 20: Ventilatory therapy, complications, and outcome.

	No (Pts.)	**Duration ICU(days)**	**Vent. (days)**	**Complics (total n.)**	**Mort**
Mask O_2	14	4.14±1.46	-	3	0
Mask CPAP	22	5.0±2.65	-	4	1*
IPPV	20	6.9±6.73	4.55±5.2	11	5 (25%)
CPPV	140	14.06±12.5	10.85± 10.07	223	44 (31.45%)

± = *S.D.*

** Patient died of a pulmonary embolus.*

Complications of the ventilator therapy occurred in 33 patients and the different complications are given in table 21.

Table 21: Complications occurring in the ICU related to ventilation .

	No. of Complications
Pulmonary Infection	8
Barotrauma	13
Accidental Extubation	3
Ventilator Failure*	2
Pulmonary Haemoptysis	4
Tracheal Bleed	2
Blocked ETT	2
CVA during CPPV	1

** Total numbers of hours of ventilation = 37608 hours.*

Forty-four patients were admitted with acute renal failure and a further 15 patients developed renal failure of whom 40 were supported with dialysis; 25 patients by haemodialysis alone, 9 by haemodialysis and peritoneal dialysis, and 6 with peritoneal dialysis, of whom 28 (70%) survived.

All patients received enteral feeding usually with either ensure or osmolite via a fine-bore nasogastric tube if the gastro-intestinal function allowed, however in 32 it was necessary to institute TPN.

Additional drug therapy included adrenaline (32 patients), and dobutamine (29 patients) for inotropic support; dopamine in a dose of <10 micro gm/kg/min for renal protection (70 patients); H2 antagonists for active treatment or prophylaxis of pre-existing ulcer disease or active gastro-intestinal bleeding (25 patients). Sedatives

usually diazepam (127 patients), fentanyl (31 patients), morphine (36 patients), and non-depolarising muscle relaxants used intermittently (33 patients).

COMPLICATIONS

The complications that occurred in these patients are shown in table 22. There were 100 patients who had no complications, 42 with one complication and 54 with two or more complications.

Table 22: Complications occurring in the ICU

	No of patients
Gastrointestinal Bleeding	17
Respiratory Infection	12
Septicaemia	8
Urinary Tract Infection	8
IV sepsis	9
Cardiac Failure	10
Arrhythmia	11
Renal Failure	16
DIC	16
Hepatic Failure	6
Diarrhoea (enteral feeds)	6
DVT	4
Skin Reaction	8
Delirium Tremens	8

MORTALITY

There were 50 deaths (25.5% mortality), with the mean time to death being 7.62 (<1 - 35) days after admission. with the time of deaths shown in figure 18. There were 15 deaths in 58 bacteraemic patients and 35 deaths in 103 non-bacteraemic patients which was not significantly different. X^2 p = 0.915)

The majority of deaths were sepsis related and the cause of death as assessed clinically are shown in table 23.

Figure 18: Relationship of time of admission to death

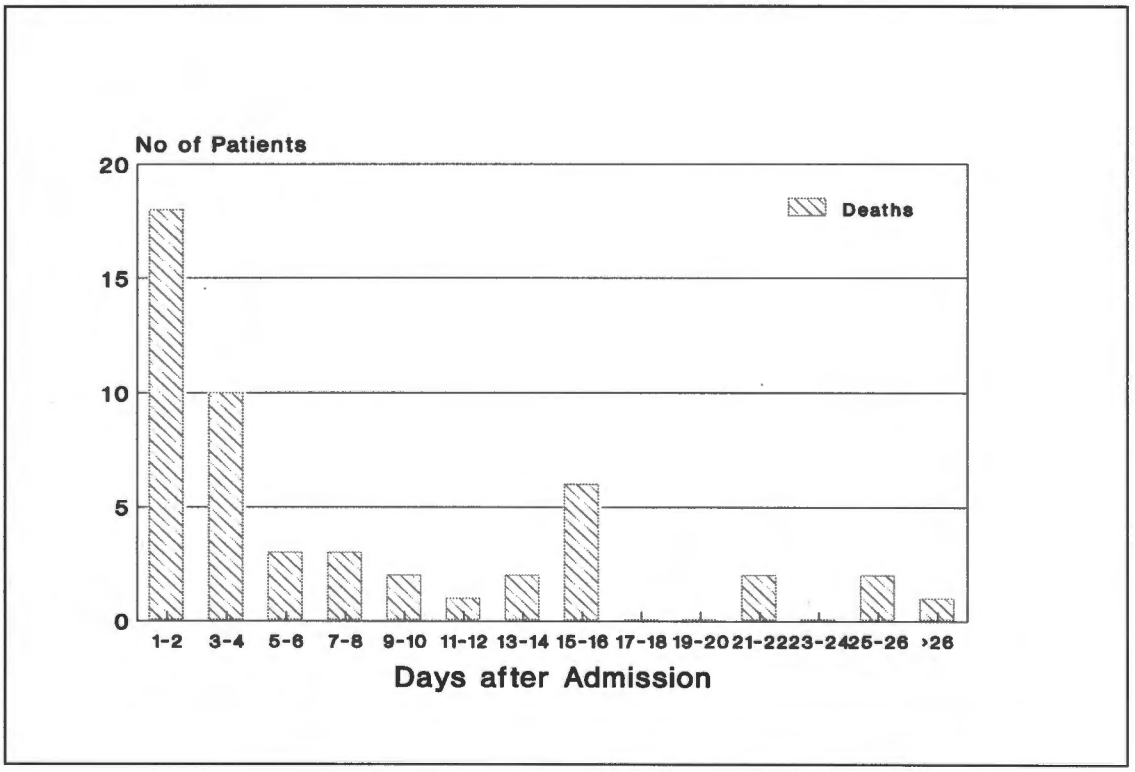


Table 23: Clinically assessed cause of death.

	No. of Patients
Septicaemia	14
Multiple Organ Failure	15
Hypoxaemia	12
Pulmonary Embolus	1
Cardiac	4
Neurological Damage	4

DISCUSSION.

The type of pathogens leading to severe disease differ significantly from those seen in less severe cases. The major difference is the increased number of Gram negative infections, particularly *K. pneumoniae* as well as an increase in *S. aureus* infections. A previous emergency room based study in our hospital showed the incidence of Gram negative pneumonia (excluding *H. influenzae*) to be less than 4% as compared with the present study with an incidence of 14%, and an incidence of *S. aureus* pneumonia of 2 and 9% respectively.[9] A similar low incidence of Gram negative and *S. aureus* infections is noted in a number of community based studies from other regions.[17,125]

This high incidence of Gram -ve infections 27 patients (14.%), with 44% mortality and *S. aureus* with a 35.7% mortality in these patients with respiratory failure requiring ventilatory support, suggests that these pathogens may produce a more severe form of disease. This is supported by the high mortality with these infections in this study and in other studies of *S. aureus* infections and by the high mortality in 17 patients with *Klebsiella* pneumonia previously reported.[104,129] Previous general

hospital based studies of primary pneumonia and studies from intensive care units have failed to recognise this important influence of etiologic agent on the severity of disease because of insufficient numbers of patients with these infections, or have not evaluated aetiology as a prognostic indicator.[2,17,20,125] The severity of disease may not necessarily be entirely dependant on the micro-organism as it may be a reflection of the predisposition of patients with co-morbid diseases to develop specific micro-organisms. This seems unlikely however as the APACHE scores of *Klebsiella* and *S. pneumoniae* infections are similar with very similar types of patients, and the low APACHE in *S. aureus* infections is largely related to the young age of the patients, yet the mortality is high.. A high incidence of *Legionella pneumophila* (30%) was seen in a previous ICU based study.[119] Our incidence of 3% was considered high when compared with the usual low incidence in our region.[9,117] Of interest, however, was that the mortality of this organism was low in both series in spite of requiring ICU admission, suggesting that although it causes a severe disease, appropriate therapy will result in a successful outcome.

It is of interest that in this group of diabetics the spectrum of causative organisms is similar to the other patients with severe pneumonia. One of the three patients with fungal infections occurred in a diabetic whereas the other two were in patients with COPD. Almost half the cases with *H. influenzae* infection as would be expected occurred in the patients with COPD.

The selection of antibiotics was appropriate in the majority of cases; there was however a tendency for excessive use of aminoglycosides and metronidazole prior to ICU admission, particularly in the less severe cases where a micro-organism known to sensitive to penicillin was present. An aminoglycoside was given in 130 patients whereas it could only be considered appropriate in only 27 patients with Gram negative and 9 with *S aureus* infections. It is questionable whether metronidazole is ever indicated as empirical therapy unless a patient has already failed to respond. In some cases there were considerable delays in the administration of the initial starting dose of antibiotic, and also in achieving early adequate serum levels because of

insufficient dosage particularly with aminoglycoside administration. In Gram negative pneumonia inadequate dosage has been shown to worsen outcome .[212] This failure of appropriate aminoglycoside therapy was in spite of a clearly defined antibiotic policy, and in an attempt to overcome this the recommendation that the starting dose should be double the calculated dose has been made. This approach is supported by recent evidence of a very much increased volume of distribution in critically ill patients.[213] Unexpected delay also occurred occasionally with staff waiting for specific time schedules before administering the starting dose. This was particularly relevant with drugs with more widely spaced dosage intervals and also with in hospital transfer, and this is of concern with new dosage schedules for aminoglycosides as well as with newer agents with long half-lives requiring widely spaced dosing intervals.[29]

Although a small number of patients were treated with face mask oxygen alone, the majority required PEEP either by CPAP mask in the milder cases, and CPPV in the more severe cases. Most patients received CPPV with a respiratory rate of in excess of 20 breaths/minute early on in the illness, which was effective in allowing comfortable ventilation in the majority of patients without having to use excessive sedation or muscle relaxation. To achieve this the pCO_2 was often between 3.5 and 4.5 kPa and this appears to have no detrimental effect on either oxygen delivery or cardiac function. The benefits of a co-operative wake patient who can be actively mobilised seems to far outweigh the benefit of normocarbia and the potential adverse depressant effects of deep sedation.[214] Sedative drugs were used sparingly and usually only to help facilitate patients who were critically hypoxaemic, or requiring excessively high ventilator pressures. There has been a trend to limit the level of PEEP and maintain oxygenation initially by a high FiO_2 and if insufficient improvement is seen, inverse ratio ventilation is applied. This is a global trend and appears effective as adequate oxygenation is invariably achieved.

The indications for intubation are unclear and no guidelines are yet widely accepted. Our practice is to encourage early intubation particularly when septic shock is present,

even if by blood gas criteria there is no absolute indication. We would recommend that patients are intubated if they are confused; are in respiratory failure and have either refractory hypoxaemia or hypercarbia; are unable to clear secretions; or are in shock. In a number of cases delay in referral, or intubation may have contributed to an adverse outcome. This was often also associated with a delay in adequate fluid resuscitation and inotropic support.

A number of agents that block various stages of the inflammatory cascade have been developed over the past decade and have shown promise. The use of anti-endotoxin immunoglobulin antibodies showed an improved outcome in severe sepsis, particularly if used prophylactically, however HIV which may be transmitted with these preparations has rendered them obsolete.[25,190] The recently developed human monoclonal antibody against endotoxin (HA-1A), despite initial encouraging reports has been shown to have little benefit[191] During this study period a number of patients were part of an international anti-TNF immunotherapy trial. The results are still being analysed but it was clear that more rapid accurate assessment of the patients by experienced medical staff, appropriate resuscitation, and early antibiotics seemed to hasten response and these agents may play an important role in the future. Other cytokine blockers may also have a protective effect and preliminary results will soon be available.[191,193]

Multiple organ failure proved to be the most frequent cause of death. This was either caused by the primary infective process, or nosocomial infection which proved to be the most common complication. Refractory hypoxaemia also occurred and contributed to death in a few cases. Gastro-intestinal bleeding occurred in 9% of patients and this complication was usually part of multiple organ failure, and was not seen more frequently following discontinuation of routine ulcer prophylaxis.

Earlier literature suggests that therapy may play a very small part in determining outcome from severe pneumonia as death occurred early within 24 hours of admission, and ICU management had thus far not influenced outcome whatsoever. Hook et al reported a mortality of 76% for bacteraemic pneumococcal pneumonia

requiring ICU admission.[99,215] Our results however, suggest that with modern intensive care the mortality of community-acquired pneumonia may be considerably lower, with mortality of less than 30% overall, and 35% for bacteraemic pneumonia. The cause of death and timing of deaths suggest that supportive therapy in ICU has played a real part in reducing early deaths, and that the cause of death is now largely due to multiple organ failure and not due to early respiratory failure or septic shock. It is however impossible to determine which aspects of therapy may have led to this reduced mortality.

Any further improvement in mortality will have to be directed at the rapid removal of infection and prevention of organ dysfunction. Complications of ICU treatment which may contribute to organ dysfunction such as secondary infection will also have to be recognised and prevented.

CHAPTER 11

FACTORS PREDICTING MORTALITY IN SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Introduction

Prediction in medicine and particularly in critical care, is one of the most important clinical attributes for patient care. With recent changes in medical practice not only are we now expected to be able to accurately quantify the risk of death or long term outcome of different diseases for decisions on patient's ICU therapy, but we are also expected to use shrinking medical resources where they will produce most benefit to society. As the cost of critical care contributes to more than 10% of hospital expenditure whilst benefiting only a small number of patients, and as most deaths now occur in this setting, it is not surprising that clinical predictions have become an important area of development in critical care. The APGAR and the Glasgow Coma Score are the forerunners of the "science" of outcome prediction, and they were followed by the therapeutic intervention score (TISS), the earliest general ICU severity scoring system which was developed by Cullen. This scoring system which measured medical and nursing intervention was soon superseded by methods that scored physiological parameters, and the APACHE (acute physiological and chronic health evaluation), followed shortly thereafter by APACHE II, [measures 11 physiological variables, age, Glasgow Coma Score and chronic health (appendix 2)] and SAPS, (simplified acute physiology score) that measures 14 readily available physiological variables have received wide validation, and are in general use.[208,216] More recently an APACHE 3 system has been developed as a commercial venture, and the exact methodology have not been made available for general scrutiny. This system is very expensive and requires sophisticated in-house computerised analysis For these reasons it has not yet received general acceptance although it does offer additional advantages as it evaluates and updates risk on a daily basis.[217]

Treatment decisions for a successful outcome in pneumonia, rely heavily on accurate assessment of the severity of the disease to determine antibiotic selection and the level of supportive and monitoring therapy necessary. There have been suggestions that the APACHE II may be a poor predictor of outcome in pneumonia,[20] however we have shown good correlation between the APACHE II score and mortality in a group of 90 patients with pneumonia.[123] A number of independent clinical features are recognised to predict the severity of pneumonia in a community and hospital population, some of which, in combination may predict a 16 to 20 fold increase in mortality (>1 of diastolic BP ≤ 60 mm Hg; respiratory rate ≥30 breaths/min; Urea > 7 mmol/l or confusion substituted for urea on admission). These clinical features while being fairly sensitive are not particularly specific and unfortunately fail to predict risk accurately in individuals.[17,22,172] A recent study that evaluated patients who failed outpatient treatment added a number of additional risk factors that need to be considered.[18] Patients with ARDS pose similar problems and once again the general scoring systems fail to give an accurate prediction of mortality particularly in individual patients.[123] This has led to the lung injury score proposed by Murray however this also needs further refining.[218,219] The assessment of the severity of pneumonia and risk factors that may predict a poor outcome have not been adequately evaluated with large groups of clearly defined patients with severe pneumonia requiring ICU admission. This study will attempt to determine factors that may define the severity of disease and evaluate previously used predictors of outcome.

Patients and Methods

All patients with community-acquired pneumonia admitted over the study period (January 1987 to December 1992) are included. The definitions for diagnosis and methods evaluation of severity of illness scores and data collection are described previously in chapter 8. In addition the clinical parameters thought to predict a poor outcome (age, confusion, tachypnoea, renal function, physiological variables for

APACHE II (see appendix 2 and 3), serum chemistry and haematology, as well as 3 parameters of the lung injury score [PaO_2/FiO_2 ratio, chest radiograph, and PEEP level (appendix 4)] were carefully documented at the time of ICU admission and stored on a D Base 4 or Epi Info data base.

The BTS and other rules previously reported to be useful in determining the severity of pneumonia were tested in this population to determine their sensitivity and specificity .[17] The young patients and those with low APACHE II scores who died unexpectedly were also evaluated separately to determine what factors were associated with to death.

Results

Severity of illness scoring systems.

The APACHE II score determined from the worst physiological abnormalities in the first 24 hours of ICU admission showed a significant difference between survivors (15.05 ± 6.27), and non-survivors (22.28 ±. 9.78 p = <0.001). The individual APACHE II scores and mortality are related in figure 19.

The APACHE II scores for total all ICU admissions from our unit over the study period are contrasted with those of patients with pneumonia.(figure 20.)

Figure 19: APACHE II severity of illness score related to mortality

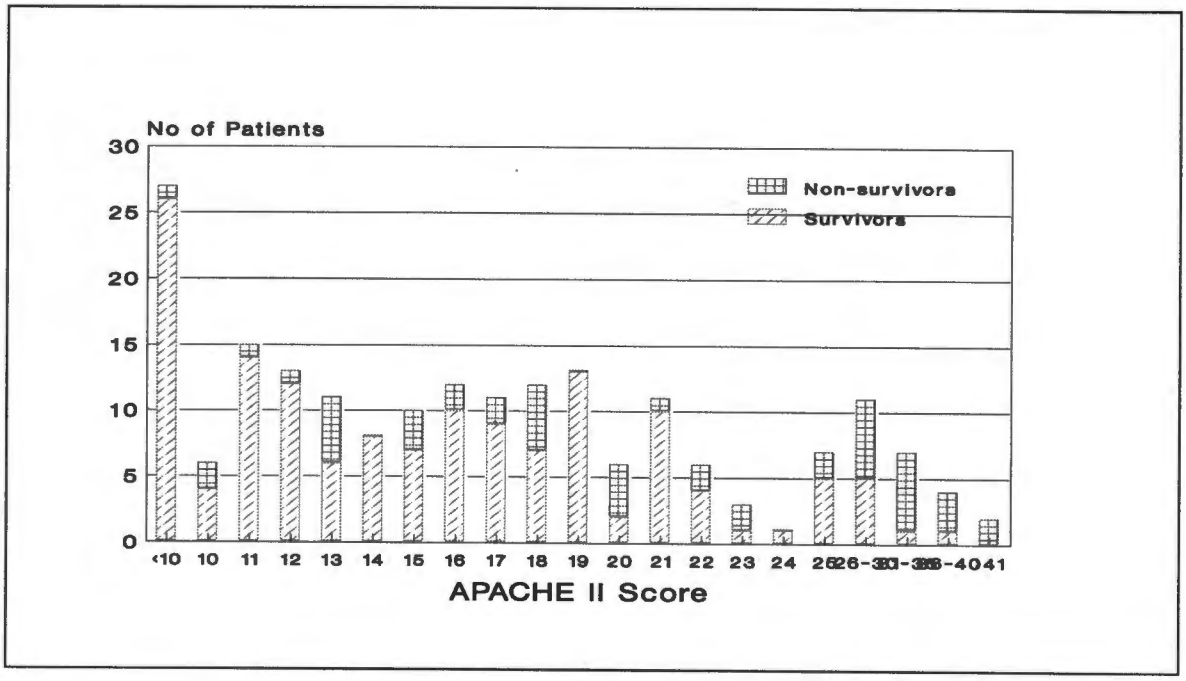
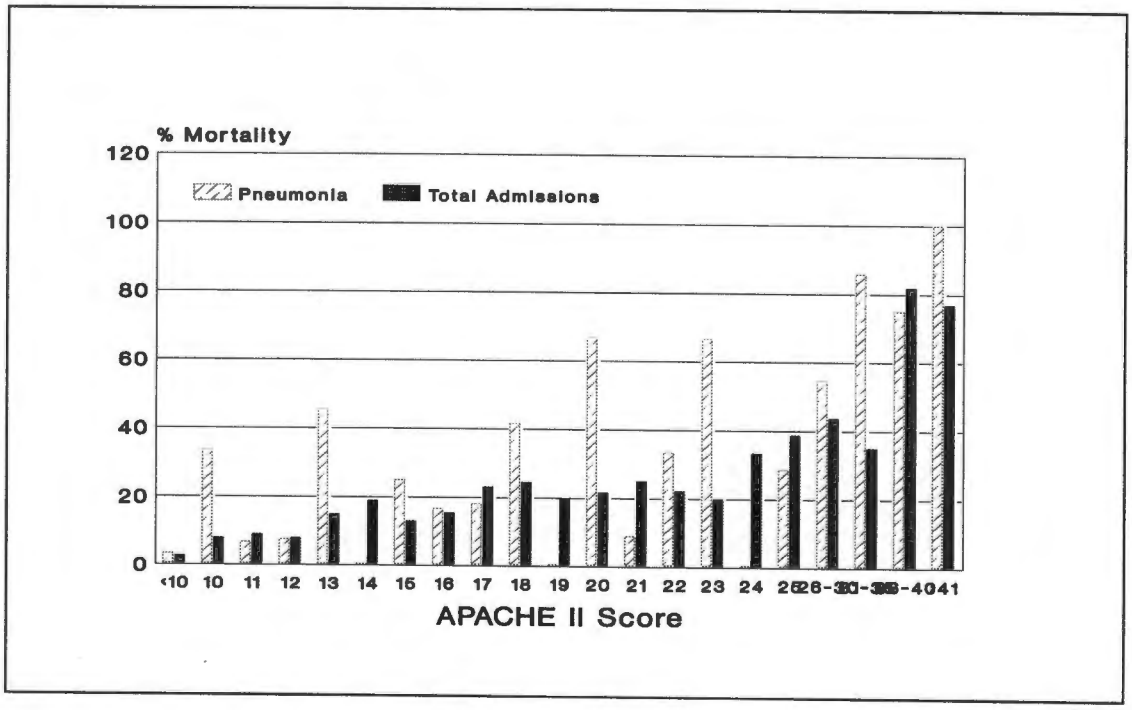


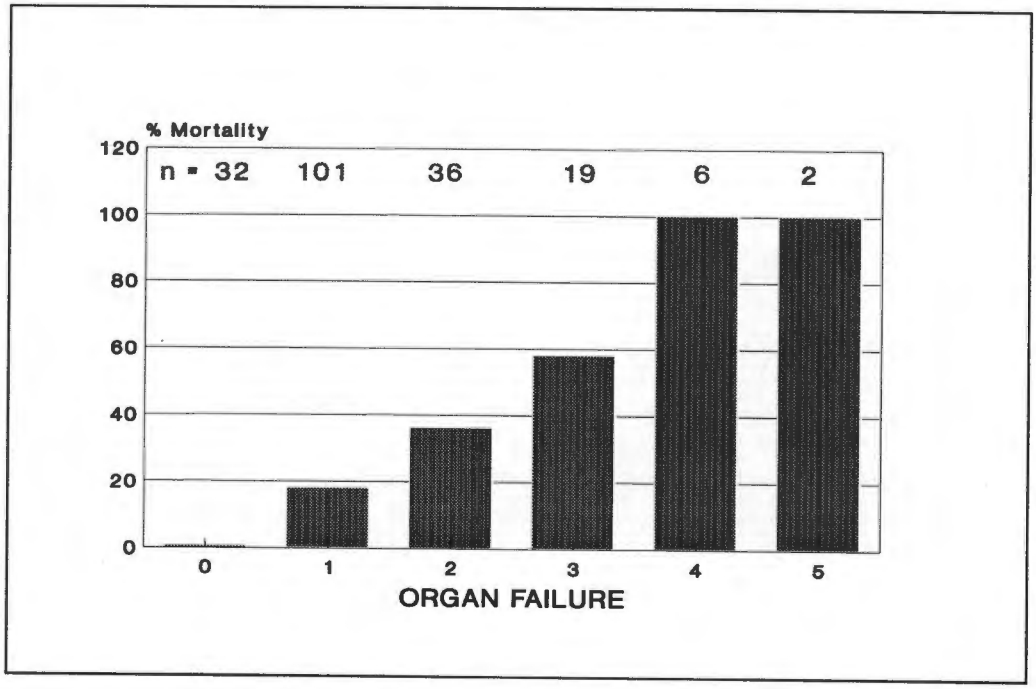
Figure 20: A comparison of APACHE II scores between pneumonia and all ICU admissions.



Organ Failure

The number of organs in failure on day one in survivors was 1.05 ± 0.77, and non-survivors 2.22 ± 1.18 (P= <.0001). The number of organs in failure on day one are related to mortality in figure 21.

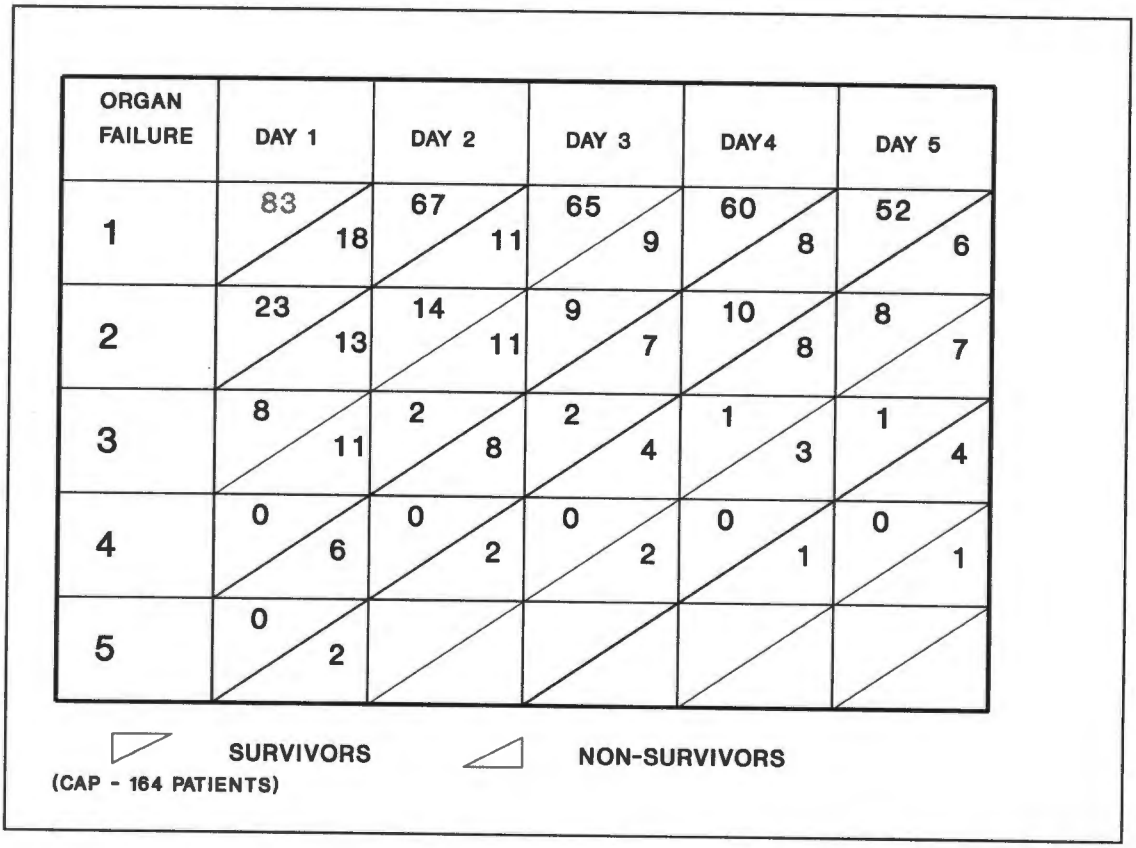
Figure 21: Organ failure on day one related to mortality



Organ failure was assessed daily for the first five days of ICU admission in patients admitted from 1988. The overall relationship of organ failure to mortality from day 1 to 5 is shown in figure 22.

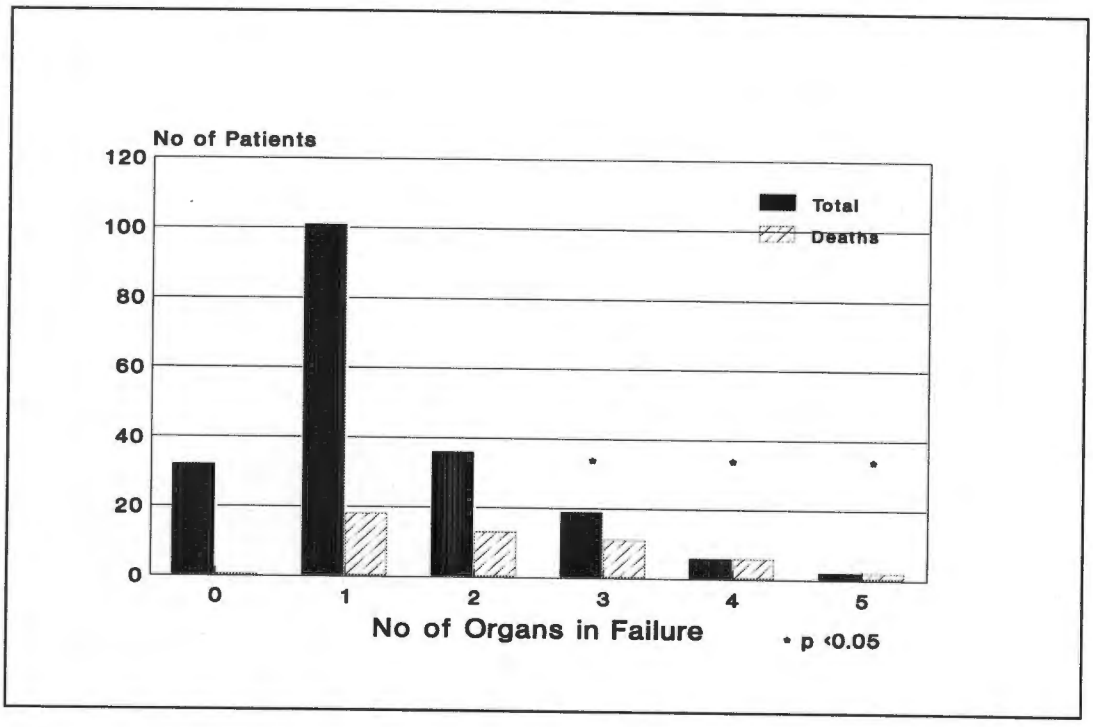
Figure 22: Organ failure on day 1 to 5 related to outcome

(164 Patients)



The relationship of organ failure in survivors and non-survivors is shown in figure 23 which shows a significant increase in mortality with 3 or more organ failure on admission.

Figure 23: Organ failure in survivors and non-survivors with CAP.

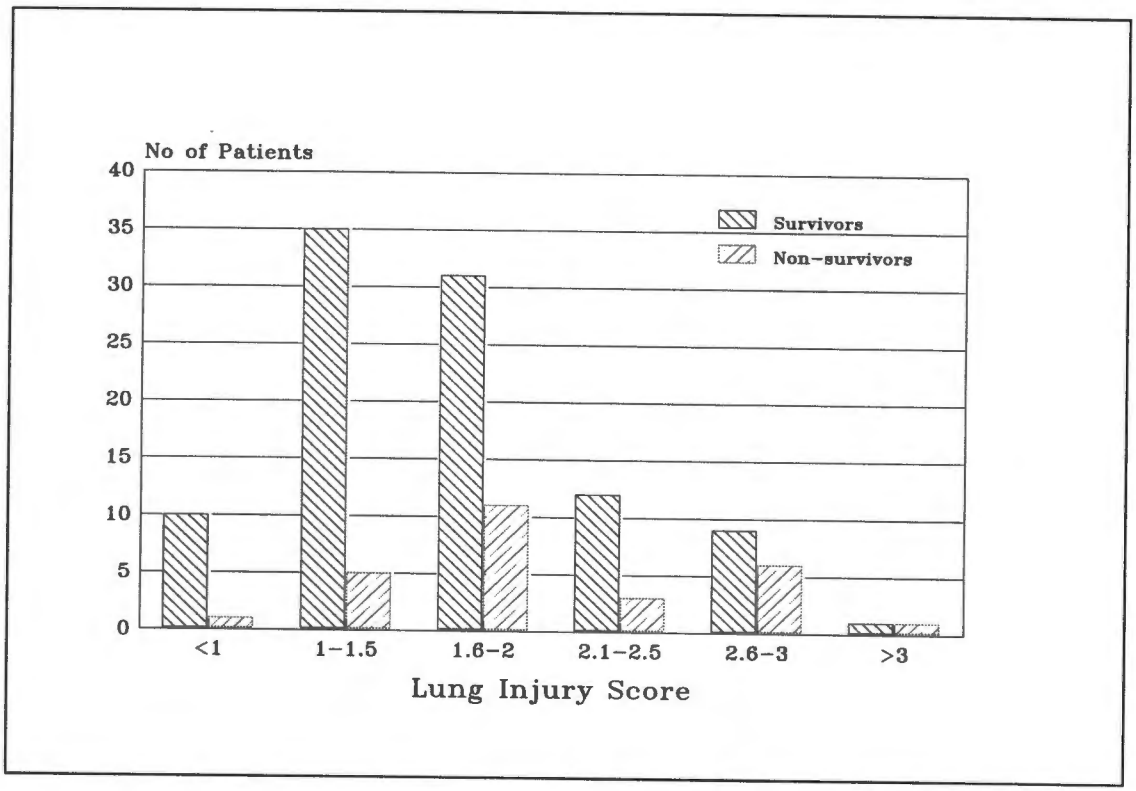


* X^2 p= <0.05

Lung Injury Score.

The lung injury score proposed by Murray was retrospectively applied to these patients. A score of 0 to 4 given for extent of radiological involvement of the lung, PaO_2/FiO_2, compliance and PEEP with the total divided by the number of parameters scored.(see appendix 4) There was a significant difference in lung injury score between 98 survivors, mean score of 1.59 +-. 0.64, and in 27 non-survivors 1.97 +- 0.64 (p = 0.007).

Figure 24 Lung injury score related to mortality



Clinical Features Predicting Outcome.

A number of clinical features have become recognised as predictors of severe pneumonia and these together with serum chemistry and haematology, are shown in survivors and non-survivors.(Table 24)

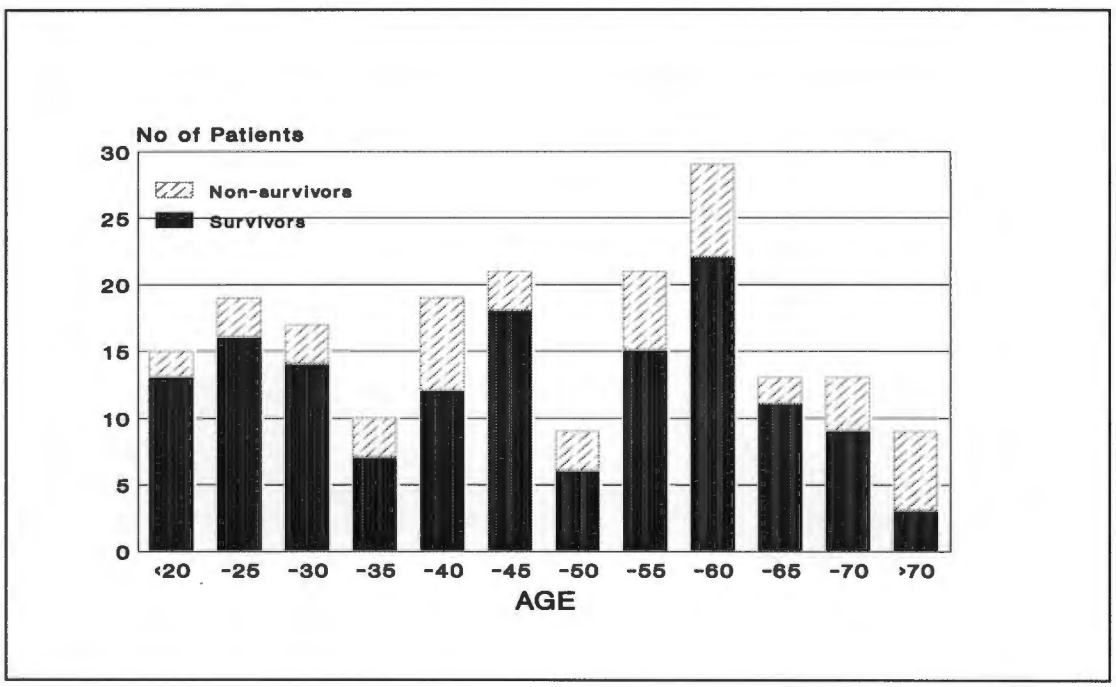
Table 24: Clinical features related to mortality

	n	Survivors	n	Non-survivors	p =
Age	143	42.9 ± 16.8	47	48.7 ± 18	0.045
Temp.^{o}C	144	37.6 ± 1.24	47	37.2 ± 1.7	0.142
Resp. Rate	140	30.3 ± 12.68	43	33.3 ± 11.1	0.164
Confused	117	17	33	10	0.068
Shock (SBP <80 mm Hg	122	20	39	23	<.001
WCC ml/l	143	18975 ± 32896	42	12044 ± 12376	0.04
Platelets ml/l	143	227503±120215	42	193366±172958	0.24
DIC*	108	2	26	5	0.002
Na^{+} m mol/l	145	136.6 ± 8.3	46	136 ± 7.13	0.66
K^{+} m mol/l	144	3.9 ± .71	43	4.11 ± 1.2	0.282
PO_4^{-} m mol/l	124	1.01 ± .6	34	1.63 ± 1.34	0.018
Urea m mol/l	145	10.86 ± 13.2	46	16.19 ± 14	0.019
Cr^{-} micro mol/l	144	183 ± 538	46	247.4 ± 220.9	0.248
ALT units/l	125	52.89 ± 71.86	37	33.46 ± 30.23	0.018
AST units/l	129	84.02 ± 96.25	37	67.97 ± 44.88	0.16
LDH units/l	121	586.5 ± 850.3	35	606.2 ± 431	0.85
Alk. Phos. IU/l	129	117.1 ± 84.3	34	113.5 ± 87.4	0.83
Bilirubin Conj. micro mol/l	131	8.51 ± 12.5	39	14 ± 16.36	0.063
Bilirubin Total micro mol/l	136	16.6 ± 14.5	39	21.5 ± 21	0.18
S albumin g/l	136	28.8 ± 6.5	39	26.2 ± 5.9	0.026

* DIC = diffuse intravascular coagulopathy [platelets <80,000 cells/ml, prolonged partial thromboplastin time (PTT), fibrinogen degredation products(FDPs)]

Age both the very young and very old have long been considered major risk factors in pneumonia however in our population this has not been adequately investigated. The mean age difference only just achieved significance (p = 0.046), but mortality was significantly increased in the 22 patients who were over 65 years of age (X^2 p= 0.005). The relationship between age and mortality is shown in the following figure.

Figure 25: Correlation between age and mortality in CAP.



Urea and ALT were significantly elevated whereas albumin and the WCC were significantly lower in the non-survivors.(see table 24) Significantly more patients who died had a DIC. The higher PO_4 in non survivors is difficult to explain. The incidence of renal failure in those with a PO_4 of >1.5 (7/32 patients) was similar to those with lower PO_4 (44/159) but the level of urea was higher in the high PO_4 group. It was possible to test 2 modified predictive BTS rules (Rule 1; 2 of hypotension i.e. SBP <80 mm Hg, renal failure i.e. urea > 7 mmol/l or respiratory rate of >29 breaths/min; Rule 2 BTS rule 1 with confusion instead of urea to make it immediately

applicable) in 193 patients .(table 25). A systolic BP was used as it can be more accurately defined by multiple observers and has been used by the severe sepsis consensus committee.[220]

Figure 26: Serum albumin, ALT, PO_4 and WCC in survivors and deaths.

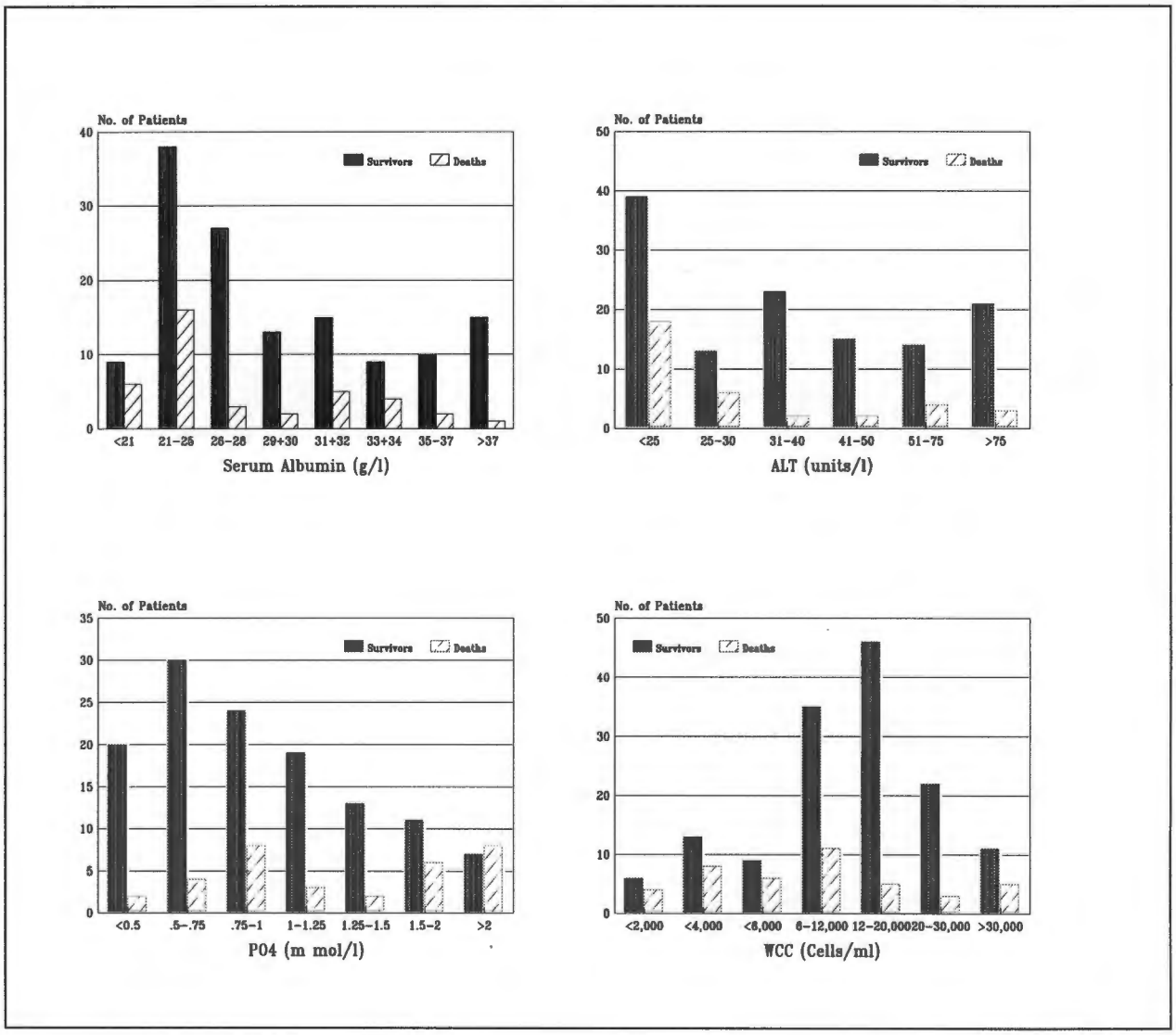


Table 25: Rules and scoring systems predictive of outcome

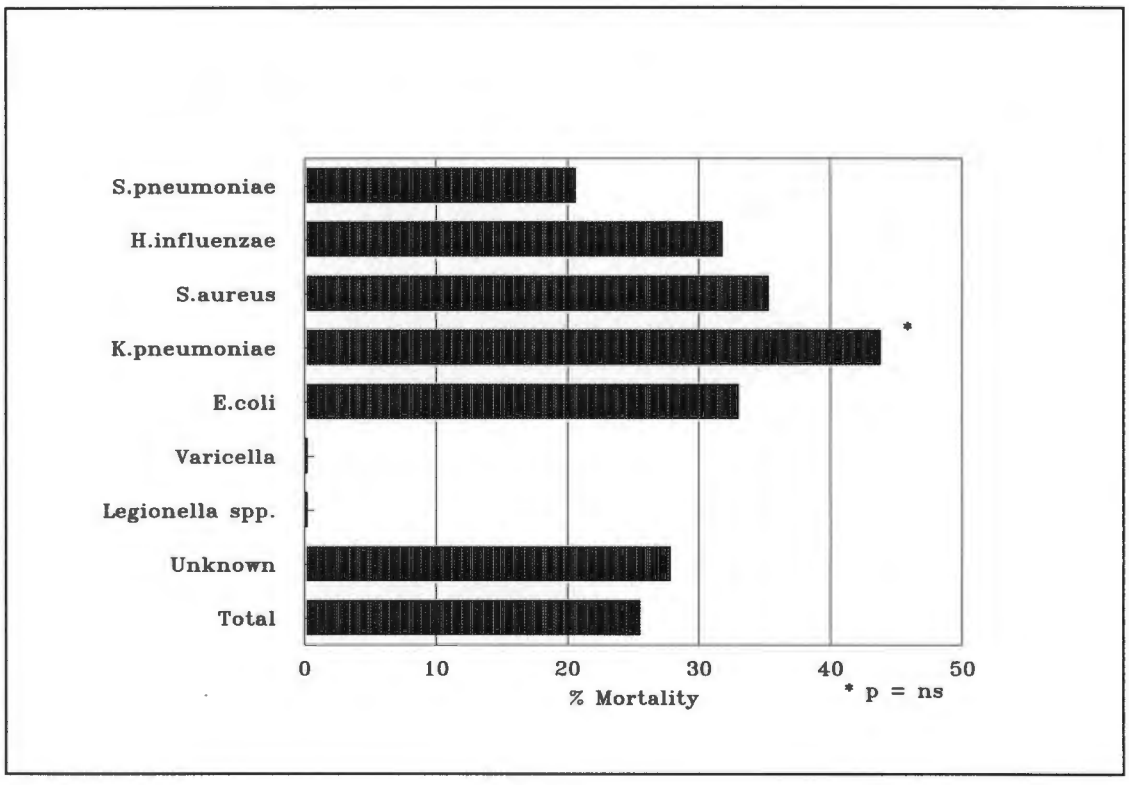
	Positive predictive value %	Overall accuracy %	Sensitivity %	Specificity %	Youden's Index %	Relative Risk %
Rule 1	42	69	65	70	35	2.5
Rule 2	41	68	71	67	38	2.4
Shock	53	77	48	86	34	3.2
APACHE II >20	45	73	46	81	27	2.5
MOSF>2	70	80	38	95	33	3.8
Lung Inj. >2	31	69	21	85	6	1.3

Positive predictive value = no. with positive function who died / no. with positive function. Overall accuracy = no. outcomes correctly identified / no tested with function. Sensitivity = no. with positive function who died / no. tested who died. Specificity = no with negative function who survived / no. tested who survived. Youden's index = specificity + sensitivity - 1.Relative risk = proportion who died with positive function / proportion who died with negative function.

Aetiology Related to Severity.

The mortality for the different causes of pneumonia is shown in figure 27.

Figure 27: Mortality related to CAP of different aetiologies



Surprisingly a number of deaths occurred in the younger age groups with 7 deaths occurring in 43 patients (mortality 16.3%) who were 30 years of age or younger and this number compared with 43 deaths in 153 patients aged 31 years or older showed no significant difference in mortality ($p = 0.17$). The demographic and clinical features of these patients are shown in table 26.

Table 26: Demographic and clinical features of younger patients

	SURVIVORS	NON-SURVIVORS
No of patients	43	8
Black	18	4
White	2	2
Mixed	23	2
Male:Female	23:20	3:5
APACHE II*	11.79 +- 51.6	15.13 +- 8.08
Organ Failure	0.84 +- 0.65	1.88 +- 1.13
Renal Failure	1	1
Septic Shock	2	3
Bacteraemia	14	3
IPPV	30	8
Duration IPPV	10.1 +- 8.3	8.63 +- 7.01
Duration ICU	11.8 +- 11.04	8.88 +- 7.34
Complications**	45 n=19	14 n=4

** T test p=0.69 ** n = number of patients*

Deaths were due to brain damage following cardiac arrest in 1, respiratory failure 1, shock 1, multiple organ failure in 5. In 3 deaths the patients had severe underlying disease including a possible collagen vascular disease, a subarachnoid haemorrhage and a patient with Prader-Willi syndrome. In 2 of the patients there was over a weeks delay in seeking medical attention.

Table 27: Organisms causing pneumonia in younger patients

Micro-organism	No.(%)	Mort.(%)
S. pneumoniae	17 (39.5)	2 (12)
S. aureus	6 (13.9)	2 (33)
H. influenzae	6 (14.0)	
K. pneumoniae	1(2.3)	1
L. pneumophila	1 (2.3)	-
Virus	6 (14)	-
Other	2 (4.6)	-
Unknown	8 (18.6)	2 (25)
Candida spp	1	-
TB	1 (2.3)	-
Dual infection	7 (16.3)	3 (43)

There were 17 patients who were bacteraemic in this group compared with 41 in the older patients but this difference did not achieve significance ($p = 0.15$), and bacteraemia occurred equally in those who survive or died. There was however significantly more infections caused by *S. aureus* ($p = 0.02$), and all the patients with *Varicella* pneumonia occurred in this group.

The patients with APACHE II scores of 12 or less points, who surprisingly died, are compared with those who survived in table 28.

Table 28: Demographic and clinical features of patients with a low APACHE II score (12 or less)

	SURVIVORS	NON-SURVIVORS
No of patients	56	5
Age	36.52 +- 15.64	40.40 +- 19.09
Race		
Black	20	4
White	5	1
Mixed	31	0
Male:Female	33:23	1:4
APACHE II	8.95 +- 3.06	10.2 +- 1.48
Organ Failure	0.75 +- 0.61	1.2 +- 0.45
Renal Failure	6	0
Shock	1	0
Bacteraemia	12 (21.4%)	1 (20%)
IPPV	31	5
PEEP cm H_2O	6.5 +- 3.8	10.8 +- 5.07
Duration IPPV	9.76 +- 12.63	9.2 +- 10.99
Duration ICU	10.25 +- 12.21	8.4 +- 8.71
Complications*	33 (n=17)	6 (n=4)

** Number of complications. n= number of patients with complications.*

Deaths were due to multiple organ failure (MOSF) in all cases other than one who died of shock.

The micro-organisms causing pneumonia in these patients with a low APACHE score with related mortality are shown in table 29.

Table 29: Organisms causing pneumonia in patients with a low APACHE II score (12 or less)

Micro-organism	No.(%)	Mort.(%)	% of Deaths
S. pneumoniae	15 (26.8%)	2 (13%)	40
S. aureus	8 (14.3%)	1 (13%)	20
H. influenzae	5 (9%)	1 (20%)	20
K. pneumoniae	2 (3.6%)	-	
L. pneumophila	1 (1.8%)	-	
Mycoplasma	1 (1.8%)	-	
Virus	6 (10.7%)	-	
Other	2 (3.6%)	-	
Unknown	19 (33.9%)	1 (20%)	20
Candida spp.	1	1	20
Dual infection	4 (7.2%)	1 (25%)	20

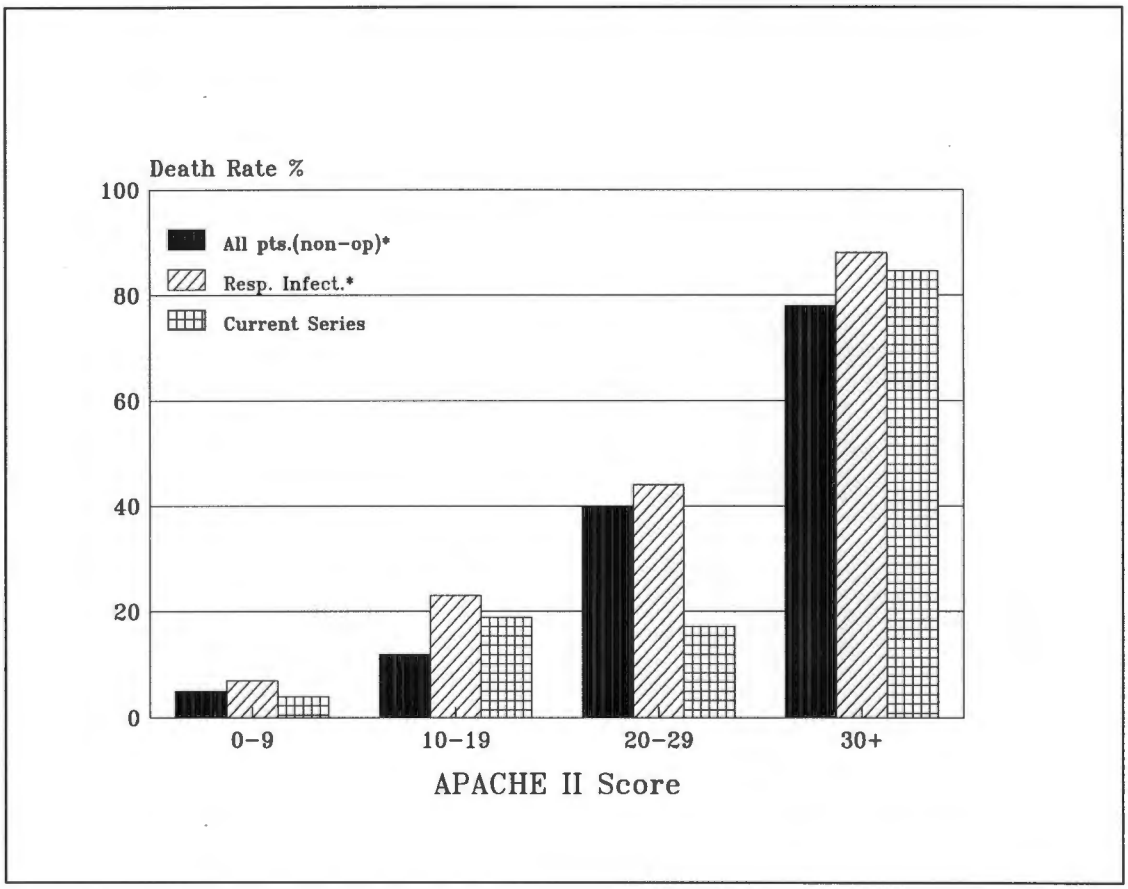
There were 13 patients who were bacteraemic in this group. The one patient with dual infection who died had *S. pneumoniae* and *H. influenzae* identified.

Discussion

Pneumonia is well known to be one of the diseases where outcome prediction is very inaccurate and conventional scoring systems such as the APACHE II predict mortality poorly, and these patients usually have a higher than predicted mortality[123,208] The unpredictability of the APACHE II score in individual patients and the increased mortality in this study is compared with the data for respiratory infections from Knaus et al. (see figure 28)[208] The mortality in our series of patients is slightly lower than those with respiratory infections and higher than the whole group that were used by Knaus to validate the system. Individual prediction however was unreliable with the

group with scores of 20 to 29 being lower than the group with scores of 10 to 19 in our patients.

Figure 28: A comparison of APACHE II scores from the validation cohort of non-operative cases, respiratory infection cases, and CAP.



In this cohort of carefully selected patients with severe CAP the poor predictability of APACHE II is again seen although the patients who died had a significantly higher APACHE II score as a group but a number of patients with low scores died.

It is possible that review of this group could shed some light on the failure of APACHE II to predict these deaths. There didn't appear to be any striking differences between the patients with low APACHE II scores who survived and those who died. Three of the five patients who died were admitted from the hospital ward or another hospital, with treatment having been started, which may have stabilised the patients giving a false low APACHE II score. In the whole group however only 67 (35%) had

been admitted directly from the emergency unit thereby making it unlikely that the low scores in these patients who died was only due to prior stabilisation. Another explanation may be that there was failure to respond to initial therapy. There were also a number of young people who died and here again it was difficult to identify any specific causes other than an increased incidence of *S. aureus* which accounted for some of the deaths, but also pre-existing associated disease seemed to be an important factor leading to death in patients who were both young and who had low APACHE II scores.

The organ failure score was the most reliable predictor of death and there was a significant difference in organ failure scores between those who survived and died. If assessed over the first few days of admission no patients with 4 or more organ failure on day 1 (8 patients) survived and all patients with 4 organ failure on subsequent days died. Applying an organ failure score of more than 2 organ failure on day one had a predictive value for death of 70% with an overall accuracy of 80% but it was only 38% specific.

The modified discriminate rules proposed by the BTS were also poor predictors of survival with rule 1 having a sensitivity of 65% and overall accuracy of 69%. This rule was modified by using a systolic blood pressure of 80 mm Hg rather than the diastolic pressure which I believe is a more objective measure and therefore more reliable particularly in sepsis where systolic pressures are currently used to define septic shock.[220]

The lung injury score also proved to be a poor predictor of individual outcome although there was a significantly higher in those who died no score predicted individual mortality.

Few clinical parameters only proved to be predictors of death on univariate analysis at a low level of significance and these included the presence of shock, a DIC, age, a low serum albumin, WCC and ALT and a high phosphate and urea. The high PO_4 were not all associated with renal failure and is difficult to explain but has been previously identified.[32] None of these parameters were highly discriminative and no

combinations proved of value as discriminative rules to predict outcome.(see table 28) As only those parameters that may on clinical grounds have been predicted to be important, were analysed statistically no correction for multiple comparisons was considered necessary. If the Bonferroni correction is applied only the presence of shock or a DIC retain any significance.

This high incidence of Gram -ve infections (27 patients, 14.3%) with 44% mortality and *S. aureus* with a 35% mortality in this group of patients with severe pneumonia in respiratory failure, requiring ventilatory support, suggests that these pathogens may produce a more severe form of disease. This is supported by high mortality with these infections in this study which surprisingly is not statistically significant in this selected group of patients. In other community based studies of *S. aureus* infections and in 17 patients with *Klebsiella* pneumonia previously reported a significant increase in mortality was found.[129] Previous general hospital based studies of primary pneumonia and studies from intensive care units have failed to recognise this important influence of etiologic agent on the severity of disease because of insufficient numbers of patients with these infections, or have not evaluated aetiology as a prognostic indicator.[2,17,20,32,125] The importance of *S. aureus*, Gram negative micro-organisms and *L. pneumophila* as determinants of CAP requiring hospitalisation and also ICU care have recently been described.[1,18] Infections with these agents with a high mortality should alert the clinician to the need for early ICU admission with appropriate antibiotic therapy.

CHAPTER 12

DIAGNOSIS OF SEVERE PNEUMONIA IN PATIENTS ADMITTED TO ICU.

Introduction

Cost effective antibiotic treatment of pneumonia relies on the accurate diagnosis of the causative organism as empirical therapy is invariably more expensive as a broad spectrum of agents need to be covered. Pivotal to the antibiotic selection is a knowledge of the factors that may influence the spectrum of infecting agents and the accuracy of diagnosis using routine microbiological evaluation. Of more importance is whether these principles apply in the intensive care setting, where the spectrum of causative pathogens may differ significantly and where the more severe patients gravitate. This study evaluates the efficacy of routine bacteriological methods in the diagnosis of severe pneumonia requiring ICU admission. This chapter is adapted from a paper published in Chest.[1] (Potgieter PD, Hammond JMJ. Etiology and Diagnosis of Pneumonia Requiring ICU Admission. Chest 1992; 101:199-203.) It is included as part of this thesis as the microbiological investigations were done in much greater detail than in the rest of the thesis, and as such can contribute to our understanding of the value of different diagnostic techniques.

Patients and Methods

All patients admitted to the respiratory intensive care unit (RICU) from January 1987 to December 1989 were included in the study. The diagnosis of pneumonia was made on clinical grounds including pyrexia, cough and purulent sputum, crackles and bronchial breathing, an increased white cell count or a left shift in the morphology of the leukocytes, and an infiltrate on the chest radiograph. Patients with tuberculosis

(18 patients) and those with eosinophilic pneumonia (2 patients) and patients in whom the subsequent course excluded a pneumonic illness were not included. No specific criteria for admission to the ICU existed other than the clinical assessment of a need for intensive care treatment and this usually included an inability to clear bronchial secretions, confusion and respiratory failure necessitating either continuous positive airway pressure (CPAP) by face mask or intermittent positive pressure ventilation (IPPV).

The pneumonia was classified as primary pneumonia, i.e. infection which occurred in the community and included patients with associated diseases such as diabetes and chronic obstructive pulmonary disease; as nosocomial pneumonia, i.e. a pneumonia developing 48 hours after the patients admission to hospital or a pneumonia in a patient who had been hospitalised within the previous four weeks; immunocompromised pneumonia included patients with major host defence abnormalities including immunosuppressive drugs, irresectable carcinoma haematological malignancies and collagen vascular disorders, of patients requiring high dose steroid therapy (>40 mg prednisone daily); aspiration pneumonia was diagnosed when there was a clear episode of aspiration or unconsciousness. The latter 2 types were divided into community-acquired or nosocomial. The etiologic diagnosis was made on microscopy and culture of sputum, or tracheal aspirate taken immediately after intubation, blood culture (Bactec system) or serology. Sputum specimens were examined by a microbiologist and were only considered diagnostic if a predominant organism was present on Gram's stain in the presence of numerous pus cells without excessive epithelial cells, and if a respiratory pathogen was cultured in significant growth. Antibiotic sensitivity was tested using routine Joan Stokes' methods, and anaerobic culture was only performed on bronchoscopy specimens. If a patient failed to respond after 48 to 72 hours, or initially in immunocompromised patients, a fibreoptic bronchoscopy was performed and special sheath brush (PSB) specimens taken. A segmental lavage and a transbronchial biopsy was performed if oxygenation permitted. Open lung biopsy was done in two patients. Serology was not

performed routinely, but done only if no pathogen could be isolated, or if the patient failed to respond, or if the clinical presentation suggested an atypical pneumonia. A fourfold rise in antibody titre on paired samples of sera was considered diagnostic. *Chlamydia* and viral serology was also not routinely tested. The patients anthropometric data, severity of illness (APACHE II), ventilatory therapy, and course in hospital was documented and in cases that died the clinical cause of death determined and autopsies were performed where possible.

Results

1171 patients were admitted to the RICU from 1 January 1987 to 31 December 1989, of whom 178 were diagnosed as having acute pneumonia and admitted to the study. 157 (88%) needed IPPV.

Table 30: Demographic features, ventilatory therapy, and outcome.

Classification	**Primary**	**Immunocomp.**	**Aspiration**	**Nosocomial**
	n = 95	n = 24	n = 28	n = 31
Age (range)	46.7 (13-84)	41.3 (12-73)	41.54 (15-79)	44.32 (20-66)
Sex M:F	61:34	11:13	27:1	18:13
Race White	12	10	5	15
Black	30	7	7	10
Mixed	53	7	16	6
APACHE II	18.4 (1-46)	19.17 (9-32)	14.21 (1-28)	14.03 (2-37)
Tracheostomy	39	2	15	13
ETT	47	16	9	16
IPPV (%)	86 (91)	18 (75)	24 (86)	29 (94)
CPAP	5	3	2	1
IPPV (range)	10.45 (1-46)	_8.67 (1-42)	11.68 (1-68)	16.07 (1-107)
ICU Stay	13.44 (1-68)	_9.46 (1-43)	14.46 (1-77)	22.61 (1-165)
Mortality (%)	**28 (29)**	**12 (50)**	**4 (14)**	**8 (26)**

These included 95 patients with primary pneumonia; 31 with nosocomial pneumonia; 24 immunocompromised patients and 28 following aspiration pneumonia. The incidence, demographic data and clinical details in the different types of pneumonia are shown in table 30.

The aetiology of this group of patients made by all diagnostic methods is shown in table 31. .

Table 31: Aetiology of pneumonia.

	Primary	**Nosoc**	**Asp**	**Immunocomp**
No. of patients	95	31	28	24
Isolate	**n (%)**	**n (%)**	**n (%)**	**n (%)**
S. pneumonia	31 (32.6)	8 (25.8)	6 (21.4)	5 (0.8)
H. influenzae	12 (12.6)	3 (9.7)	4 (14.3)	2
S. aureus	7 (7.4)	7 (22.6)	4	3
K. pneumoniae	10 (10.5)	1	4	2
E. coli	2	1	3	0
Pseudomonas spp.	1	1	2	0
Mycoplasma spp.	1	0	0	0
Legionella spp.	5	0	0	0
Viruses	1	0	0	2
Fungal	2	0	0	1
Other Gram +ve	1	2	1	0
Unknown	24 (25)	16 (51.6)	10 (35.7)	8 (33.3)
Other pathogens	2	0	0	2
Multiple	11	3	8	3

All isolates of *S. pneumoniae* were penicillin-sensitive and one *H. influenzae* strain was resistant to ampicillin. One cloxacillin resistant *S. aureus* was cultured from the community, whereas 29% of those involved in nosocomial infections were cloxacillin-resistant

An aetiologic diagnosis was made in 118 (70.1%) of the 178 patients by culture of sputum and or tracheal aspirate; 44 (25%) of 178 patients by positive blood culture; 6 (15%) of 40 patients by serology; 7 of 35 by fibreoptic bronchoscopy and both patients who had open lung biopsies had a positive diagnosis made. Fibreoptic bronchoscopy was performed in 24 patients with primary pneumonia in whom no diagnosis had been made and who failed to respond to treatment or who had failed to respond despite appropriate treatment. A positive diagnosis was made in 3 patients with bronchial brushings; two patients underwent transbronchial biopsy and an incorrect presumptive diagnosis was made on histology in one patient. Fibreoptic bronchoscopy was performed in six immunocompromised patients with a positive diagnosis in three. The method of diagnosis in the different types of pneumonia is shown in Table 32.

Table 32: Method of diagnosis

Diagnosis	**Primary(%)**	**Nosoc(%)**	**Asp(%)**	**Immunocomp(%)**
Total patients	**95**	**31**	**28**	**24**
Sputum or TA	59 (62)	15 (48)	14 (50)	8 (33)
Blood culture	33 (35)	3 (10)	3 (11)	5 (21)
Serology (40pts)	6 (6)	0	0	0
FOB (30pts)	1	1	0	3
Open Lung Biopsy	0	0	0	2
Other	5	0	1	3
No diagnosis	24 (25)	16 (52)	10 (36)	8 (33)

Blood culture was positive in 33 (35%) of the 95 patients with primary pneumonia. An identical pathogen was cultured in sputum or tracheal aspirate in 30 of these patients. The diagnostic accuracy for Gram's stain and culture of sputum and aspirates in patients with CAP and positive blood cultures is shown in Table 33.

Table 33: Correlation between blood culture and Gram's stain and culture of sputum and tracheal aspirate.

	n=	Gram's stain			Culture			
Result		**+ve**	**+ve**	**-ve**	**+ve**	**+ve**	**False +ve**	**False +ve**
Type of Bacteria		Gm +ve	Gm -ve		Gm +ve	Gm -ve	Gm +ve	Gm -ve
Sputum	19	9	6	4	8	6	1	0
Trach. Asp.	15	5	3	7	4	3	1	0
Total	**31**	**14**	**9**	**8***	**12**	**9**	**2**	**0**

** Three patients had both negative sputum and tracheal aspirates.*

Discussion

This group of patients with severe pneumonia pre-selected because of respiratory failure that necessitated ICU admission comprise a group of patients with a high mortality. A high incidence of gram negative and *S. aureus* infections in patients with CAP was found, however the standard classification is as useful in this group of patients, as it is in those with less severe disease. The diagnosis of primary CAP Gram negative pneumonia (14 patients) was confirmed by blood culture in 11 patients, and made on pleural aspirate (1) and culture of sputum/tracheal aspirates only, in 2. In 13 of the 14 patients the sputum or initial tracheal aspirate on intubation showed significant Gram negative organisms on Gram's stain and the cultures were

identical to the blood culture in all 11 cases. There were no false -ve sputum cultures in these patients. None of these patients had been intubated other than immediately prior to obtaining the bronchial secretions. In the 20 patients with blood culture proven *S. pneumoniae* infection; the identical diagnosis was made from Gram's stain of sputum (12) or tracheal aspirate (4) in 16 patients. These findings confirm the value of well processed Gram's stain for the diagnosis of community-acquired pneumonia shown in previous studies.[33,131] In three patients the additional culture of *H influenzae* from bronchial secretions was considered as dual pathogens a feature noted in recent studies.[116] Fibreoptic bronchoscopy using a special sheathed brush and quantitative culture which differentiates between colonisation and pneumonia has been shown to be useful in diagnosing diverse pulmonary infections, was well as nosocomial pneumonia in ventilated patients.[130,137] This technique has been shown to be useful in patients in intensive care with undiagnosed pneumonia[156] This study however found no pathogens in culture of brush specimens in seven patients with pneumonia that failed to respond to treatment within 72 hours, and considered this negative result valuable. In our study we only considered positive cultures valuable and in only three of 24 patients was a definitive diagnosis made. This new diagnosis did not however result in any change in antibiotic therapy, which suggests that fibreoptic bronchoscopy is seldom clinically useful in these patients. As in general hospital based studies the aetiologic diagnosis is not made in a large number of cases. In this study a diagnosis was not made in 25% of cases despite proceeding to invasive techniques including fibreoptic bronchoscopy with brushing and biopsy as well as serology for *Mycoplasma pneumoniae* and *Legionella pneumophila.* Serological investigation or viral studies were not performed routinely and also did not include *Chlamydia* , and no special techniques to detect antigens to pneumococci were performed. This may have underestimated the incidence of these infections. In those patients who died, however, autopsy did not suggest an alternative aetiologic diagnosis. It is also possible that in this study a number of infections with multiple pathogens were not recognised because once an identifiable pathogens was recorded

no further investigations were performed unless the patient failed to respond to therapy. The Gram's stain of well collected sputum samples or early tracheal aspirates provides an accurate guide for empirical antibiotic therapy and a definitive diagnosis is more frequently confirmed by blood culture in these patients with more severe disease than in less severe disease. More invasive procedures such as fibreoptic bronchoscopy add little to the diagnosis in primary pneumonia but is of more value in patients who are immunocompromised.

CHAPTER 13

NOVEL THERAPY FOR COMMUNITY-ACQUIRED PNEUMONIA

SURGERY IN THE MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Introduction.

Most patients with community-acquired pneumonia will respond to appropriate antibiotic therapy. In 3 to 5% of patients, however, in spite of adequate therapy the disease process may progress to produce irreversible respiratory failure and death.[9,17,18] In a small proportion of these cases, frequently those in whom initiation of treatment is delayed, low grade infection may progress to involve the entire lung in a necrotic process, termed massive pulmonary gangrene. This may result in ongoing tissue damage, release of cytokines and persisting infection, septicaemia and multiple organ failure ensues.[1,28] Occasionally in other instances the necrotising nature of the infection may lead to the development of acute lung abscess with similar effects.[27] In such cases where adequate and appropriate antibiotic therapy has been given with inadequate response, there may rarely be instances where surgical management is indicated to prevent the progression to multiple organ failure and death.[95,96]

PNEUMONECTOMY IN SEVERE PNEUMOCOCCAL PNEUMONIA.

Pneumonectomy was considered necessary in 2 patients who developed massive pulmonary gangrene secondary to pneumococcal pneumonia that failed to respond to appropriate antibiotics and ICU therapy, including mechanical ventilation with differential lung ventilation.[28]

Case 1

A 39 year old man with a background of both heavy smoking and prolonged alcohol abuse was admitted to our Emergency Unit with a 2 week history of progressive dyspnoea, cough, blood-stained sputum, fever and pleuritic chest pain. On examination he was pyrexial 38.7°C, hypotensive and found to have clinical features of a right sided pneumonia. The white cell count was 5,800 cells/ml, platelets 28,000 cells/ml with an ESR of 120 mm/hour. Arterial blood gases on room air: pH 7.41 PaO_2 7.4 kPa pCO_2 4.0 kPa with a standard bicarbonate of 20.6 mmol/l. Sputum culture grew *S. pneumoniae* sensitive to penicillin and blood cultures were also positive for this micro-organism.

The patient was admitted to the ICU where he was treated with intravenous penicillin and tobramycin, and required intubation ventilation, and inotropic support.

Over the next few days the pneumonia was noted on the chest radiograph, to have extended to involve the entire right lung, and this was associated with the development of a right sided bronchopleural fistula, and worsening of his respiratory function. Chest radiograph showed extensive consolidation of the right lung, with loss of volume, a persistent sub-pulmonic pneumothorax in spite of chest drains, and an area of breakdown in the midzone. The left lung was initially normal. The possibility of spread of infection to the opposite side prompted the insertion of a double lumen endotracheal tube, and the institution of independent lung ventilation. There was a concomitant deterioration in his renal function, and the development of disseminated

intravascular coagulation. Following 7 days of intensive supportive therapy during which he showed progressive deterioration with the development of multiple organ failure, and a PaO_2 of 5.8 kPa , pCO_2 5.3 kPa pH 7.44 on 35% oxygen it was decided to perform a right pneumonectomy.

At surgery the lung was noted to be oedematous and frankly necrotic, with breakdown of the anterior segment of the right upper lobe. Postoperatively he developed a right empyema that was treated with a thoracostomy, and then subsequently successfully closed. His recovery was otherwise uneventful and he was able to be discharged from the ICU after 35 days.

Three month follow-up found him well with some reduction in his lung volumes and moderate airflow limitation. (FEV_1 = 1030 ml, FVC 2050 ml) He was still alive 5 years later.

Case 2

A 33 year old stable-hand with a long history of alcohol abuse presented to this hospital with a one week history of fever, cough, and dyspnoea. On examination he was found to have signs of left-sided consolidation and the chest radiograph showed dense, homogeneous opacification of the left lung; the right lung was uninvolved. Arterial blood gases on room air were pH 7.14, PaO_2 7.6 kPa, pCO_2 of 10.1 kPa, and the white cell count was 12,800 cells/ml with a marked left shift in the morphology. His serum urea was elevated at 11.7 mmol/l with a creatinine of 160 micro mol/l and normal liver function tests.

He was admitted to the ICU for ventilation. Antibiotic therapy was commenced on admission with both cefotaxime and cloxacillin. Gram's stain of the sputum showed numerous Gram positive diplococci and Gram negative cocco-bacilli, and culture of the tracheal aspirate grew *S. pneumoniae* and *H. influenzae*.

His course in the ICU was stormy and he developed evidence of multiple organ failure over the next 6 days. A double lumen endotracheal tube was inserted on day 7 because of copious secretions, and independent lung ventilation was commenced. His

condition remained critical with ongoing deterioration of his renal function, and need inotropic support was needed to maintain his blood pressure. On the 9th day he was taken to surgery for a left pneumonectomy as he was not responding to conventional therapy.

The findings at thoracotomy were of a non-viable, infective process involving the entire left lung. His postoperative course was complicated by wound haematoma and a post pneumonectomy empyema from which a cloxacillin resistant *S. aureus* was cultured. Three weeks later he was able to be discharged from the ICU. Eventually he was discharged from hospital with a thoracostomy in situ.

Discussion

Severe community-acquired pneumonia still has a mortality of between 29 and 54% despite intensive care and appropriate antibiotic therapy.[1,119] A number of factors including septic shock , a white cell count <4 000 cells/ml and Gram negative organisms are recognised as indicators of an increased mortality with death usually occurring in the first few days after admission.[17,32] The cause of these deaths is usually due to overwhelming infection and endotoxaemia leading to ARDS, septic shock and multiple organ failure.[1]

Massive pulmonary gangrene resulting from both *Klebsiella pneumoniae* and *S. pneumoniae* pneumonia was recognised as a rare complication in the pre-antibiotic era, and successful outcome often relied on surgical management of such cases.[95,96,221] Whereas the natural history of severe overwhelming pneumonia is usually rapid spread bilateral involvement, these 2 cases differ substantially in that the process remained confined to one lung for some days before spread to the opposite, uninvolved lung occurred. It was thought that this unusual course was due to the development of massive necrosis of the involved lung with subsequent spill-over to the opposite side.

In both these cases the development of the typical late radiological features of pulmonary gangrene[97], including the presence of a lobar sized cavity containing freely moveable tissue, were not seen, probably because its development was anticipated and treated with early surgery.

Many cases of pneumonia which have been thought on radiological criteria to have unilateral involvement, are shown at autopsy to have involvement of both lungs - especially in those where the progression to death is rapid; this makes the decision as to when to proceed to pneumonectomy difficult. Special investigations including computerised tomographic scans and perfusion scans of the chest may contribute to the clinical decision to proceed to surgery but these have not yet been adequately evaluated. Evaluation of the pulmonary reserve using lung function testing is impossible in this situation and a clinical assessment of pulmonary function needs to be made, taking the history of previous effort tolerance and co-existing lung disease into consideration.

Serotype 111 pneumococci are recognised to cause more severe necrosis than other types; the mechanism is multifactorial including both host and microbial factors. The phagocyte activity of the alveolar macrophages and polymorphonuclear leukocytes may be overwhelmed by the rapid accumulation of capsular polysaccharides often seen with type 111 infections. This mechanism as well as a large antigenic load of capsular polysaccharide leads to reduced humoral and mechanical defences. This together with toxin production including leukocidin, haemolysin, pneumolysins and hyaluronidase may predispose to lung necrosis.[96,221] The pathology of the lung frequently shows significant vascular thrombosis which undoubtedly is particularly important in the pathogenesis of massive pulmonary gangrene.

Numerous host factors have been implicated, however, in our patients, alcoholism and smoking were the only common factors, although aspiration may well have played a role. Both were young (aged 33 and 39 respectively) ,and the white-cell counts (5,800 cells/ml and 12,800 cells/ml) were inappropriately normal. Massive pulmonary gangrene frequently occurs in patients who are at risk of aspiration - as in our two

patients - however anaerobic bacteria have only occasionally been cultured in this setting. The association of both *S pneumoniae* and *K pneumoniae* with aspiration is well recognised, as is the synergistic tissue necrosing effect of a combined aerobic/anaerobic infection. It is therefore likely that aspiration is a factor in some cases of massive pulmonary gangrene.[221] Although successful medical management has been described in three cases of massive pulmonary gangrene,[222] the majority have been treated surgically either by drainage or resection. In both our cases, medical therapy had already failed making surgery the only option. Surgery, in these circumstances has a high morbidity and mortality,[223] and both patients developed a post-pneumonectomy empyema, a distressing, difficult problem to treat; one also had a wound haematoma. It is uncertain whether earlier surgical drainage would have modified the outcome.

This late complication of massive pulmonary gangrene is rare and has only been seen in these 2 cases while over the same 9 year period 446 patients have been admitted to our ICU with severe community-acquired pneumonia. The successful outcome in these two cases where there was ongoing clinical deterioration with extension of their disease after 7 days of full therapy suggests that surgery should be considered in patients with a similar pattern of disease.

SURGICAL DRAINAGE OF LUNG ABSCESS COMPLICATING COMMUNITY-ACQUIRED PNEUMONIA.

Introduction

Community-acquired pneumonia may occasionally be complicated by necrosis and the development of an acute lung abscess. In the setting of a critically ill ventilated patient this may lead to soiling of areas of normal lung, as well as an ongoing inflammatory response from inadequately drained abscess necessitating prompt intervention. Two cases of acute community-acquired pneumonia complicated by pulmonary necrosis which was successfully managed by surgical drainage have been previously reported.[27]

Case 1.

A 41 year old white male smoker and alcoholic, having had no recent binge, was admitted with a 2 day history of cough, fever and right sided chest pain. On examination he was fully conscious, pyrexial with a tachycardia, signs of a right sided pneumonia and stigmata of chronic liver disease. The chest radiograph showed dense upper lobe consolidation and patchy, ill-defined opacification of the lower lobe. A Gram's stain of his sputum showed pus cells and Gram positive cocci in pairs, and a blood culture was positive for a penicillin sensitive *S. pneumoniae.* Penicillin was commenced intravenously. The following day he became confused and hypoxaemic on 40% face mask oxygen, requiring intubation and intermittent positive pressure ventilation (IPPV). 5 days later the chest radiograph showed extension of the pneumonia to involve the lower zone with areas of breakdown in the mid zone. Because of the deterioration in his condition, with large amounts of purulent secretions being suctioned from the endotracheal tube and obvious cavitation of the pneumonia on the chest radiograph, open drainage of the lung was performed via a

mini thoracotomy on day 7. The pleural space was fused; about 1 cm of lung was incised before entering a cavity from which approximately 150 ml of watery brown pus was drained. A de Pezzar drain was inserted with an underwater drainage system. Culture of the pus was negative; histology showing acute pulmonary inflammation and necrosis. Following surgery his condition showed marked radiological and clinical improvement. 100 ml of pus drained daily from the chest drain and there was a marked reduction in the volume of tracheal secretions but there was a persistent air leak. Amikacin and metronidazole were added to his treatment. A computerised tomographic (CT) scan of the chest on day 16 showed consolidation of the right upper lobe, with breakdown and small areas of liquefaction but no pleural, or significant intrapulmonary collection of pus requiring further drainage.The patient and was weaned from the ventilator on day 19, at which stage his sputum which was still purulent and cultured *H. influenzae*. He was commenced on cotrimoxazole, his other antibiotics being discontinued. He was discharged home two weeks later but was readmitted 4 weeks thereafter with an empyema which responded well to surgical drainage.

Case 2.

A 56-year old man who had been well until the previous week, developed back pain with abdominal distension, following a day's swimming in the sea. Distended loops of bowel and linear atelectasis at the left base were demonstrated on the chest radiograph, and were interpreted as indicating intra-abdominal pathology. The patient underwent a laparotomy which was negative. Post-operatively he developed respiratory distress with radiographic features of a worsening pneumonia which was treated with cephamandole. His white cell count which was 4,700 cells/ml post-operatively dropped to 1,300 cells/ml and his PaO_2 fell to 6.2 kPa on 40% oxygen by face mask on the second day after surgery. Intravenous erythromycin was added and subsequently netilmicin, when a *Klebsiella spp.* was cultured from his sputum. His condition continued to deteriorate and he was transferred by air ambulance to our

ICU, intubated and hypotensive with a severe left lower lobe pneumonia. A tracheal aspirate on admission grew *K. pneumoniae* sensitive to amikacin and ceftriaxone.

A diagnosis of pneumonia presenting with abdominal pain and ileus was made and therapy was changed to ceftriaxone and amikacin. The following day his chest radiograph was suggestive of cavitation in the left lower zone and this was confirmed by CT scanning. Surgical drainage of the abscess was performed after a double lumen endotracheal tube had been inserted to prevent spillage, as there were copious purulent secretions. At surgery an abscess involving the lingula with an adjacent empyema was found. *E. coli, Pr. mirabilis* and *Enterococcus spp.* were cultured from the pus and also from a throat swab; there was no preceding history of aspiration. Following the thoracotomy, profuse pus was drained and the patient rapidly improved. His general condition improved with pyrexia, hypoxaemia and chest radiograph resolving and he was discharged from the ICU 10 days later.

Discussion

Lung abscess is recognised as a rare complication of community-acquired pneumonia, seen commonly in the alcoholic, and occasionally in immunocompetent patients. Pneumonia complicated by abscess formation has a high mortality and although many respond to antibiotics, surgical treatment using pneumonotomy and open drainage has been recommended if endobronchial drainage has failed, and where there is ongoing clinical evidence of toxicity, or where the abscess cavity fails to diminish in size.[223-225] Percutaneous or open drainage of lung abscess has also been recommended for lung abscesses in patients requiring IPPV where there is failure to wean from mechanical ventilatory support or where the size of the abscess cavity is greater than 4 cm.[226] In patients who require endotracheal intubation, the copious secretions from the abscess cavity may be difficult to control adequately by suction, and the concomitant use of intermittent positive pressure ventilation (IPPV) exacerbates the problem by causing wide dissemination of pus. Spill-over of pus to unaffected areas

may be temporarily prevented by the use of double lumen intubation with isolation of the affected lung, but suctioning through these tubes is difficult and ineffective. At this stage endobronchial manipulation is possibly contraindicated because of the critical hypoxaemia. Surgical drainage of the lung abscess provides an alternate route for removal of this infected material, and it can prevent further intrapulmonary spread and result in rapid resolution of the infection. In this setting the main reason for drainage is to prevent endobronchial spill of pus into the lungs. Wide bore percutaneous or surgical drainage is probably preferable to the use of fine bore tube drainage. Death from community-acquired pneumonia is usually the result of multiple system organ dysfunction (MODS), either due to fulminant septicaemia or the persistence of infection, complicated by abscess formation or empyema. In other sites of severe sepsis, surgical drainage and removal of the infection has been demonstrated to result in the resolution of MODS and survival of the patient.[227] The rapid response and defervescence of sepsis in our two patients following surgical drainage suggest that this is a similar situation and that surgery may prevent the development of MODS and lead to more rapid recovery. The decision as to when to proceed to surgery is difficult, particularly in critically ill patients on ventilators where only antero-posterior supine or semi-erect chest radiographs, without lateral projections, are available, which generally do not give sufficient definition to define the extent, or localisation of intrapulmonary disease. The onset of cavitation is difficult to determine by these methods and we have utilised CT scanning to define cavitation more clearly, both for diagnosis and planning surgery. In the first case CT scanning was performed to confirm the adequacy of surgical drainage, whereas in the second, it was used to localise the site of cavitation and to plan surgery. CT scanning is extremely reliable in this situation as it can clearly differentiate between pleural and pulmonary disease. Cavitation and abscess formation in community-acquired pneumonia has been seen as a rare complication of infections both with *S. pneumoniae* and *K. pneumoniae*; more frequently the causative organisms are multiple and often include anaerobes.[94,221,228] These features, combined with the higher

incidence in alcoholics, support the postulate that these pneumonias are probably the result of micro or macro aspiration of oropharyngeal flora. In this situation antibiotic selection should cover the primary isolate and include anaerobic cover, particularly if the sputum is fetid.

We therefore suggest that in addition to the established indications for surgical intervention in community-acquired pneumonia complicated by a lung abscess; that is, failure of toxicity to settle and failure of the cavity to decrease in size, one should consider surgery for those with respiratory failure necessitating IPPV. These patients should be regarded as surgical emergencies and the abscess should be drained immediately.

SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT IN PREVENTION OF SUPERINFECTION IN COMMUNITY-ACQUIRED PNEUMONIA.

Introduction

Selective decontamination of the digestive tract (SDD) is used to prevent the development of secondary infections in high risk patients within the ICU.[229-231] While controversial, it is thought to benefit primarily non-infected patients e.g. trauma and post-operative cases; most studies have excluded patients already infected on admission.[230,232,233]

Patients with primary pneumonia requiring ICU admission, usually require prolonged ventilation and antibiotic therapy; the mortality is reported to be in excess of 29%[1]. Pneumonia itself has been shown to predispose to further episodes of respiratory tract infection, which may prolong the hospital stay[234]. It is therefore not too surprising that Sir William Osler made the following observation and stated that *"Recurrence is more common in pneumonia than in any other acute disease"*

Thus these patients with CAP, who may be at particular risk for the development of secondary pulmonary infection, may benefit from prophylaxis with selective decontamination of the digestive tract (SDD). The efficacy of SDD has not previously been evaluated in patients with pneumonia requiring ICU therapy who may be considered to be at greater risk for the development of super infection.

Patients and Methods

All patients admitted to a respiratory ICU who were expected to require intubation for more than 2 days and ICU admission for 5 days, were randomised to receive either SDD (oral gel 5g: amphotericin B 2%, polymyxin E 2%, tobramycin 2% and enteral solution 10 ml containing amphotericin B 500 mg, polymyxin E 100 mg and tobramycin 80 mg) or placebo. All patients received intravenous cefotaxime, 1g 8 hourly for 72 hours.

Inclusion criteria included:

- Aged 16 or older
- Duration of intubation > 48 hours
- Duration of ICU admission > 5 days
- Informed consent

Exclusion criteria:

- Allergy to investigation drugs

These patients with community-acquired pneumonia formed part of a larger study on selective decontamination which have been previously reported.[231] Analysis of this group was decided a priori, and the disease 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. Patients were fully examined on entry, the admission diagnosis was defined and the severity of illness was assessed according to the APACHE II and organ failure.[208,235] Factors recognised as likely to affect the development of secondary infection,[236,237] 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.

Microbiological surveillance included culture of oropharynx and tracheal secretions, stomach aspirate, urine and rectal swabs on entry, and twice weekly, until 3 days after ICU discharge; these results were withheld from the clinicians to avoid unblinding. Clinical monitoring which included biochemical, and haematological investigation, and clinical and radiological examination was performed daily looking in particular for evidence of secondary infection. Nosocomial infection was diagnosed if signs of infection developed more than 48 hours after admission to the ICU. 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 were available to the clinicians.

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 cells/ml), or a left shift in its morphology.

evidence of organ dysfunction.

Criteria for organ dysfunction were defined as follows:

lung: PaO_2 <8 kPa on 40% oxygen, or respiratory rate <5 breaths/minute or >49 breaths/minute, or $PaCO_2$ >6 kPa, or $AaDO_2$ >46 kPa, or dependent on ventilator for >4 days.

kidney: urine output <479 ml/24 hours, or <159 ml/8 hours, or serum creatinine >300 µmol/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 cells/ml, or platelets 20 000 cells/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^{o}C, white blood cell count >10,000 cells/ml, 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 2 kPa or more.

Bronchial infection was defined by the presence of all the features of pneumonia, except the radiographic changes were absent.

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 fungi, 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 10,000 cells/ml 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.

No routine prophylaxis against gastrointestinal bleeding was used. Ranitidine was prescribed 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, and also because of its own antibacterial properties which might have caused difficulty with the interpretation of results.[238,239]

Patients already receiving an antibiotic for their pneumonia 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 1g 8 hourly was substituted and continued as therapy. In all cases attempts were made to avoid antibiotics which might interfere with the anaerobic flora.

RESULTS

Forty-four patients fulfilled criteria for inclusion in this subgroup, and there were a further three who were not included, because their duration of stay was unexpectedly prolonged, but who subsequently proved suitable and were analysed separately. Eight patients were withdrawn as they did not meet the criteria for duration of ICU stay or intubation (including 6 early deaths). There was no difference in demographics or severity of illness scores between the SDD and placebo groups (Table 34).

Table 34: Demographic Data

	SDD	Placebo	Withdrawn	Suitable
No of patients	12	24	8	3
Age	43.2+-13.1	45.7+-18.3	56.9+-14.4	47+_ 3.5
Male:female	8:4	16:8	2:5	1:2
Hospit >48 hrs #	6	13	1	3
APACHE II *	14.6± 6.4	17.1± 5.9	27.4±13.7	15.2±6.5
Organ failure	1.4± 0.7	1.5± 0.6	1.7± 1	1
Shocked**	4	1	2	0

** p = 0.25 Student's t test, **P = 0.06 Chi-square test, # Hospitalised for more than 48 hrs before ICU admission.*

Factors such as carcinoma, underlying diabetes which have previously been described as predisposing to the development of secondary infection, were equally distributed between the active and placebo groups. The use of invasive and therapeutic monitoring procedures whilst in the ICU was of equal frequency in all patients: haemo-dialysis in 2 SDD and 3 placebo patients; pulmonary artery catheters in 9 and

18 respectively; central line in 10 and 23; chest drains in 3 and 10; parenteral nutrition in 4 and 15. Four SDD and 9 placebo patients had tracheotomies (mean duration 16.3 days vs. 17.2 days).

Complications occurred infrequently in both groups (11 vs. 27). Five patients developed pneumothoraces related to positive pressure ventilation.

There was only one nosocomial infection in the decontaminated patients, compared with 10 infections in the placebo group (Table 35).

Table 35: Types of Infections and Number of Infected Patients.

	SDD	Placebo	Withdrawn	Suitable
No of patients	12	24	8	3
Infected patients*	1	8	0	1
Total Infections	1	10	0	1
Bronchial	1	3	0	1
Nosoc. pneumonia	0	2	0	0
IV catheter	0	2	0	0

* X^2 p =0.22

The micro-organisms causing secondary infection are shown in Table 36.

Table 36: Aetiology of Secondary Infection

	SDD	Placebo	Withdrawn	Suitable
No of patients	12	24	8	3
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 both groups, although unfortunately the numbers are too small for meaningful comparison (Table 37).

Table 37: Duration of Hospitalisation and Mortality

	SDD	Placebo	Withdrawn	Suitable
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
Duration IPPV	11.1± 9.7	12.8± 5.6	1.9± 1.2	19.3±16.2
ICU deaths	0	5	6	0
Hospital deaths	1	1	0	0
Mortality	8.3%	25%	75%	0%

Discussion

There were ten infections in the placebo patients, while only one SDD patient developed secondary infection. There was only 1 death in the SDD group where

therapy was withdrawn because of hypoxic brain damage sustained following cardiac arrest on intubation. 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 the groups were largely comparable 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 has been shown to be a predictor of poor outcome, in both pneumonia and severe sepsis (Hammond,JMJ; SA Pulmonology Congress, Wilderness, 1989). Although 47 patients with pneumonia were admitted over the study period, only 36 met criteria for analysis, as the others failed to meet the criteria for inclusion because of too short a duration of intubation or ICU stay; these included six patients who died early within five days from respiratory or multiple organ failure. Most studies of SDD in heterogeneous groups of ICU patients have shown a reduction in the rate of respiratory infection, however there has been little or no effect on mortality.[229] In a study from our unit we were unable to show a significant reduction in infection although a number of deaths could be directly attributable to secondary infection. Our study differed from those studies that showed a striking reduction in infection in that we had a very low incidence of infection (30%) compared with infection rates of over 50%, and also we used cefotaxime for 72 hours in the control group as well as the SDD group, which may have reduced early onset infections.[231] These conflicting results have led clinicians to believe that this technique may be valuable in certain subgroups of patients, and previous analysis have concentrated on primarily non-infected groups as it was thought that these may derive more benefit from SDD.[230] Although the numbers are insufficient in this study to show significant differences in outcome , it is very suggestive that SDD exerted a protective effect in these patients with severe pneumonia, and may both reduce secondary infection and even mortality, and it may well be that primarily infected patients may derive significant benefit from this technique.

CHAPTER 14

SEVERE COMMUNITY-ACQUIRED PNEUMOCOCCAL PNEUMONIA.

Introduction.

Streptococcus Pneumoniae is the most common type of micro-organism leading to CAP in all settings, and accounts for 8.5 to 23% of cases where the diagnosis relies on standard microbiological evaluation,[8,9] to as many as 76% where specific immunological tests for pneumococcal antigen detection are added.[51] This micro-organism is also the most frequent pathogen in other types of severe pneumonia, and in this study it accounted for 16% of pathogens in nosocomial pneumonia, 20% following aspiration, and 17.1% in immunocompromised patients.

In spite of having effective antibiotics for the past 50 years this micro-organism causes fatal disease in as many as 15-50% of patients with community-acquired bacteraemic pneumonia,[2,99,173,240,241] and this high mortality has apparently not been influenced by intensive care management.[215] The majority of deaths occur within the first 24 hours of admission,[99] and are frequently associated with underlying disease and old age. Infection in young adults has a mortality of 20%, whereas in patients aged between fifty and sixty years it is 25 to 40%, and in the over 70's, 50 to 60%.[98] In those with AIDS, the incidence is 5.5 to 17.5 times higher than in the normal population, and they have been shown to have a mortality of 57% compared with 18% in non-AIDS, aged matched patients.[34] In a recent study significant differences in outcome between patients in Sweden and the USA of 5 and 26% respectively have been unexplained, other than by an increased incidence of associated disease with an attributable mortality in patients from the latter country.

This chapter characterises the clinical features of severe community-acquired pneumococcal pneumonia leading to respiratory failure requiring ICU admission, and contrasts bacteraemic with non-bacteraemic disease.

Patients and Methods

All patients with community-acquired pneumonia and a diagnosis of pneumococcal infection made on grounds of a positive blood culture, or the presence of Gram positive diplococci on a Gram's stain of sputum or of tracheal aspirate, or a positive culture of *S. pneumoniae* from bronchial secretions, were included in this analysis. Further methodology described in chapter 8 applies to this study.

Results.

There were 63 patients who had pneumonia caused by *S. pneumoniae,* representing 32% of the total number of 196 patients with CAP, Of these 52 had *S. pneumoniae* as the sole isolate, and 11 had a second organism isolated. *H. influenzae* in 8, *S. aureus* 1, *Ps. aeruginosa* 1, and a Group A *Beta haemolytic streptococcus* was the second micro-organism isolated in 1. In 34 (54%) of these patients the diagnosis of *S. pneumoniae* was made on blood culture.

The severity of illness, clinical features associated with an adverse outcome, and demographics of the bacteraemic and non-bacteraemic patients are shown in table 38.

Table 38: Clinical features.

	Bacteraemic	Non-Bacter.	Total
n =	34	29	63
Age	45.5 +-15.88	43.79 +- 18.22	44.7 +- 16.88
Male:Female	20:14	12:17	32:31
Race:Black	15	7	22
Mixed	18	22	40
White	1	0	1
APACHE II	18.9 +- 8.87	17.72 +- 8.6	18.35 +-8.7
Organ Failure	1.53 +- 0.96	1.28 +- 1.16	1.41 +- 1.06
Shock	5	4	9
Acute Renal Failure	12	4	16
Associated.Dis.(n=)	24	20	44
Asthma	5	1	6
Chronic Lung Dis.	8	11	19
Diabetes	5	2	7

The clinical features on presentation are illustrated in table 39.

Table 39: Clinical features of bacteraemic patients on presentation .

	Bacteraemic	Non-Bacteraemic
	(n = 30)	(n = 29)
Age >60 years	5	6
Temperature > 38.5 °C	6	3
< 35.5 °C	2	4
Resp. rate >30 breaths/min	14	15
WCC < 5,000 cells/ml	7	11
5000 - 18,000 cells/ml	14	11
>18,000 cells/ml	8	7
DIC	1	4
S.albumin < 35 g/l	26	24
Urea > 7 mmol/l	21	16
Impaired level of consciousness	5	4
Shock (SBP < 80 mm Hg)	3	4
Compromising disease	24	20
Arterial blood gas	(n = 29)	(n = 29)
PaO_2(mm Hg)/FiO_2 *	178.2±103	206.5±151*
$PaCO_2$ kPa	4.55±1.33	4.67±1.09
pH	7.35±0.29	7.37±0.12
Base excess	7.35±0.29	-4.71±4.74

*t test * p= 0.417*

All patients required ventilatory support; IPPV was necessary in 50 patients (79%); CPAP by face mask in 9, and 4 were treated with face mask oxygen only. The duration and mode of ventilatory therapy is shown in Table 40.

Table 40: Ventilatory therapy

	Bacteraemic	**Non-Bacteraemic.**	**Total**
No of Patients	**34 (54%)**	**29 (46%)**	**63**
O2 only	2	2	4
CPAP	5	4	9
IPPV	27	23	50
PEEP (cm H_2O)	7.74 +- 4.09	7.91 +- 3.57	7.81 +- 3.84
Tracheostomy	13	8	21
Duration IPPV *	8.97 +-7.14	9.22 +-7.13	9.08 +-7.07
ICU admission	11.47 +-8.98	11.03 +- 11.99	11.27 +- 10.38
Pts.with complications**	n = 14	n = 17	31
Complications (n)	38	36	74
Mortality (%)***	5(15%)	8(28%)	13(21%)

** t test p = 0.89; ** X^2 p =0.25; *** p = 0.34.*

Fifty-three of the patients received intravenous penicillin, one erythromycin, one amoxicillin, one cotrimoxazole, and the remaining seven a third generation cephalosporin. Three of the non-survivors were not given penicillin.

Complications occurred frequently in both groups, with almost half the patients developing complications, many multiple complications.(see table 41)

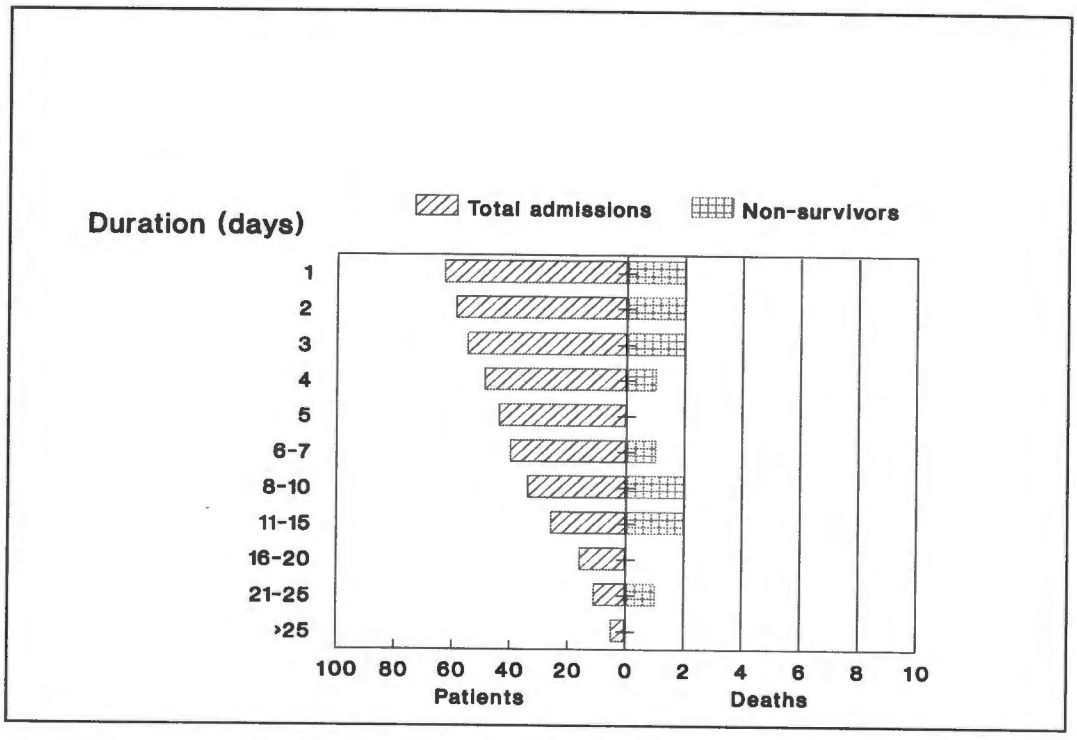
Table 41: Complications occurring in the ICU.

Complication	No of Patients
GIT Bleeding	3
Cardiac Failure	4
Liver Failure	2
Renal Failure	9
Respiratory infection	2
Other nosocomial infection	20
Pulmonary haemorrhage	1
Ventilatory complications*	4
Pneumothorax	5
Delirium Tremens	3
Diarrhoea	4
Drug complications	2
Other	16

** Accidental extubation; blocked tube; CVA on IPPV.*

Thirteen of the sixty-three patients died; eight deaths were clinically assessed as being due to multiple organ failure, four to respiratory failure, and one due to brain death sustained after a cardiac arrest. Two deaths occurred within 24 hours of admission and 50% within 72 hours; the duration of admission and time of death following admission are shown in figure 29.

Figure 29: Time of death following admission.



The duration of ventilation, ICU admission, number of complications and mortality are shown in table 42.

Table 42: Duration of treatment, morbidity, and mortality

	Survivors	Deaths	Total
No of Patients	50	13	63
Duration of IPPV	9.97 +- 7.25	6.31 +- 5.88	9.1 +- 7.1
Duration ICU stay	12.5 +- 11	6.54 +- 6.05	11.3 +- 10.4
No of Complications	54	20	74
Patients with Comp.	23	8	31
Mortality (%)			13(21%)

A number of clinical features are recognised to be associated with an increased mortality and these clinical parameters are tabulated for survivors and non-survivors.(see table 43)

Table 43: Clinical features that may influence outcome

	Survivors	**Non-survivors**	**p =**
	(n=46)	(n=12)	
Age >60 years	6	5	0.078
Temperature> 38.5 ^{o}C	8	0	ns
< 35.5 ^{o}C	4	2	ns
Resp. rate >30 breaths/min	23	7	0.962
WCC < 5,000 cells/ml	10	4	ns
5,000 - 18,000 cells/ml	23	5	ns
>18,000 cells/ml	14	1	0.207
DIC	2	3	0.102
S.albumin < 35 g/l	41	10	ns
Urea > 7 mmol/l	30	7	0.768
Impaired level of consciousness	8	2	0.761
Shock (SBP < 80 mm Hg)	3	4	0.048
Bacteraemia	26	5	0.454
Compromising disease	27	7	0.886
Arterial blood gas	n=48	n=11	
PaO_2(mm Hg)/FiO_2	189±104.6	201±209.3	0.859
$PaCO_2$ kPa	4.59±1.19	4.54±1.34	0.902
pH	7.39±0.13	7.23±0.41	0.268
Base excess (n=18)	-4.43±5.90	-3.15±4.45	ns

Discussion

In this group of patients with severe CAP requiring ICU management, *S. pneumoniae* still remains the most common causative organism occurring in 32% of cases, despite an increased incidence of both *S. aureus* and Gram negative infections. This incidence may have been even higher if more sensitive immunological tests were used to detect the offending agent, as in 29.6% of cases the pathogens still remained unknown, and many of these, particularly those who had received antibiotics, may have been caused by *S. pneumoniae.* The diagnosis of pneumococcal pneumonia was made by blood culture in 54% of patients which may further suggest that the overall incidence of 32% is an under estimate as Macfarlane using antigen detection as well as other common techniques, found an incidence of pneumococcal pneumonia of 76% with only 14% positive on blood culture.[51] The patient profile was in many respects similar to other reported studies of pneumococcal pneumonia, however the age (mean 44.7 years) with only 11 patients over the age of 60 years tended to be younger. Other studies have reported mean ages of 45 to 66 years with most tending towards the older age group.[173,242,243] The usual predominance of males was also not seen and pneumococcal pneumonia occurred as commonly in females. The disease was also more frequent in lower socio-economic groups of patients. Seventy percent of patients had underlying disease with COPD, asthma and diabetes being common. Alcoholism has been shown to be high in these patients, particularly in some countries, and in Sweden it occurred in 27% compared with 10% in the USA.[243] The incidence of alcoholism was low with only four patients with a definite history however it was difficult to determine alcoholism accurately, and two patients neither of whom had a documented history of ethanol abuse, developed frank delirium tremens. A recent study from Halifax has also shown the increased number of females, but also increased alcoholism.[241]

In our study all isolates of *S. pneumoniae* were sensitive to penicillin, and this contrasts with pneumococcal pneumonia reported from Israel (55 adults and 49 children with pneumococcal bacteraemia), of which 6 (5.8%) were penicillin resistant,

with 3 of these isolates occurring in adults.[173] In two of our cases who died appropriate antibiotic therapy was delayed which further emphasises the importance of appropriate antibiotic therapy.

The patients were critically ill with 79% requiring CPPV, and the APACHE II score was over 18 with most of the score being derived from deranged physiology because of the young age of the patients. Bacteraemia which is also considered to be an adverse prognostic factor was also present in 54% of cases. There were however no significant differences between the bacteraemic and non-bacteraemic patients in any clinical parameters which have been reported to be associated with an increased mortality and more died in the non-bacteraemic group.[134,173,244] The only clinical feature that predicted an adverse outcome was the presence of shock. More elderly patients succumbed, but this did not achieve significance.

The overall mortality was 21% with a mortality of 15% in the well defined group of bacteraemic patients; other recent studies have reported mortalities of 18, 19,25.9, 28.5 and 33% in bacteraemic patients.[173,241,242,244,245] The difference in outcome between bacteraemic and non-bacteraemic patients didn't achieve statistical significance but this may be due to small numbers. If it is real, it is difficult to explain as the patients were similar in all clinical parameters that were measured. Previous antibiotic therapy and duration of symptoms prior to admission were not documented, and the non-bacteraemic group may have included more patients who had received antibiotics and failed to respond initially.

Our mortality is however low for patients requiring ICU admission with pneumococcal pneumonia in whom mortalities of 62 and 76% have been previously reported.[173,215] This suggests that modern intensive care may have a favourable influence on outcome in pneumococcal pneumonia.

A recent comparison of outcome in bacteraemic pneumococcal pneumonia between patients from the USA and Sweden showed a significant difference in outcome of 5%

versus 26% ($p<0.001$), which was largely unexplained, other than that there were more American patients with underlying chronic ill health.[243]

Four of the 13 deaths occurred within 48 hours of admission and it has been suggested that in these patients little can be done to influence outcome.[99] Whilst this may be correct with the use of conventional therapy, it may not apply to techniques using new modalities such as tumour necrosis factor, and interleukin monoclonal antagonists used to block the cytokine prostaglandin and other inflammatory pathways.[193] This group of patients may in fact be the only patients who may benefit from this form of therapy, and the small number of these patients in contemporary cytokine blocking trials may be the reason for the clinical studies with these agents being inconclusive.

As intravenous penicillin was the antibiotic used in most cases it would suggest that intensive care treatment which is the only additional therapeutic change will result in mortality of under 25%, contradicting the conclusions of other previously reported studies that suggest that mortality is uninfluenced by intensive care.[173,215]

CHAPTER 15

SEVERE COMMUNITY-ACQUIRED KLEBSIELLA PNEUMONIA

Introduction

Klebsiella pneumoniae (Friedlander's bacillus) is an uncommon cause of community-acquired pneumonia, particularly in the general population of the developed world. It causes a destructive lobar pneumonia with a high mortality and serious complications such as lung abscess, empyema and Gram negative septicaemia.[92] *Klebsiella spp.* infections account for 1.5% of general hospital admissions with pneumonia[125] yet, significantly, in this study, *Klebsiella. spp.* accounted for 8% of ICU admissions with community-acquired pneumonia. These patients are drawn from an outpatient pneumonia population with a similar incidence of *Klebsiella* pneumonia as is seen in the United States or United Kingdom.[9] The incidence of *Klebsiella* in nosocomial pneumonias is much higher - approximately 12%.[246,247]

These cases with community-acquired *Klebsiella* pneumonia represent all cases admitted to our ICU over a 10 year period (since computerisation of our ICU patient records). This enlarged data base has been used because of the rarity of this form of pneumonia in an attempt to draw more definitive conclusions. The first 17 cases were published previously and this group has now been expanded with the recent cases to confirm the earlier findings statistically if possible in a larger group.[129] I have attempted to describe the clinical features of the disease, define features which may predict a poor outcome, and document therapeutic interventions which may help to improve the prognosis.

Patients and Methods

All cases of community-acquired *Klebsiella* pneumonia treated in our ICU between January 1982 and December 1992. Data was obtained from our Intensive Care Unit's patient records and computer data collected routinely on all patients during hospitalisation. The severity of illness was scored using the therapeutic intervention scoring system in the earlier cases, and the organ failure score and APACHE II score in later admissions.[208,235,248] Cases were selected on the basis of the culture of *Klebsiella. spp* in the sputum or tracheal aspirate and/or blood within 24 hours of admission to the ICU. Cases with a history of aspiration or possible aspiration were excluded. No patients had been admitted or treated in hospital in the month prior to admission.

Microbiological investigations were performed using routine laboratory methods. Initial respiratory therapy with CPAP by face mask was administered if the patient was co-operative and had an effective cough. If patients were unable to clear secretions, showed deterioration in gas exchange, or had persisting hypoxaemia (PaO_2 <8.0 kPa) despite conservative therapy, nasotracheal intubation was performed and mechanical ventilation instituted using a Bear I or IIE, CPU1 or Bennett MA1 ventilator usually in the IMV mode. Inspired oxygen concentration and PEEP were adjusted to maintain a PaO_2 of over 8 kPa. A tracheostomy was performed if tracheal toilet was difficult or if a duration of intubation of > 7 days was anticipated, provided the patient had no increased risk of bleeding. Our antibiotic protocol in severe pneumonias usually involved the initial administration of intravenous penicillin and an aminoglycoside with the addition of cloxacillin if staphylococcal pneumonia was suspected, until the nature of the underlying organism is known, when therapy is adjusted. In patients with contra-indications to the use of aminoglycosides, a third generation cephalosporin was generally substituted. Over the past 5 years when *Klebsiella* pneumonia was suspected, a third generation cephalosporin was combined with the aminoglycoside. Septic shock was managed using a combination of intravenous fluids consisting of a limited volume (500 ml) of balanced salt solution

initially, followed by fresh frozen plasma or stabilised human serum. Additional balanced salt solution was given to maintain an adequate pre-load and blood to maintain a haemoglobin of 12g%. Inotropic support using dopamine HCL 10 micro gm/kg/min and dobutamine or adrenaline in a dose sufficient to maintain a blood pressure of > 90 mm Hg was used. The therapeutic goal was evidence of adequate organ perfusion, i.e. adequate hourly urine output with no worsening in level of consciousness, and maintenance of acid-base status. Pulmonary artery catheters were used in all cases who did not achieve the therapeutic goal or in whom > 15 cm PEEP was used. H_2 antagonists were used prophylactically to reduce gastric bleeding in all earlier cases and recently sucralfate in 4 cases prior to 1986. Since 1986 no routine prophylaxis for stress ulceration has been used.

Nominal data was tested using the Chi squared test, normally distributed interval data using a simple "t" statistic, and other data using a Mann Whitney rank test.

Results

Thirty-two (8%) of 421 patients with community-acquired pneumonia admitted to the ICU over this period because of severe respiratory failure were considered to have *Klebsiella* pneumonia. These included 26 males and 6 females with a median age of 46 years (range 19 to 65 years). There were 10 blacks, 5 whites and 17 patients of mixed race; 26 were of lower socio-economic class (defined as an annual household income of under R8000 ($ 2000). All patients were critically ill: The mean severity of illness score using the Apache II system performed on 21 recent patients was 19.99 (range 9-44), with a mean of 17.2 in survivors and 23 in non-survivors (p= 0.028; last 16 patients only).[208] Therapeutic intervention scoring system used in 14 patients yielded mean scores of 31.7 (range 13-60) and 28.3 and 34.3 (ns) in survivors and non-survivors respectively. The majority of patients all had one or more severe associated medical disease; alcoholism (14 patients), diabetes (6), chronic lung

disease (13), carcinoma (2), epilepsy (3), pancreatitis (2), cardiac disease(3), chronic renal disease (2), acromegaly (1), and hyperlipidaemia (1). Only two patients had no underlying disease.

TABLE 44: Clinical features on admission in 32 patients.

	Survivors	**Non-Survivors**
	(n = 13)	(n = 19)
Age >60 years	1	3
Temperature > 38.5 °C	5	8
< 35.5 °C	1	2
Resp. rate >30 breaths/min	5	10
WCC < 5,000 cells/ml	8	7
5,000 - 18,000 cells/ml	1	5
>18,000 cells/ml	2	2
DIC	5	9
S.albumin < 35 g/l	12	19
Urea > 7 mmol/l	9	9
Impaired level of consciousness	5	12
Shock (SBP < 80 mm Hg) *	4	16
Compromising disease	10	16
Arterial blood gas	**(n = 13)**	**(n = 15)**
PaO_2(mm Hg)/FiO_2	194	190
$PaCO_2$ kPa	3.7	3.34
pH	7.42	7.37
Base excess (S = 7, NS =7)**	-4.43	-8.8

** $p = 0.08$; ** $p = 0.23$*

All patients presented with classical clinical features of severe pneumonia, the median duration of illness prior to presentation being 1 day (range 12 hours - 3 weeks). The majority of clinical features indicative of severe pneumonia present on admission showed no difference in incidence between survivors and non-survivors.(Table 44).

In twenty-seven of twenty-eight patients in whom arterial blood gases were available prior to ventilation significant hypoxaemia was present, but there was again no difference between survivors and non-survivors (Table 44). Eight of ten patients who had an uncompensated metabolic acidosis on admission died. Most patients showed segmental or lobar opacification on the chest radiograph (see table 45)

Table 45: Radiological features in *Klebsiella spp.* pneumonia

Chest radiograph	**Survivors**	**Non-survivors**
No of Patients	13	14
Lobar/Segmental pneumonia	13	13
Bronchopneumonia	0	1
Effusion	1	2
ARDS	3	6

In those with segmental opacification there was usually rapid spread to involve the whole lobe. The classical feature of a bulging fissure was seen infrequently. Nine patients who developed a rapidly spreading opacification adjacent to the initial changes and involving the opposite lung were considered to have developed ARDS. Six of these 9 patients failed to respond to treatment.

Twenty-eight patients required ventilatory support by constant positive pressure ventilation (CPPV) and in 11, PEEP of more than 10 cm H_2O was necessary to achieve adequate oxygenation. One was given CPPV only, because of severe COPD. Differential, asynchronous lung ventilation using two ventilators and a double lumen

endotracheal tube was unsuccessfully used in 3 patients, and with success in one patient who subsequently required a drainage procedure. One required double lumen intubation and independent lung ventilation for a large bronchopleural fistula and in the other three this was used to try and avoid spread of unilateral disease. The median duration of ICU admission was 8 days (Mean 9.29 days, range 12 hours to 84 days). There were 19 deaths, 6 of which occurred within 24 hours from septicaemia, the remainder occurred from 2-52 days after admission from unremitting sepsis. Fifteen of the 19 deaths resulted from the development of multiple organ failure. In 2 patients death was due to severe respiratory failure leading to inability to achieve adequate ventilation; one died of shock and one developed a fatal pulmonary embolism.

Table 46: Complications on Admission or Developing During Therapy.

	No. of Patients
Shock	20
Coma	14
Renal failure	15
Hepatic failure	6
Delirium Tremens	5
Pneumothorax	4
Pulmonary Super infection	10
GIT bleeding	5
GIT perforation	2
Arrhythmia	5
Other*	10

** Ischaemic limb, anaphylaxis, CVA, venous thrombosis, pulmonary embolus, diarrhoea, pancytopenia, and pressure sores.*

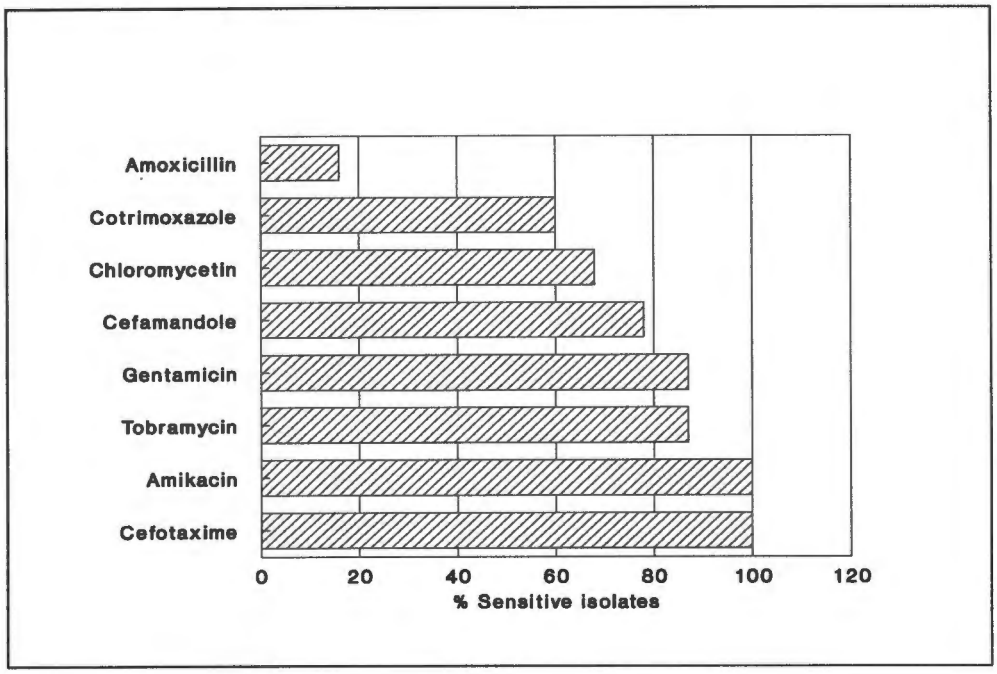
All but five patients developed significant complications. Barotrauma occurred in 4 patients leading to bronchopleural fistulae. Super infection was common and developed in 10 patients (Table 46).

Five of 15 patients who developed renal failure were haemodialysed of whom two survived. Only one patient who developed G.I.T. complications survived.

Twenty seven patients received aminoglycosides, 21 in combination with a third generation cephalosporin. Four patients received a third generation cephalosporin only, and 1 clindamycin and cloxacillin. Only 1 of the patients receiving aminoglycosides without a third generation cephalosporin survived, as compared with 9 of 21 patients receiving aminoglycosides in combination with a third generation cephalosporin. Delay in appropriate antibiotic therapy was common and in 2 non-survivors there was more than 24 hours delay.

Thirty cases had *Klebsiella pneumoniae* cultured from their tracheal secretions; the Gram stain showing numerous pus cells and Gram negative bacilli, with *Klebsiella spp.* predominating on culture. In 25 patients these came from tracheal aspirates performed immediately on intubation and in five from initial sputum. Most sputum specimens were blood stained. Blood culture was positive in 14 (44%). The sensitivity pattern of the early isolates is shown in Figure 30.

Figure 30: Initial isolates of *Klebsiella species* showing sensitivities by disc.



Discussion

These patients with severe, community-acquired *Klebsiella* pneumonia presented with a characteristic clinical picture. This included a history of chronic disease particularly alcoholism and diabetes with an acute, fulminating, febrile illness characterised by confusion, shock, spreading lobar consolidation on chest radiograph, and copious, purulent, blood-stained sputum with numerous Gram negative organisms evident on Gram stain. Recent studies of community-acquired pneumonia have shown that there are no pathognomonic clinical features that can accurately predict an aetiological diagnosis.[17,43,122] Radiological changes in pneumonia are also generally an unreliable predictor of the causative organism.[249,250] The influence of specific, pathogenic micro-organisms causing a more severe pneumonia has not been considered, nor the accuracy of the Gram's stain of tracheal secretions, or radiological features in this setting of severe pneumonia. The spectrum of infecting pathogens causing pneumonia has also not been adequately defined in patients requiring ICU management. Our study indicates that the incidence of *Klebsiella* pneumonia is as

high as 8%. In this clinical setting, therefore, particularly when there is copious sputum and significant Gram negative organisms present on the Gram's stain, *Klebsiella pneumoniae* should be considered as the most likely pathogen and appropriate therapy, i.e. an aminoglycoside in an adequate dose plus a third generation cephalosporin, should be instituted early. Patients with the above clinical features as well as other markers of severe pneumonia including the elderly (> 60 years), tachypnoea > 30 breaths/min, diastolic BP < 60 mm Hg, confusion, urea > 7 mmol/L, PaO_2 < 8 kPa, leukocyte count < 4 ,000 or > 30,000 cells/ml and serum albumin < 35 g/L. require urgent intervention with intensive care management.[250].

The APACHE II scoring system, although useful in determining the severity of disease in large groups of patients, is generally unreliable in predicting mortality in individuals when scored over the first 24 hours. In patients with respiratory failure from infection, a lower than expected score predicts mortality and thus respiratory infection has been accorded a higher risk index.[188] In our patients the high mortality for a relatively low APACHE II score would confirm a higher risk index.

Survivors had a significantly lower APACHE II score than non-survivors suggesting that in patients with *K. pneumoniae* infections the APACHE II score is a useful predictor of outcome. The presence of septicaemic shock and confusion present on admission also appeared to predict a less favourable outcome; complications including ARDS, renal failure requiring dialysis, and gastro-intestinal bleeding also indicated a high mortality.

Intubation and ventilation should be instituted in any patient who is confused and unable to clear secretions, even if the arterial blood gases are maintained above a level regarded as being satisfactory. In this setting, deterioration with respiratory and cardiac arrest can occur rapidly, and respiratory deterioration may be halted with early, active, ventilatory support and effective bronchial toilet. Empiric antibiotic therapy in patients with this early presenting clinical picture should include appropriate Gram negative cover to achieve early, effective antibiotic serum levels. Previous studies have shown an increase in mortality if the serum aminoglycoside levels are inadequate

in severe Gram negative infections.[212] In an earlier smaller study which forms part of this group, many patients had low serum aminoglycoside levels despite careful dosage according to nomograms using 1.5 mg/kg 8 hourly for gentamicin and tobramycin, and 15 mg/kg daily for amikacin.[129] Others have also found wide variability in aminoglycoside serum levels in critically ill patients.[213] In this particular group of patients where the frequency of acute renal insufficiency is very high, therapy with aminoglycosides is even more complicated. Experimental studies of *Klebsiella* pneumonia in animal models have demonstrated the efficacy of continuous infusions of third generation cephalosporins in controlling *Klebsiella pneumoniae*.[251] In immunocompromised patients, a combination of aminoglycosides and a third generation cephalosporin has been shown to be more effective than single agent therapy.[252] We have more recently adopted an antibiotic regimen for Klebsiella spp. infection, combining aminoglycosides with a third generation cephalosporin in an attempt to achieve maximum, effective antibiotic therapy and our early clinical results suggest that this may be a more effective antibiotic regimen in these severely compromised patients who have an exceptionally high mortality. This approach has recently been supported in a study of 230 patients with *Klebsiella pneumoniae* infections that were found to respond better to combination than monotherapy.[176] I would recommend with the foregoing information that combination antibiotic therapy is mandatory for severe community-acquired *Klebsiella* pneumonia.

Mechanical ventilatory manoeuvres used in an attempt to decrease the spread of a disease such as independent lung ventilation and postural drainage, appear to have little effect on the spread of the disease. However, they do positively influence the gas exchange in critically hypoxaemic patients, and may help to buy time for therapy to become effective, and thus should be attempted. The most important aspect of management however, is the early recognition of this potentially fatal pneumonia, which will permit early effective antibiotic treatment, and ventilatory support.

CHAPTER 16

CHICKENPOX PNEUMONIA

Introduction

Chickenpox (varicella) usually a mild disease of childhood, may cause a severe pneumonia in adults. The true incidence of pneumonia complicating chickenpox in adults is unknown, however in a report of 114 patients from a military institution with chickenpox infection, who all underwent radiological investigation, the incidence of abnormality suggesting pneumonia on the chest radiograph was 16.3%.[253] There have also been reports of small series of varicella pneumonia in adult patients from Spain (13 cases over 10 years) and Hungary where 13 of 93 adult patients with varicella requiring hospital admission had pneumonia and 34% of cases in a series of 253 hospitalised adults in the USA.[254-256]

Varicella pneumonia has a reported mortality of between 10 to 20% in the general population; in pregnancy it may be as high as 41%, although recent studies report a mortality of only 10 and 11%, respectively, for non-pregnant and pregnant patients.[253,257,258]

Anti-viral agents (particularly acyclovir) are reported to have little influence on mortality in severe varicella pneumonia in adults, however this is based largely on anecdotal reports and has not been adequately evaluated.[257] We have shown in one of the earliest cases treated with acyclovir, that the virus can be cleared from the vesicles within 24 hours, and that cropping of vesicles ceases almost immediately on commencing acyclovir.[259] In a recent report of 13 cases of varicella pneumonia, acyclovir was thought to be of value in cases with hypoxaemia, and a current review of its use in pregnancy suggests a reduced mortality.[254,260] A suggested reason for lack of efficacy in some reports is the possible delay in treatment, or the development of secondary bacterial infection.[257]

This descriptive study reports the clinical presentation and management of 15 cases of varicella pneumonia with respiratory failure admitted to our respiratory intensive care unit over a period of 10 years from 1984 to 1993. Because of the rarity of this disease and small numbers a longer study period was used.

Patients and Methods

These 15 cases with a clinical diagnosis of varicella, and radiological and clinical features of pneumonia, represent 4% of patients with community-acquired pneumonia who were treated in the ICU over this time period. All patients were in respiratory failure with hypoxaemia and required ventilatory support either with face mask oxygen, continuous positive airway pressure (CPAP) by face mask or intermittent positive pressure ventilation with PEEP (CPPV). Indication for mask CPAP was persisting hypoxaemia (PaO_2 <8 kPa), despite 40% oxygen by mask, adequate alveolar ventilation ($PaCO_2$ <5.5 kPa), with an adequate cough, in a fully co-operative patient who was capable of protecting the airway. Failure to meet the above criteria for adequate respiratory function despite CPAP, was an indication for immediate intubation and CPPV. A free-flow design CPAP apparatus with an oxygen blender and heated humidification was used for CPAP. (Cape CPAP system.), and patients requiring CPPV were ventilated using constant volume ventilators (Bear 2 or 2e) with a heated humidifier (Fisher-Paykel).

Patients were fed enterally as soon as possible, with a normal diet or by enteral tube feeds with the majority receiving 1000 to 1,500 kcals /day. No prophylaxis was used for stress ulceration.

Continuous ECG and oxygen saturation was monitored and routine two hourly recording of pulse, respiratory rate, blood pressure, temperature was done by nursing personnel.

Patient demographic data were recorded and the severity of illness was calculated using the APACHE II scoring system with the worst physiological parameters in the

first 24 hours following admission being used.[208] All associated diseases and compromising factors present on admission were recorded. The duration of ventilation, indications for different ventilatory modalities, and complications were documented. A special note of all procedures and their complications, and all other complications were recorded. Drug therapy was also documented.

All information was collected during the patients stay in the ICU by the investigator or deputy and stored on a data base programme (D Base-IV, Ashton-Tate, Mountain View, Calif.), designed for this ICU information. Analysis was performed 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 USA). Numerical data is reported as mean and standard deviation. Comparison between data was done by Students t for nominal data, and Chi square testing for categorical variables where appropriate.

Results

Nine of the fifteen patients were young females, only one of whom was pregnant, and the remainder had no underlying disease, but had had direct exposure to chickenpox. The two elderly male patients also had close direct exposure to grandchildren who had chickenpox and only one patient, a 16 year old boy, had a major immunocompromising disease (Hodgkin's disease). No patients were suspected of having HIV infection and serological investigation was not performed. The average age was 27.3 ± 12.12 years, and the duration of ICU admission was 6.07 ± 1.91 days. The demographics and severity of illness, ventilatory therapy, and duration of ICU admission are shown in table 47.

Table 47: Demographic features, severity of illness and ventilatory therapy

Patient	Age	Sex	Compromising factors	APACHE II	Vent.Rx	ICU Days
1	30	F	pregnant(32/52)	3	CPAP	7
2	25	F	-	5	Mask	4
3	22	F	-	1	CPAP	3
4	27	M	-	5	CPAP	5
5	24	F	-	12	CPAP	9
6	18	F	-	4	CPAP	4
7	55	M	-	15	CPPV	8
8	16	M	Hodgkin's +splenectomy	-	Mask	6
9	21	M	-	-	Mask	6
10	24	M	-	-	CPPV	7
11	29	F	-	-	CPPV	8
12	18	F	-	12	CPAP	5
13	24	F	-	13	CPAP	8
14	20	F	-	9	CPAP	4
15	56	M	COAD	-	CPPV	23

The diagnosis was clinically obvious in all patients with a history of exposure, a febrile illness (mean temperature 38.5 $^{o}C \pm 0.96$), and a typical vesicular rash, which usually involved the oropharyngeal and buccal mucosal surfaces. The patients were all sick and toxic with marked respiratory distress and hypoxaemia on admission. The mean respiratory rate was 37.7 ± 9.44 breaths /minute and the mean ratio of PaO2 mm Hg to FiO2 was 216 ± 99.2. All patients had a typical diffuse nodular infiltrate on the chest radiograph, however in some, in addition to the interstitial infiltrate, areas of

confluent opacification were also present. In three cases the diagnosis was confirmed with serology. The presenting clinical features are shown in table 48.

Table 48: Presenting clinical features in patients with chickenpox pneumonia.

Patient	Temp. ^{o}C	Resp.Rate	PaO_2/FiO_2	WCC*	Plts *	Onset**
1	38.2	38	218	12,200	155,000	5
2	37.1	40	184	8,000	239,000	5
3	38.8	34	300	5,100	101,000	3
4	38	40	286	9,660	144,000	4
5	40	42	250	2,640	120,000	4
6	38.3	44	203	8,180	62,000	4
7	37.8	28	126	6,300	58,000	6
8	38.5	32	178	4,800	381,000	4
9	40	30	196	9,510	78,000	14
10	38.2	60	139	7,700	60,000	5
11	38.1	32	203	9,700	79,000	6
12	39	54	167	16,700	193,000	2
13	39.8	40	481	10,100	127,000	4
14	37.8	40	180	13,000	207,000	11
15	37.9	40	137	-	-	7

** cells/ml; ** Time of onset to admission (days).*

The serum urea, creatinine and bilirubin were normal in all cases; mean serum albumin 34.1 ± 3.4 mmol/l; the mean serum Na+ was 132.2 ± 2.91 mmol/l, and the liver enzymes were all elevated with a mean ALT of 49.7 ± 27 units/l, AST 67.7 +- 42 units/l and LDH 811 ± 231 units/l.

All patients were treated immediately on diagnosis with intravenous acyclovir 250 to 500 mg 8 hourly for 2 to 3 days, then orally for a total of 5 days. Two patients were admitted with recognised bacterial super infection: one patient had a bronchial infection with *H. influenzae* considered significant on Gram's stain and culture of tracheal aspirate, and the other, the patient with Hodgkin's disease with an extensive bronchopneumonia with *H. influenzae* on Gram's stain and culture of sputum. Only those patients who were thought to have a bacterial infection using both clinical and bacteriological criteria, were given broad spectrum antimicrobial therapy (including anti-staphylococcal agents).

Four patients including the two elderly patients required intubation and CPPV. Two of these patients were considered to have secondary bacterial infection and required CPPV 24 hours after admission after failing to respond to CPAP. The one elderly patient who failed to respond to initial CPAP therapy and required CPPV developed early onset nosocomial pneumonia. The other patients all responded well to ventilatory support with CPAP by face mask (8 patients), and 3 patients face mask oxygen only; this improved oxygenation in all cases. It was however necessary to maintain oxygen therapy at all times, particularly at meal times, when nasal prong oxygen therapy was given. The patients were monitored continuously using pulse oximetry, and in all patients temporary discontinuation of oxygen at the peak of illness led to desaturation. The average duration of CPAP was 3.25 ± 2.19 days and CPPV 7.8 ± 7.04) days. One patient on CPAP developed significant atelectasis that responded to fibreoptic bronchoscopy and chest physiotherapy, and one patient on CPPV developed secondary lower respiratory tract infection. One patient was complicated by axillary vein thrombosis which responded to heparinisation. All patients survived.

Discussion

In our community chickenpox pneumonia most commonly affects young females with young families, probably because of the likelihood of exposure. They present with a high fever, ill and toxic, dry cough, marked tachypnoea, and are very hypoxaemic; provided that secondary bacterial infection is prevented, recovery should occur within a few days. The severe hypoxaemia responds well to CPAP by face mask and this therapy is ideal as it avoids intubation with its attendant increased risk of infection. Although varicella pneumonia is said to have a high mortality there were no deaths, and it is of particular importance that severity of the pulmonary defect is recognised, and appropriate early ventilatory support with PEEP, and the management protocol described above is used.[259,261] The degree of hypoxaemia is often difficult to detect clinically, and blood gas measurement or pulse oximetry are essential to diagnose the defect, and if oxygen therapy is indicated it should not be discontinued without ensuring that oxygenation is adequate.

The use of acyclovir for varicella remains controversial. In two large prospective trials in children aged 2 to 18 years who were given oral acyclovir (20 mg/kg to a maximum of 800 mg 6 hourly) starting within 24 hours of rash onset, the duration of disease was reduced by a median of 1 to 2 days.[262,263] This is a disease which usually only lasts 7 days and is seldom complicated in children, and this coupled with the fact that acyclovir is expensive and unlikely to influence the transmission of varicella, has brought about the recommendations that acyclovir should not be used routinely in uncomplicated varicella.[264] Serious complications of varicella are however so rare that these controlled trials would have insufficient power to detect any effect on the incidence of these complications. There is a place for acyclovir therapy for immunocompromised individuals and adults where varicella is a much more severe disease, with an increased likelihood of pneumonia. A recent review of 19 patients (8 of whom were pregnant), reported a mortality of 38%; acyclovir was thought not to influence outcome however in these patients as it was often given late, and death was frequently associated with secondary bacterial infection.(van Eeden,

South African Pulmonology Society Congress, Abstract, 1991) The lack of efficacy was thought possibly to be due to a delay in therapy, however in the group of fifteen patients reported in this analysis with no deaths, the average time of onset of illness to the administration of acyclovir therapy was as long as 6 days. Although a number of other uncontrolled studies have also suggested that acyclovir has no effect on mortality[257], a recent report suggests that it may be of value in adult patients with respiratory symptoms and hypoxaemia.[254] Pregnancy requires special consideration as it is thought to increase the risk of varicella pneumonia 20 fold, as well as increasing the associated mortality to both the infant and mother. Previous studies have reported mortalities of as high as 45% , however a recent review of over 21 cases reported in the English literature where acyclovir was used in pregnancy, found a mortality of only 14%, and reports in other languages would support this reduced mortality since the introduction of acyclovir.[260] Reviews of small series of patients in whom acyclovir has been used suggest that the mortality should not be much greater than 10% even if pregnant patients are considered.[257,258]

Varicella zoster is exquisitely sensitive to acyclovir and rapid cessation of cropping of vesicles is usually seen shortly after starting this agent. Following our experience in patients in respiratory failure, we would strongly recommend the use of acyclovir as it will hasten resolution and shorten the time that ventilatory support is necessary.[259,265] The recommended dose of acyclovir is 7.5 to 10 mg/kg 8 hourly intravenously or 800 mg 6 hourly orally which will give serum trough levels above the ID50 of 1.12 micro gm/ml.[265,266] The use of acyclovir in pregnancy appears safe during the latter trimesters of pregnancy and no foetal abnormalities have been seen in 77 cases where acyclovir was used in the first trimester.[260] Varicella infection in the first trimester may itself increase the incidence of foetal abnormalities, and embryopathy has been shown to occur in 2.2% of cases. Prophylactic varicella hyper immune globulin should be considered in individuals who have not had the disease and who have been exposed, or varicella vaccine may reduce this risk in unexposed individuals when given before pregnancy.[264]

The use and efficacy of CPAP by face mask for ventilatory support in varicella pneumonia has been recommended in a number of case reports[267], and we would endorse this form of ventilatory support as it significantly reduces the risk of secondary respiratory infection. Although this has not been confirmed in patients with pneumonia where it is usually suitable for only 5% of cases requiring respiratory support,[268] it has been found useful in a small number of cases when the patients fall short of the requirement for intubation and CPPV.[268] Mask CPAP has however been clearly shown to reduce complications and infection in other causes of respiratory failure particularly when secondary to chest trauma.[218]

This study suggests that the early administration of acyclovir, coupled with recognition of the severe hypoxaemia that results from varicella pneumonia, which can be reversed with PEEP and particularly CPAP by mask, should reduce the mortality of severe varicella pneumonia to single figures.

CHAPTER 17

STAPHYLOCOCCAL PNEUMONIA.

Introduction

S. aureus is an uncommon cause of CAP with an incidence of 1.5% to 4 % in emergency room or community based studies.[9,17,52,125] There is however a suggestion that this disease is becoming more common not only in hospital acquired, but also in community-acquired infections.[104] When more severe disease is considered, however, the incidence is considerably higher with an incidence of 3 to 9%,[32,119] and in a previous report we noted an increased mortality of 50%.[1] The diagnosis of staphylococcal pneumonia from the community is usually easy both on clinical, microbiological, and radiological grounds.[102] The disease may either be haematogenous in origin, with typical lobular opacification on the chest radiograph, often with seeding and other sites of infection, and occurring more commonly in third world settings in previously fit young patients; or of an aerogenous aetiology which is clinically less distinctive.[68,102] This latter form is commonly seen during influenza epidemics where it is recognised to have a high mortality.[105] The microbiological diagnosis is usually not difficult, with numerous Gram positive cocci in clusters present on the Gram's stain of sputum, and a blood culture which is often positive.[102,104]

This type of pneumonia is therefore of particular interest both from our geographical setting where a higher prevalence of haematogenous disease may occur, and also because of the severity of the pneumonia in our ICU patient population.

Patients and Methods.

This is a sub-group analysis of the major study population and the same diagnostic and therapeutic approach, and data collection described in chapter 8 was applied. The definition of a haematogenous infection was a distinctive lobular pattern on the chest radiograph, or a patient who had other sites of infection in addition to the pneumonia. Any other staphylococcal pneumonia was considered aerogenous.

Results.

Seventeen of the 196 patients with CAP had pneumonia caused by *S. aureus*. In two, there were dual infections with *S. pneumoniae* in one, and Group A *Beta haemolytic streptococcus* in the other. Seven were considered to have haematogenous infection and ten aerogenous infection. No patient had the disease clearly associated with influenzae, however one patient had severe asthma, another mild asthma, two COPD, one diabetes, and one developed pneumonia one week after a minor stab in the neck. The patients were aged from 13 to 75 with a median age of 37 years (mean 37.1 ± 20.93). There were 2 white, 4 black and 11 of mixed racial origin, and 14 male and 3 female.

The mean APACHE II score was 14.4 ± 6.21; organ failure score 1.29 ± 0.85. The clinical features are shown in table 49.

Table 49: The clinical features on admission.

Pt.	Age	APACHE II	Aet.*	Resp. Rate	PaO_2/FiO_2	X-ray	Outcome
JC	64	18	Aerog.	-	262.5	Inters.**	Surv.
RA	39	18	Haem.	24	264.4	Lobular	Surv.
GD	20	12	Haem.	50	330	Lobular	Surv.
AZ	42	9	Aerog.	40	137.5	Lobar	Surv.
TJ	14	7	Haem.	15	315	Lobular	Surv.
PX	18	15	Haem.	46	118.8	Lobular	Surv.
MN	16	11	Haem.	50	163.1	Lobar	Surv.
JK	54	11	Aerog.	14	431.3	-	Surv.
JD	13	8	Haem.	16	300	Lobular	Sure.
EI	36	18	Aerog.	40	240	Segmental	Surv.
KM	22	11	Aerog.	46	366	Broncho.	Surv.
CH	75	22	Aerog.	30	191.3	Segmental	Died
DP	26	15	Aerog.	48	127.5	-	Died
NZ	20	18	Haem.	14	113.1	Lobular	Died
PT	72	32	Aerog.	30	313.6	Broncho.	Died
JS	39	17	Aerog.	34	257.1	Broncho.	Died
JZ	49	10	Aerog.	20(V)	110.6	-	Died

* *aetiology - Haem.= haematogenous; Aerog. = aerogenous or endogenous.*

***Interstitial*

A number of clinical features are thought to predict a poor outcome and these are shown in the following table 50.

Table 50: Clinical predictors of a poor outcome.

	Survivors	**Deaths**	**p =**
	(n = 11)	(n = 6)	
Age >60 years	1	2	ns
APACHE II Mean +- S.D.	11.8 ± 3.71	19 ±7.48	0.118
Temperature > 38.5°C	1	3	ns
< 35.5°C	1	1	ns
Resp. rate >30 breaths/min	6	3	ns
WCC < 5,000 cells/ml	2	2	ns
5,000 - 18,000 cells /ml	5	1	ns
>18,000 cells/ml	3	2	ns
DIC	1	1	ns
S.albumin < 35 g/l	6	4/4	ns
Urea > 7 mmol/l	4	5	0.178
Creatinine.micro mol/l +- S.D.	130.7±106	446.2±358	0.104
Impaired level of consciousness	0	2	ns
Shock (SBP < 80 mm Hg)	0	4	0.017
Compromising disease	3	3	ns
Bacteraemia	6	3	ns
Arterial blood gas			
PaO_2(mm Hg)/FiO_2	260.1	185.5	0.11
$PaCO_2$	4.99	4.05	0.41
pH	7.39	7.38	0.86
Base excess	-3.39	-6	0.094

The diagnosis was made in 9 cases by blood culture, 3 of whom also had a positive Gram's stain of the sputum and 4 another site of infection. In addition there were 8 patients with the diagnosis made on sputum or tracheal aspirate only; 2 patients had a positive pleural culture and in 4 a distant abscess cultured *S. aureus* as well. One patient with haematogenous infection (following the minor stab neck), had both *S. aureus* and Group A *Beta haemolytic streptococcus* on blood culture.

All isolates of *S. aureus* were sensitive to cloxacillin.

The chest radiographs showed a variety of abnormalities particularly in aerogenous infection where 1 patient had lobar consolidation, 2 segmental, 1 interstitial, and 3 broncho-pneumonic changes; in the haematogenous group 5 had the typical lobular opacification associated with haematogenous origin and 1 had lobar changes.

The clinical characteristics of patients with haematogenous infections are contrasted with those of aerogenous origin in table 51.

Table 51: Haematogenous vs. aerogenous staphylococcal pneumonia.

	Haematogenous	Aerogenous
No of Patients	**7**	**10**
Age*	20 ± 8.81	49.1 ± 18.44
APACHE II	11.57 ± 3.87	16.3 ± 6.96
Male:female	5:2	9:1
Temperature ^{o}C	37.73±0.59	37.63±1.47
Resp. rate	28.6±15.16	33.6±11.4
PaO_2/FiO_2	229	244
WCC cells/ml	8,529±5,190	36,313±63,196
Platelets cells/ml	160,000±123,000	242,000±129,000
Renal failure	5	4
Urea m mol/l	27.03±31.6	14.18±14.7
Creatinine micro mol/l	183.7±154.2	282±325.9
Shock	2	3
Duration (days)	20 ± 6.83	11.2 ± 8.69
IPPV (n)	6	10
IPPV (days)	15.57 ± 7.91	8.8 ± 7.05
Mortality**	1 (14.3%)	5 (50%)

** $p = 0.0014$, ** $p = 0.32$*

Therapy

Sixteen patients required intubation and IPPV, whereas one patient was treated with CPAP by face mask. The duration of ventilation is shown in table 51. Five patients with acute renal failure required haemodialysis, and of these two survived. Seven patients required chest drains to be inserted, five for barotrauma developing during

IPPV, and two for drainage of empyemata. All but 3 patients received cloxacillin with the majority receiving a combination of cloxacillin and an aminoglycoside (2 patients), cloxacillin and fusidic acid (2 patients), cloxacillin and fusidic acid and vancomycin (1), cloxacillin and vancomycin (1), cloxacillin and clindamycin (1), clindamycin and vancomycin (1), cloxacillin, clindamycin and amikacin (1), cloxacillin, clindamycin, fucidic acid and vancomycin (1), cloxacillin and cefotaxime (1), vancomycin (1), and cloxacillin only (2), penicillin and amikacin (1). Three of the deaths occurred in patients receiving multiple anti-staphylococcal agents whereas in two deaths, one which occurred within hours after admission to hospital, inappropriate antibiotics were used.

Complications

Seven patients had an uncomplicated course, but in the remainder, numerous complications occurred.(see table 52)

Table 52: Complications in staphylococcal pneumonia

Complication	No of Patients
Gastro-intestinal Bleeding	3
Pneumothorax	5
Pulmonary Bleeding	1
Tracheal Bleed	1
Blocked ETT	1
Accidental extubation	1
Nosocomial Infection	7
Other	7

Mortality

Two patients died within a short time of being admitted and were considered to have died from overwhelming septicaemia, and the remaining deaths occurred after 13 to 22 days of admission and were considered to have multiple organ failure. Only one death occurred in the 7 patients considered to have haematogenous infection, whereas there were 5 deaths in the patients considered to have aerogenous infection.

Discussion

This study confirms the high mortality in severe community-acquired staphylococcal pneumonia with a mortality of 35.7% compared to the overall mortality in this study of 25.5%. This is lower than previously reported, both by us, and in other studies.[1,108] The differences in the possible mechanisms of aetiology have not previously been reported as a separate disease entity, however in this study there are substantial differences in the clinical presentation with a younger age group and classical lobular radiological changes being typical of the patients with haematogenous aetiology. Many of these patients also had deep seated staphylococcal abscesses and only one of seven patients died. The group with aerogenous infection had no distinguishing clinical or radiological features and 5 of 10 patients died. This high mortality with staphylococcal pneumonia has previously been noted particularly when associated with influenza. Infection with influenzae causes an environment which is particularly conducive to multiplication of *S. aureus* and may in part account for the increased mortality, however in our patients there was no apparent association with influenza, and the mortality remained particularly high in the aerogenous group.
All isolates were cloxacillin sensitive and the majority of patients received cloxacillin and an aminoglycoside and surgical drainage of localised abscesses either soft tissue, osteitis, pleural or arthritis was performed as early as possible and repeated if no resolution occurred.

CHAPTER 18

CONCLUSION

Severe pneumonia requiring ICU admission, particularly when ventilatory support is necessary, is one of the major clinical challenges for the intensivist. We have shown that the mortality associated with severe pneumonia is high, but it is considerably lower than previous studies, and some recent some studies where the patients severity of illness scores have been similar to our population.[32,119,215,269] A mortality similar to that found in this study has also been reported in some recent studies, and this suggests that the mortality can be reduced with modern intensive care. Knaus suggests that differences in mortality between intensive care units may be related to a well orchestrated team approach using proven therapeutic protocols with full time medical direction and our results add support to this suggestion.[208] The management protocols which have evolved over the past 20 years in our ICU, including antibiotic therapy, diagnostic procedures, and ventilatory techniques have been well justified by the satisfactory outcome of these patients with severe pneumonia reported in this study. CAP nevertheless, still has a high mortality and deaths may be divided into those occurring early from severe sepsis with cardiac and respiratory failure, or those that occur late where complications of therapy, nosocomial infection, and multiple organ failure are the main contributors. The approach to therapy used in our ICU which included early supportive therapy with ventilation, fluid and inotrope therapy, and optimal antibiotic therapy with an appropriate spectrum of activity plus adequate serum levels, may also have contributed to this favourable outcome. Prevention of secondary infection with meticulous aseptic techniques as well as other prophylactic techniques such as SDD to prevent colonisation, may also play a role particularly in preventing later deaths. The introduction of new immuno-therapy particularly monoclonal antagonists of the inflammatory pathways may also influence early

deaths, as well as later organ failure. These new modalities will have to be tested in carefully selected patient populations with a known mortality, with well defined criteria for entry into studies to avoid equivocal results. It patients with pneumonia it will be necessary to control for factors such as co-morbid diseases, delay in therapy, appropriateness of therapy, type of micro-organism and the severity of illness; all of which is extremely difficult if not impossible.

While the classification used in this thesis has proved useful in defining the incidence of aetiological agents of the different pneumonias, their therapeutic response and outcome, certain inadequacies with this classification have become apparent. The most important deficiency is found with the patient who is admitted with a co-morbid disease which will inevitably result in a pneumonia, often within 48 hours of admission, and in whom the underlying disease and not the pneumonia is the main factor which determines the final outcome. These patients fall by definition into the CAP group, but in terms of outcome, empirical antibiotic and other therapy behave differently, and would probably be better classified separately. This group should be considered as separate subgroups of CAP, with the precipitating disease specified e.g. muscular weakness (Guillain Barre' syndrome, myasthenia gravis etc.). In this study some of these patients particularly those young patients who died, death was a result of the co-morbid disease (chapter 11). In others with similar co-morbidity the pneumonia itself was mild and the patient responded rapidly once adequate respiratory support was instituted making the association with co-morbid disease an even greater confounding factor.

The previously reported high incidence of both Gram negative and staphylococcal infections has been confirmed, and although the mortality for these infections is almost double that of the other pneumonias, it is not statistically significant because of small numbers. *S. pneumoniae* nevertheless still remains the most common pathogen in patients with severe pneumonia. Most patients with *L. pneumophila* treated in hospital during this period required ICU admission , however there were no deaths in this group given appropriate therapy. Mycoplasma and other atypical pneumonias

were seldom seen and also tend to produce a mild pneumonia. It is however conceivable that the incidence of *M pneumoniae*, *Clamydia pneumoniae* and *Legionella spp.* infections were under diagnosed as serology was not done routinely but only when clinically indicated.

The standard diagnostic approach used proved moderately successful in detecting 72% of pathogens with a 30% positive yield on blood culture. The value of the Gram's stain of a well collected sputum specimen, particularly a tracheal aspirate obtained soon after intubation, especially where a single organism predominated in large numbers was shown to be particularly useful. The early Gram's stain of appropriate bronchial secretions proved to be of particular value in detecting patients with *Klebsiella* and staphylococcal pneumonia. The sensitivity of the Gram's stain of tracheal aspirate or sputum in 31 patients with a positive blood culture had a sensitivity of 74% and specificity of 100% , and the culture a sensitivity of 68% and specificity of 91% (chapter 12) in identifying most *Klebsiella spp.* and *S. aureus* infections, and there were few false positives or false negatives. The sputum was also valuable in detecting pneumococcal infections where the Gram's stain findings were often confirmed by the blood culture.

Specimens obtained by fibreoptic bronchoscopy with a PSB seldom contributed to a positive diagnosis, although this may be because the specimen was usually taken after antibiotics had already been given. Similar findings have been reported by other authors, some of whom have suggested that a negative finding is useful, but the value of a negative procedure is still open to debate.

When all clinical parameters were considered there was no delay in diagnosing any cases of *K Pneumoniae* or *S aureus* infections.(chapter 15,16) Individual clinical features including the chest radiograph were poor predictors of aetiology. Most patients with haematogenous *S aureus* and Chickenpox pneumonias were however identified using the chest radiograph. The specificity was however low.

A number of previously accepted beliefs regarding pneumonia, particularly in relation to the determination of outcome have been shown to be of little use in patients with

severe pneumonia requiring ICU care. Severity of illness scoring systems including the APACHE II, organ failure and lung injury scoring systems all accurately predicted mortality in these patients as a group, and there was a significant difference in the scores between survivors and non-survivors. As previously shown, a lower score in pneumonia predicted a higher mortality than for other diseases The prediction for individuals with the APACHE II was unreliable and no level could accurately predict death.

The organ failure score was found to be a more reliable predictor of outcome in individuals: all patients with 4 or more organ failure on day 1 died, 11 of 19 (58%) with 3 organ failure, 13 of 36 (36%) patients with 2 organ failure, and only 18 of 101 patients with 1 organ failure on day 1 died; however on subsequent days less than 4 organ failure was not predictive of individual outcome, as even patients with 3 organ failure on day 3, eight of 19 patients (42%) survived (unfortunately the numbers of patients with higher organ failure scores were too small for adequate evaluation). The acute lung injury score proved no better than the APACHE II score for individual prediction.

The rules suggested by the BTS and other studies that proved valuable in hospital based populations of pneumonia, failed to perform in this selected group, all of whom had severe pneumonia. Rule 1 had a positive predictive value of only 42% with a sensitivity of 65% and specificity of 70%. Whilst age of more than 60 years was a significant predictor of mortality, a number of young patients died. In these patients death was often due to co-morbid disease rather than the pneumonia itself.

The presence of septic shock was the most significant predictor of an adverse outcome, however this clinical feature on its own predicted less than 50% of deaths. Other clinical features that were significantly different between survivors and non-survivors included a low serum albumin, WCC, a DIC and an elevated inorganic phosphate, ALT and urea. Only one of the 6 patients with very high white cell count (> 40,000 cells/ml) died, whereas 46% of 39 patients with a count of < 4,000 cells/ml died (X^2 $p = 0.225$). When the Bonferroni correction for multiple comparisons was

applied only shock retained its predictive value. The serum albumin was significantly lower in non-survivors than in survivors, but even in survivors the mean level was only 28.6 g/l illustrating the difference between the local population and more developed populations.

There are a number of other important factors that related to death in the individual patients, the most remediable of these being the incorrect selection and use of antibiotics. We found that in some cases inappropriate antibiotics were initially selected, in others inadequate doses were administered, and in a number of cases a delay in antibiotic administration occurred. A number of patients presented after days of delay, most without having received any treatment, and this almost certainly contributed to death in some instances. This reflects the poor community-based medical facilities provided, and the lack of health education in our patient population. Although some of these factors have been shown to be associated with deaths in this thesis , they have not yet been used in any scoring systems. In order to accurately predict the outcome in pneumonia, these factors will need to be incorporated into future scoring systems. (This statement is now dated as Leroy has reported at the International Congress of Antimicrobials and Chemotherapy in 1984 and 1985 in two abstracts. The first defining similar prognostic factors and weighting them according to their statistical values and showing some value in a retrospective cohort, and the second applying this system to a prospective group and showing rather disappointing results. This particular aspect of this thesis has now been updated with additional patients and an updated discussion and is included as appendix 5.)

The antibiotic policy adopted during this study using penicillin and an aminoglycoside, usually amikacin, with the addition of cloxacillin, a third generation cephalosporin, or erythromycin in special circumstances, would seem to be appropriate, as the outcome for all groups was as low or lower than any previous mortality figures reported in the literature. Low serum levels of aminoglycoside were not infrequent, serving to emphasise the need to give appropriate, often larger than

usual doses of antibiotic, because of the increased volume of distribution in this group of critically ill patients.

The efficacy of the use of early intubation and the ventilatory techniques employed were confirmed by the infrequency of both of ventilatory complications and of death due to irreversible hypoxaemia. Following on from this, I would recommend that intubation should be expedited in any patient who is confused, shocked, unable to clear secretions, exhausted or who has unresponsive hypoxaemia.

The need for a multidisciplinary approach was highlighted by the low mortality in those patients who required dialysis, and also the overall low mortality of only 24.5%.

The cause of death was usually early shock, or more commonly multiple organ failure after many days of ICU support suggesting that in order to achieve any further reduction in mortality attention will need to be directed at these two areas. The reversal of early shock may be improved by early diagnosis with optimal antibiotic support, and this is the area where the newer methods of immunomodulating the inflammatory cascade may have an important role to play; while the prevention of progressive multiple organ failure may be achieved by providing a high degree of support and preventing secondary complications Any innovation however, should only be incorporated into common practice once it has undergone rigorous and critical evaluation.

Implicit to the successful achievement of all of the above, is the need for a highly trained and motivated critical care team, drawing on the support of ancillary services and efficiently utilising the ever-increasing armamentarium at their disposal.

Summary of Important Findings

1. Classification should include: CAP with subgroups according to co-morbid disease, aspiration pneumonia, nosocomial pneumonia with VAP as well as time of onset, and pneumonia in immunocompromised patients. The severity of pneumonia should also be considered e.g. severe CAP vs. mild CAP.
2. Aetiology differs in severe CAP

    Gram negative, *S. aureus* and *L. pneumophila* increased

    M. pneumoniae, *C. pneumoniae* uncommon.
3. Prediction of outcome

    Group mortality predicted well by APACHE II and Organ failure scores.

    Organ failure score best individual predictor

    Modified BTS rules perform poorly.

    Lung injury score is a poor predictor
4. Therapeutic approach works well

    Early intubation

    Conventional ventilation

    CPAP when tolerated
5. Antibiotic protocol appropriate and cheap.
6. Mortality in bacteraemic pneumococcal pneumonia is not increased.
7. Acyclovir and CPAP for Varicella pneumonia.
8. Staphylococcal pneumonia has 2 distinctive types depending on pathogenesis
9. ICU care reduces mortality in severe pneumonia.

BIBLIOGRAPHY

1. Potgieter PD, Hammond JMJ. Etiology and Diagnosis of Pneumonia Requiring ICU Admission. Chest 1992; 101:199-203.

2. Ortqvist A, Sterner G, Nilsson A. Severe Community-acquired Pneumonia: Factors Influencing Need of Intensive Care Treatment and Prognosis. Scand J Infect Dis 1985; 17:377-386.

3. Bartlett CLR, Harrison BDW, Macfarlane JT, et al. The aetiology, management and outcome of severe community-acquired pneumonia on the intensive care unit. Respiratory Medicine 1992; 86:7-13.

4. Tsai TF, Finn DR, Plikaytis BD, McCauley W, Martin SM, Fraser DW. Legionnaires' Disease: Clinical Features of the Epidemic in Philadelphia. Ann Intern Med 1979; 90:509-517.

5. Nguyen MLT, Yu VL. Legionella Infection. Clinics in Chest Medicine 1991; 12:257-268.

6. Cameron EWJ. Treatment of chronic destructive pneumonia with cephalosporin, penicillin and metronidazole. S Afr Med J 1978; 54:57-60.

7. Pareja A, Bernal C, Leyva A, Piedrola G, Maroto C. Etiologic Study of patients with Community-acquired Pneumonia. Chest 1992; 101:1207-1210.

8. Bates JH, Campbell GD, Barron AL, et al. Microbial Etiology of Acute Pneumonia in Hospitalised Patients. Chest 1992; 101:1005-1012.

9. Prout S, Potgieter PD, Forder AA, Moodie JW, Matthews J. Acute Community-acquired Pneumonias. S Afr Med J 1983; 64:443-446.

10. Potgieter PD, Hammond JMJ. Non-Responding Pneumonia. S Afr Med J (CME) 1991; 9:683-690.

11. Woodhead MA, Arrowsmith J, Chamberlain-WebberR, Wooding S, Williams, I. The Value of routine microbiological investigation in community-acquired pneumonia. Respiratory Medicine 1991; 85:313-317.

12. Murray PR, Washington JA. Microscopic and Bacteriologic Analysis of Expectorated Sputum. Mayo Clinic Proc 1975; 50:339-344.

13. Rankin JA. Getting the Bugs Out of BAL. Chest 1991; 100:1-2.

14. Meduri GU, Baselski, V. The Role of Bronchoalveolar Lavage in Diagnosing Nonopportunistic Bacterial Pneumonia. Chest 1991; 100:179-190.

15. Boersma WG, Lowenberg A, Holloway Y, Kuttschrutter H, Snijer JAM, Koeter GH. Pneumococcal capsular antigen detection and pneumococcal serology in patients with community acquired pneumonia. Thorax 1991; 46:902-906.

16. Venkatesan P, Macfarlane JT. Editorial. Thorax 1992; 47:329-331.

17. Andrews BE, Bartlett CLR, Connolly CK, Ellis DA, Farr BM, Harrison BDW. Community-acquired Pneumonia in Adults in British Hospitals in 1982-1983: A Survey of Aetiology,Mortality,Prognostic Factors and Outcome. Q J Med 1987; 62:195-220.

18. Fine MJ, Smith DN, Singer DE. Hospitalisation decision in patients with Community-acquired pneumonia: a prospective cohort study.. Am J Med 1990; 89:713-721.

19. Karalus NC, Cursons RT, Leng RA, et al. Community acquired pneumonia: aetiology and prognostic index evaluation. Thorax 1991; 46:413-418.

20. Van Eeden SF, Coetzee AR, Joubert JR. Community-acquired pneumonia - factors influencing intensive care admission. S Afr Med J 1988; 73:77-81.

21. Fine MJ, Singer DE, Hanusa BH, Lave JR, Kapoor WN. Validation of a pneumonia prognostic index using the MedisGroups Comparative Hospital Database. Am J Med 1993; 94:153-159.

22. Farr BM, Sloman AJ, Fisch MJ. Predicting Death in Patients Hospitalized for Community-acquired Pneumonia. Ann Int Med 1991; 115:428-436.

23. Marcy TW, Marini JJ. Inverse ratio ventillation in ARDS. Rationale and implementation. Chest 1991; 100:494-504.

24. Greenbaum DM, Eugene Millen J, Eross B, Snyder JV, Grenvik A, Safar P. Continuous Positive Airway Pressure without Tracheal Intubation in Spontaneously Breathing Patients. Chest 1976; 69:615-620.

25. Kvetan, V, Carlon GC, Howland WS. Acute pulmonary failure in asymmetric lung disease:approach to management. Crit Care Med 1982; 10:114-118.

26. Hammond JMJ, Potgieter PD, Musson G, Odell J. Surgical drainage of lung abscesses complicating acute community acquired pneumonia. Chest 1991; 99:1280-1282.

27. Hammond JMJ, Potgieter PD, Musson G, Odell J. Surgical drainage of lung abscess complicating acute community-acquired pneumonia. Chest 1991; 99:1280-1282.

28. Hammond JMJ, Lyddell C, Potgieter PD, Odell J. Severe Pneumococcal Pneumonia complicated by by Massive Pulmonary Gangrene. Chest 1993; 103:

29. Potgieter PD, Linton DM, Forder AA, Plumb H. Ceftriaxone in the management of severe pneumonia. S Afr Med J 1986; 15:495-497.

30. Potgieter PD, Louw SJ, Forder AA, Roditi D. Cefotaxime in adults with severe infections.. Proceedings of the 13th International Congress of Chemotherapy 1983; 98:10-11.

31. Ali NJ, Sillis M, Andrews BE, Jenkins PF, Harrison BDW. The Clinical Spectrum and Diagnosis of Mycoplasma pneumoniae Infection. Q J Med 1986; 58:241-251.

32. Feldman C, Kallenbach JM, Levy H, et al. Community-acquired pneumonia of diverse aetiology: prognostic features in patients admitted to an intensive care unit and a severity of illness score. Intensive Care Med 1989; 15:302-307.

33. Levy M, Dromer F, Brion N, Leturdu F, Carbon C. Community-Acquired Pneumonia. Chest 1988; 92:43-48.

34. Pesola GR, Allison C. Pneumococcal Bacteraemia with Pneumonia. Mortality in Acquired Immunodeficiency Syndrome. Chest 1992; 101:150-155.

35. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection: epidemiologic clinical and immunologic perspectives. Ann Intern Med 1992; 117:314-324.

36. Meduri GU. Introduction to the Consensus Conference on Ventilator-Associated Pneumonia. Chest 1992; 102s1:551s-552s.

37. 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.

38. Anonymous. Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assesment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 1993; 148:1418-1426.

39. 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.

40. Fein AM, Feinsilver SH, Niederman MS. Nonresolving and slowly resolving pneumonia. Diagnosis and management in the elderly patient. [Review]. Clinics in Chest Medicine 1993; 14:555-569.

41. Orens JB, Sitrin RG, Lynch JP. The approach to nonresolving pneumonia. [Review]. Medical Clinics of North America 1994; 78:1143-1172.

42. Wald ER. Recurrent and nonresolving pneumonia in children. [Review]. Seminars in Respiratory Infections 1993; 8:46-58.

43. Stratton CW. Bacterial Pneumonias - An overview with emphasis on pathogenesis, diagnosis, and treatment.. Heart and Lung 1986; 15:226-243.

44. 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.

45. Harada R, Repine JE. Pulmonary Host Defense Mechanisms. Chest 1985; 87:247-252.

46. 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.

47. 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.

48. 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.

49. 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.

50. 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.

51. Macfarlane JT, Finch RG, Ward MJ, Macrae AD. Hospital Study of Adult Community-acquired Pneumonia. Lancet 1982; 255-258.

52. Fang G, Fine M, Orloff J, et al. New and Emerging Aetiologies for Community-Acquired Pneumonia with Implications for Therapy. Medicine 1990; 69:307-316.

53. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspirataion in normal adults and patients with depressed consciousness. Am J Med 1978; 64:564-568.

54. Rogers LA, Osterhout S. Pneumonia following tracheostomy. Am Surg 1970; 59:39-46.

55. 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.

56. Potgieter PD, Linton DM, Oliver S, Forder AA. Nosocomial infection in a respiratory intensive care unit. Crit Care Med 1987; 15:495-498.

57. Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalised patients. N Engl J Med 1969; 281:1137-1140.

58. Roth RM, Gleckman RA. Pneumonia in the Elderly: A Nursing Home Perspective. AFP 1985; 31:131-137.

59. Bartlett JG. Anaerobic bacterial infections of the lung. Chest 1987; 91:901-909.

60. Newhouse MT, Bienenstock J. Respiratory tract defense mechanisms. In: Baum GL, Wolinsky E, eds. Textbook of pulmonary disease. 4th ed. Boston: Little Brown, 1989:21-27.

61. Levin S. The Atypical Pneumonia Syndrome. JAMA 1984; 251:945-948.

62. Mufson MA, Chang, V, Gill, V, Wood SC, Romansky MJ, Chanock RM. The Role Of Viruses, Mycoplasmas, and Bacteria in Acute Pneumonia in Civilian Adults. Am J Epidem 1967; 86:526-543.

63. Niederman MS, Rafferty TD, Sasaki CT, Merrill WW, Matthay RA, Reynolds. Comparison of bacterial adherence to ciliated and squamous epithelial cells obtained from the human respiratory tract. Am Rev Respir Dis 1983; 127:85-90.

64. Tashiro M, Ciborowski P, Klenk H-D, Pulverer G, Rott R. Role of Staphylococcus protease in the development of Influenza Pneumonia. Nature 1987; 325:536-537.

65. Knowles MR, Gilligan P, Boucher RC. Cystic Fibrosis. In: Mandell GL, Gordon Douglas R, Bennett JE, eds. Principles and Practice of Infectious Diseases. 3rd ed. New York: Churchill Livingston, 1990:579-582.

66. 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.

67. 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.

68. Naraqi S, McDonnell G. Hematogenous Staphylococcal Pneumonia Secondary to Soft Tissue Infection.. Chest 1981; 79:174-175.

69. Jaffe RB, Koschmann MD. Septic Pulmonary Emboli. Radiology 1970; 96:527-532.

70. Griffith GL, Maull KI, Sachatello CR. Septic Pulmonary Embolization. Surg Gynecol Obstet 1977; 144:105-108.

71. Bennett JE. Aspergillus Species. In: Mandell GL, Gordon Douglas R, Bennett JE, eds. Principles and Practice of Infectious Diseases. 3rd ed. New York: Churchill Livingston, 1990:1958-1962.

72. Bruyn GAW, Zegers BJM, Van Furth R. Mechanisms of host defence against infection with Streptococcus pneumoniae. Clin Infect Dis 1992; 14:251-262.

73. Wanner A. Clinical aspects of mucociliary transport.. Am Rev Respir Dis 1977; 116:73-75.

74. Rhodin JAG. Ultrastructure and function of the human tracheal mucosa. Am Rev Respir Dis 1966; 93:S1

75. Sleigh MA. Some aspects ofthe comparative physiology of cilia. Am Rev Respir Dis 1966; 93:16-20.

76. Fawcett DW. What makes cilia and sperm tails beat.. N Engl J Med 1977; 297:46-48.

77. Egberg H, Mohr J, Schmiegalow K, et al. Linkage relationships of paraoxonase (PON) with other markers: Indication of PON-cystic fibrosis synteny. Clin Genet 1985; 28:265-271.

78. Tsui L, Buchwald M, Barker D, et al. Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker. Science 1985; 230:1054-1057.

79. Wainwright BJ, et al. Localization of cystic fibrosis locus to human chromosome 7cen-q22.. Nature 1985; 318:384-385.

80. Stutts MJ, Schwab JH, Chen MG, et al. Effects of Pseudomonas aeruginosa on bronchial epithelial ion transport. AM Rev Respir Dis 1986; 134:17-24.

81. Kaltreider HB. Expression of immune mechanismsin the lung.. Am Rev Respir Dis 1976; 113:347-349.

82. Lawrence EC, Blaese RM, Martin RR, et.al. Immunoglobulin secreting cells in normal human bronchial lavage fluids. J Clin Invest 1978; 62:832-835.

83. Fels AOS, Cohn ZA. The alveolar macrophage.. J Appl Physiol 1986; 60:353-355.

84. Sibille Y, Reynolds HY. Macrophage and Polymorphonuclear Neutrophils in Defence and Injury. Am Rev Respir Dis 1990; 141:471-501.

85. Reynolds HY, Atkinson JP, Newball HH, Frank MM. Receptors for immunoglobulin and complement on human alveolar macrophages. J Immunol 1975; 114:1813-1819.

86. Lewis JF, Brake SR, Anderson DJ, et al. Urinary tract infection due to coagulase-negative staphylococcus. Am J Clin Pathol 1982; 77:736-739.

87. Creger WP, Coggins CH, Hancock EW. Annual review of medicine. Palo Alto: Annual Reviews Inc 1981; 31:624

88. Melly MA, Thomison JB, Rogers DB. Fate of staphylococci within human leukocytes. J Exp Med 1960; 112:1121

89. Woods DE, Straus DC, Johanson WG, et al. Role of pili in adherence of Pseudomonas aeruginosa to mammalian buccal epithelial cells. Infect Immun 1980; 29:1146-1149.

90. Heck LW, Morihara K, Abrahamson DR. Degradation of soluble laminin and depletion of tissue-associated basement membrane laminin by *Pseudomonas aeruginosa* elastase and alkaline protease.. Infect Immun 1986; 54:149-152.

91. Liu PV. Toxins of *Pseudomonas aeruginosa*. In: Dogget RG, ed. *Pseudomonas aeruginosa*. New York: Academic Press, 1979:63

92. Spencer. The Bacterial Pneumonias. In: Spencer, ed. Pathology of the Lung. 3rd ed. London: Pergamon Press, 1977:168-170.

93. Barnes P. The Pathology of Community-Acquired Pneumonia. Seminars in Respiratory Infections 1994; 9:130-139.

94. Isaacs RD. Necrotizing Pneumonia in Bacteraemic Pneumococcal Infection. Br J Dis Chest 1986; 80:295-296.

95. Knight L, Fraser RG, Robson HG. Massive pulmonary gangrene: a severe complication of Klebsiella pneumonia.. CMA Journal 1975; 112:196-198.

96. Yangco BG, Deresinski SC. Necrotising or cavitating pneumonia due to streptococcus pneumoniae: a report of four cases and a review of the literature.. Medicine 1980; 59:449-457.

97. Danner PK, McFarland DR, Felson B. Massive pulmonary gangrene.. Am J Roentgenol 1968; 103:548-554.

98. Mufson MA. Streptococcus pneumoniae. In: Mandell GL, Gordon Douglas R, Bennett JE, eds. Principles and practise of Infectious Diseases. 3rd ed. New York: Churchill Livingston, 1990:1539-1550.

99. Austrian R. Pneumococcal Pneumonia. Diagnostic, Epidemiologic, Therapeutic and Prophylactic Considerations. Chest 1986; 90:738-743.

100. Mercat A, Nguyen J, Dautzenberg B. An Outbreak of Pneumococcal Pneumonia in Two Mens Shelters. Chest 1991; 99:147-151.

101. Symmers D, Hoffman AM. J Amer Med Ass 1923; 81:297

102. Musher DM, Olbricht McKenzie S. Infections Due to Staphylococcus Aureus. Medicine 1977; 56:383-409.

103. Musher DM, Franco M. Staphylococcal Pneumonia. A new perspective.. Chest 1981; 79:172-173.

104. Woodhead MA, Radvan J, Macfarlane JT. Adult Community-acquired Staphylococcal Pneumonia in the Antibiotic Era: A Review of 61 Cases. Q J Med 1987; 64:783-790.

105. Robertson L, Caley JP, Moore J. Importance of Staphylococcus Aureus in the 1957 Epidemic of Influenza A. Lancet 1958; 233-236.

106. Kaye MC, Fox MJ, Bartlett JG, Braman SS, Glassroth J. The Clinical Spectrum of Staphylococcus aureus Pulmonary Infection. Chest 1990; 97:788-792.

107. Warshauer D, Goldstein E, Akers T, et al. Effect of influenza viral infection on the ingestion and killing of bacteria by alveolar macrophages.. Am Rev Respir Dis 1977; 115:269-277.

108. Wiita RM, Cartwright RR, Davis JG. Staphylococcal Pneumonia in Adults. Unknown 1961; 86:1083-1091.

109. Eykyn S. Staphylococcal bacteraemia and endocarditis and fusidic acid. Journal of Antimicrobial Chemotherapy 1990; 25:33-38.

110. Bloomfield AL. Amer Rev Tuberc 1921; 4:847

111. Winn WC, Myerowitz RL. The pathology of the legionella pneumonias. Hum Pathol 1981; 12:401-422.

112. Lepow ML, Balassanian N, Emmerich J, Roberts RB, Rosenthal MS, Wolinsky E. Interrelationships of Viral, Mycoplasmal, and Bacterial agents in uncomplicated pneumonia. Am Rev Respir Dis 1968; 97:533-543.

113. Forgie IM, O'Neil KP, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infection in Gambian children:Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital. Pediatric Infectious Disease Journal 1991; 10:42-47.

114. Weitekamp MR, Aber RC. Nonbacterial and unusual pneumonias in the elderly. Geriatrics 1984; 39:87-100.

115. Venkatesan P, Gladman J, Macfarlane JT, et al. A hospital study of community acquired pneumonia in the elderly. Thorax 1990; 45:254-258.

116. Brown RB, Sands M, Ryczac M. Community-acquired Pneumonia Caused by Mixed Aerobic Bacteria. Chest 1986; 90:810-814.

117. Hammond JMJ, Potgieter PD, Forder AA. Legionella pneumoniae - a need for epidemiological alert. S Afr Med J 1989; 75:144-145.

118. Mycoplasma pneumoniae. (editorial). Lancet 1991; 337:651-652.

119. Woodhead MA, Macfarlane JT, Rogers FG, et al. Aetiology and outcome of severe community acquired pneumonia. J of Infection 1985; 10:204-210.

120. Leroy O, Santre C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. Intensive Care Med 1995; 21:24-31.

121. Karolyi A. Diagnostic difficulties in Community-acquired Pneumonia. Chest 1993; 104:648-649.

122. Macfarlane J. Community-acquired Pneumonia. Br J Dis Chest 1987; 81:116-127.

123. Turner JS, Potgieter PD, Linton DM. Systems for scoring the severity of illness in intensive care.. S Afr Med J 1989; 76:17-20.

124. Kurashi NY, AL-Hamadan A, Ibrahim EM, Al-Idrissi HY, Al-Bayari TH. Community-acquired acute bacterial and atypical pneumonia in Saudi Arabia. Thorax 1992; 47:115-118.

125. White RJ, Blainey AD, Joy Harrison K, Clarke SKR. Causes of Pneumonia presenting to a district general hospital. Thorax 1981; 36:566-570.

126. Ortqvist A. Prognosis in community-acquired pneumonia requiring treatment in hospital. Scandinavian Journal of Infectious Diseases 1990; Supplement 1:1-62.

127. Farr BM, Kaiser DL, Harrison BDW, Connolly CK. Prediction of microbial aetiology at admission to hospital for pneumonia from the presenting clinical features. Thorax 1989; 44:1031-1035.

128. Finnegan OC, Fowles SJ, White RJ. Radiographic appearances of mycoplasma pneumonia. Thorax 1981; 36:469-472.

129. Hammond JMJ, Potgieter PD, Linton DM, Forder AA. Intensive care management of community-acquired Klebsiella pneumoniae.. Respiratory Medicine 1990; 84:11-16.

130. Wimberley NW, Bass JB, Boyd BW, Kirkpatrick MB, Serio RA, Pollock HM. Use of a Bronchoscopic Protected Catheter Brush for the Diagnosis of Pulmonary Infections. Chest 1982; 81:556-562.

131. Gleckman R, DeVita J, Hibert D, Pelletier C, Martin R. Sputum Gram Stain Assesment in Community-Acquired Bacteraemic Pneumonia. J Clin Microbiol 1988; 26:846-849.

132. Kahn FW, Jones JM. Diagnosing Bacterial Respiratory Infection by Bronchoalveolar Lavage. J Infect Dis 1987; 155:862-869.

133. Thorpe JE, Baughman RP, Frame PT, Wesseler TA, Staneck JL. Bronchoalveolar Lavage for Diagnosing Acute Bacterial Pneumonia. J Infect Dis 1987; 155:855-861.

134. Bartlett JG. Diagnostic Accuracy of Transtracheal Aspiration Bacteriologic Studies. Am Rev Respir Dis 1977; 115:777-782.

135. Hahn HH, Beaty HN. Transtracheal Aspiration in the Evaluation of Patients with Pneumonia. Ann Int Med 1970; 72:183-187.

136. Moser KM, Maurer J, Jassy L, et al. Sensitivity, Specificity, and Risk of Diagnostic Procedures in a Canine Model of Streptococcus pneumoniae Pneumonia. Am Rev Respir Dis 1982; 125:436-442.

137. Villers D, Derriennic M, Raffi F, et al. Reliability of the Bronchoscopic Protected Catheter Brush in intubated and Ventilated Patients. Chest 1985; 88:527-530.

138. Sodeman TM, Colmer J. Microbiology of the Respiratory Tract. Laboratory Med 1983; 14:96-102.

139. Tobin MJ. Diagnosis of Pneumonia: Techniques and Problems. Clinics in Chest Medicine 1987; 8:513-527.

140. Gleckman R, DeVita J, Hibert D, Pelletier C, Martin R. Sputum Gram Stain Assesment in Community-Acquired Bacteremic Pneumonia. J Clin Microbiol 1988; 26:846-849.

141. Kalin M, Lindberg A, A, Tunevall G. Etiological Diagnosis of Bacterial Pneumonia by Gram Stain and Quantitative Culture of expectorates. Scand J Infect Dis 1983; 15:153-160.

142. Rein MF, Gwaltney JM, O'Brien WM, Jennings RH, Mandell GL. Accuracy of Gram's Stain in Identifying Pneumococci in Sputum. JAMA 1978; 239:2671-2673.

143. Fine MJ, Orloff JJ, Rihs J, D, et al. Evaluation of Housestaff Physicians' Preparation and interpretation of sputum Gram Stains for Community-acquired Pneumonia. J Gen Intern Med 1991; 6:189-198.

144. Spencer RC, Philp JR. Effect of Previous Antimicrobial Therapy on Bacteriological Findings in Patients With Primary Pneumonia. Lancet 1973; 349-351.

145. Pecora DV, Yegian D. Bacteriology of the lower respiratory tract in health and chronic disease. N Engl J Med 1958; 258:71

146. Unger KM, Moser KM. Fatal complication of transtracheal aspiration. Arch Intern Med 1973; 132:437

147. Spencer DC, Geaty HN. Complications of transtracheal aspiration. N Engl J Med 1972; 286:304

148. Sorensen J, Forsberg P, Hakason E, et al. A New Diagnostic Approach to the Patient with Severe Pneumonia. Scand J Infect Dis 1989; 21:33-41.

149. Zavala DC, Schoell JE. Ultrathin needle aspiration of the lung in infectious and malignant disease. AM Rev Respir Dis 1981; 123:125-131.

150. Chen CH, Kuo ML, Shih JF, Chang TP, Perng RP. Etiologic diagnosis of pulmonary infection by ultrasonically guided percutaneous lung aspiration. Chung Hua i Hsueh Tsa Chih - Chinese Medical Journal 1993; 51:333-339.

151. Bella F, Tort J, Morera MA, Espaulella J, Armengol J. Value of bacterial antigen detection in the diagnostic yield of transthoracic needle aspiration in severe community acquired pneumonia. Thorax 1993; 48:1227-1229.

152. Willcox PA, Benatar SR, Potgieter P, Ferguson AD, Bateman ED. Fibre-optic bronchoscopy- Groote Schuur Hospital experience. S Afr Med J 1981; 60:651-654.

153. Willcox PA, Benatar SR, Potgieter PD. Use of the flexible fibreoptic bronchoscope in diagnosis of sputum-negative pulmonary tuberculosis. Thorax 1982; 37:598-601.

154. Willcox PA, Bateman ED, Potgieter PD, Benatar SR. Experience with fibreoptic bronchoscopy in the diagnosis of pulmonary shadows in renal transplant recipients over a 12-year period. Respiratory Medicine 1990; 84:297-304.

155. 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.

156. Ortqvist A, Kalin M, Lejdeborn L, Lundberg B. Diagnostic Fiberoptic Bronchoscopy and Protected Brush Culture in Patients with Community-Acquired Pneumonia. Chest 1990; 97:576-582.

157. Teague RB, Wallace RJ, Awe RJ. The Use of Quantitative Sterile Brush Culture and Gram Stain Analysis in the Diagnosis of Lower Respiratory Tract Infection. Chest 1981; 79:157-161.

158. Meduri GU, Chastre J. The Standardisation of Bronchoscopic Techniques for Ventilator-Associated Pneumonia. Chest 1992; 102s:557s-564s.

159. 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.

160. Chastre J. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections. Am Rev Respir Dis 1984; 130:924-929.

161. Pugin J, Suter PM. Diagnostic bronchoalveolar lavage in patients with pneumonia produces sepsis-like systemic effects. Int Care Med 1992; 18:6-10.

162. Meduri GU, Chastre J. The Standardisation of Bronchoscopic Techniques for Ventilator-Associated Pneumonia. Chest 1992; 102s:557s-564s.

163. Sorenson J, Cederholm, I, Carlsson C. Pneumonia: A Deadly Disease despite Intensive Care Treatment. Scand J Infect Dis 1986; 18:329-335.

164. Jimenez P, Saldias F, Meneses M, Silva ME, Wilson MG, Otth L. Diagnostic Fiberoptic Bronchoscopy in Patients With Community-acquired Pneumonia. Chest 1993; 103:1023-1027.

165. Feinsilver SH, Fein AM, Niederman MS, Schultz DE, Faegenburg DH. Utility of fiberoptic bronchoscopy in non-resolving pneumonia.. Chest 1990; 98:1322-1326.

166. Pereira W, Kovnat DM, Snider GL. A Prospective Cooperative Study of Complications following Flexible Fiberoptic Bronchoscopy. Chest 1978; 73:813-816.

167. Edelstein PH, Meyer RD. Legionnaires' Disease. Chest 1984; 85:114-120.

168. Kohorst WR, Schonfeld SA, Macklin JE, Whitcomb ME. Rapid Diagnosis of Legionnaires' Disease by Bronchoalveolar Lavage. Chest 1983; 84:186-190.

169. Toledo-Pereyna LG, DeMeester TR, Kinnealy A, et al. The benefits of open lung biopsy in patients with previously nondiagnostic transbronchial lung biopsy: Guide to appropriate therapy.. Chest 1980; 77:647-649.

170. Guzzetta P, Toews GB, Joy Robertson K, Pierce AK. Rapid Diagnosis of Community-Acquired Bacterial Pneumonia. Am Rev Respir Dis 1983; 128:461-464.

171. 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.

172. Cassel G, Bates J, Drnec J. Clarithromycin Versus Erythromycin in the treatment of Atypical Community-acquired Pneumonia. 18th Int Congress of Chemotherapy 1993; (abstract)

173. Kramer MR, Rudensky B, Haddas-Halperin, I, Isacsohn M, Melzer E. Pneumococcal bacteraemia: no change in mortality over 30 years- analysis of 104 cases and review of the literature.. Isr J Med Sci 1987; 23:174-180.

174. Moss FM, McNicol MW, McSwiggan DA, Miller DL. Survey of Antibiotic Prescribing in a District General Hospital 2 Lower respiratory tract infection. Lancet 1981; 407-409.

175. Pickering CAC. Antibiotics for Chest Infection. SA J Hosp Med 1976; 144-147.

176. Korvick JA, Bryan CS, Farber B, et al. Prospective Observational Study of Klebsiella Bacteraemia in 230 patients: Outcome for Antibiotic Combinations versus Monotherapy. Antimicrobial Agents and Chemotherapy 1992; 36:2639-2644.

177. Rahal JJ. Antibiotic combinations: The clinical relevance of synergy and antagonism. Medicine 1978; 57:179-195.

178. Drusano GL, Schimpff SC, Hewitt WL. The Acylampicillins: Mezlocillin,Piperacillin, and Azlocillin. Rev Infect Dis 1984; 6:13-29.

179. Hui KP, Tan WC, Chan TB, Chin NK. Community-acquired Pneumonia in the Far East. Chest 1993; 103:1637

180. Chan CHS, Cohen M, Pang J. A prospective study of community-acquired pneumonia in Hong Kong. Chest 1992; 101:442-446.

181. Brett A, Sinclair DG. Use of continuous positive airway pressure in the management of community acquired pneumonia. Thorax 1993; 48:1280-1281.

182. Pepe PE, Hudson LD, Carrico CJ. Early application of ppositive end-expiratory pressure in patients at risk for the adult respiratory-distress syndrome. N Eng J Med 1984; 311:281-286.

183. Shapiro BA, Cane RD, Harrison RA. Positive end-expiratory pressure in acute lung injury. Chest 1983; 83:558-563.

184. Anonymous. Intensive Care Manual. 3rd ed. Cape Town: University of Cape Town, 1990:

185. Marcy TW, Marini JJ. Inverse ratio ventilation in ARDS. Chest 1991; 100:494-504.

186. Shoemaker WC. A new approach to Physiology, Monitoring, and Therapy of Shock States. World J Surg 1987; 11:133-146.

187. The Veterans Administration Systemic Sepsis Cooperative Study Group. Effect of High-Dose Glucocorticoid Therapy on Mortality in Patients With Clinical Signs of Systemic Sepsis. N Engl J Med 1987; 317:659-665.

188. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A Controlled Clinical Trial of High-Dose Methylprednisolone in the Treatment of Severe Sepsis and Septic Shock. N Engl J Med 1994;

189. Baumgartner J, McCutchan JA, Van Melle G, et al. Prevention of Gram-negative Shock and Death in Surgical Patients by Antibody to Endotoxin Core Glycolipid. Lancet 1985; ii:59-63.

190. Greenberg RN, Wilson KM, Kunz AY, Wedel NI, Gorelick KJ. Observations using antiendotoxin antibody (E5) as adjuvent therapy in humans with suspected, serious, Gram-negative sepsis. Crit Care Med 1992; 20:730-735.

191. Ziegler EJ, Fisher CJ, Sprung C, et al. Treatment of Gram-negative bacteraemia and septic shock with HA-1A human monoclonal antibody against endotoxin. N Engl J Med 1991; 324:429-436.

192. McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR. Treatment of septic shock with human monoclonal antibody HA-1A. A randomised, double-blind, placebo-controlled trial. CHESS Trial Study Group.. Ann Int Med 1994; 121:1-5.

193. Christman JW. Potential Treatment of Sepsis Syndrome with Cytokine Specific Agents. Chest 1992; 102:613-617.

194. Glauser MP, Zanetti G, Baumgarter J-D, Cohen J. Septic shock: pathogenesis. Lancet 1991; 338:732-739.

195. Wright AE, Parry Morgan W, Colebrook L, Dodgson RW. Prophylactic Inoculation Against Pneumococcus Infections. Lancet 1914; 1:1-10,87-95.

196. Austrian R. Pneumococcal Infection and Pneumococcal Vaccine. N Engl J Med 1977; 297:938-939.

197. Smit P, Oberholzer D, Hayden-Smith S, Koornhof HJ. Protective Efficacy of Pneumococcal Polysaccharide Vaccines. JAMA 1977; 238:2613-2616.

198. Ammann AJ, Addiego J, Wara DW, Lubin B, Bryon Smith W, Mentzer WC. Polyvalent Pneumococcal-Polysaccharide Immunisation of Patients with Sickle-cell anemia and Patients with Splenectomy. N Engl J Med 1977; 297:897-900.

199. McBean AM, Babish JD. The Utilization of Pneumococcal Polysaccharide Vaccine Among Eldery Medicare Beneficiaries, 1985 Through 1988. Arch Intern Med 1991; 151:2009-2016.

200. Garibaldi RA. Epidemiology of Community-Acquired Respiratory Tract Infections in Adults. JAMA 1985; 78(suppl 6B):32-37.

201. Woodhead MA, Macfarlane JT. Legionnaires' disease: a review of 79 community acquired cases in Nottingham. Thorax 1986; 41:635-640.

202. Grayston JT. Chlamydia pneumoniae, strain TWAR. Chest 1989; 95:664-669.

203. Grayston JT, Kuo CC, Wang SP, Altman J. A new Chlamydia psittaci strain called TWAR from acute respiratory tract infections. N Engl J Med 1986; 315:161-168.

204. Scully RE, Mark EJ, McNeely WF, McNeely BU. Case Records of The Massachusetts General Hospital. New Engl J Med 1992; 326:326-336.

205. Woodhead MA, Macfarlane JT. Comparative Clinical and Laboratory Features of Legionella with Pneumococcal and Mycoplasma Pneumonias. Br J Dis Chest 1987; 81:133-139.

206. Andrews CP, Coalson JJ, Smith JD, Johanson WG. Diagnosis of Nosocomial Bacterial Pneumonia in Acute, Diffuse Lung Injury. Chest 1981; 80:254-258.

207. Rice TW, Ginsberg RJ, Todd TRJ. Tube drainage of lung abscesses. Ann Thorac Surg 1987; 44:356-359.

208. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE 2: A severity of disease classification system.. Crit Care Med 1985; 13:818-829.

209. Anonymous. NCCLS Antimicrobial Susceptibiltiy Testing. 3rd ed. 1991:

210. Marrie TJ. Community-acquired pneumonia. [Review]. Clinical Infectious Diseases 1994; 18:501-13; quiz 514.

211. Petty TL, Fowler AA. Another look at ARDS. Chest 1982; 82:98-104.

212. Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with therapeutic outcome in Gram negative pneumonia. Am J Med 1984; 77:657-662.

213. Zaske DE, Difolle LJ, Strata RG. Gentamicin dosage requirements: wide inter-patient variations in 242 surgery patients with normal renal function.. Surgery 1980; 87:164-169.

214. Ledingham IM, Watt, I. Influence of Sedation on Mortality In Critically Ill Multiple Trauma Patients. Lancet 1983; 1270

215. Hook EW, Horton CA, Schaberg DR. Failure of Intensive Care Unit Support to Influence Mortality From Pneumococcal Bacteraemia. JAMA 1983; 249:1055-1057.

216. Le Gall JR, Loirat P, Alperovitch A. Simplified acute physiological score for intensive care patients.. Lancet 1983; ii:741

217. Knaus WA, Wagner DP, Draper EA. The APACHE III prognostic system.. Chest 1991; 100:1619-1636.

218. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720-723.

219. Kraus PA, Lipman J, Lee CCJ. Acute Lung Injury at Baragwanath ICU.An eight month audit and call for consessus for other organ failure in the Adult Respiratory Distress Syndrome. Chest 1993; 103:1832-1836.

220. 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.

221. Leatherman JW, Iber C, Davies SF. Cavitation in bacteraemic pneumococcal pneumonia: Causal role of mixed infection with anaerobic bacteria.. Am Rev Respir Dis 1984; 129:317-321.

222. O'Reilly GV, Dee PM, Otteni GV. Gangrene of the lung: Successful medical management of three patients.. Radiology 1978; 126:575-579.

223. Postma MH, le Roux BT. The place of external drainage in the management of lung abscess.. SA Journal of Surgery 1986; 24:156-158.

224. Weissberg D. Percutaneous drainage of lung abscess.. J Thorac Cardiovasc Surg 1984; 87:308-312.

225. Snow N, Lucas A, Horrigan TP. Utility of pneumonotomy in the treatment of cavitary lung disease. Chest 1985; 87:731-734.

226. Rice TW, Ginsberg RJ, Todd TRJ. Tube drainage of lung abscess. Am Thorac Surg 1987; 44:356-359.

227. Fry DE. Multiple system organ failure. Surgical Clinics of North America 1988; 68:107-122.

228. Cameron EW, Whitton ID. Percutaneous drainage in the treatment of Klebsiella pneumoniae lung abscess.. Thorax 1977; 32:673-676.

229. Selective Decontamination of the Digestive Tract Trialists'Collaborative Group. Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. Lancet 1993; 307:525-532.

230. Ledingham IM, 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.

231. 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.

232. 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.

233. 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.

234. 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.

235. Knaus WA, Draper EA, Wagner DP. Prognosis in acute organ system failure. Ann Surg 1985; 202:685-690.

236. 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.

237. 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.

238. McCarthy DM. Drug therapy: Sucralfate. N Engl J Med 1991; 325:1017-1025.

239. Tryba M, Mantey-Stiers F. Antibacterial activity of sucralfate in human gastric juice. Am J Med 1987; 83s3b:125-127.

240. Gruer LD, McKendrick MW, Geddes AM. Pneumococcal bacteraemia; a continuing challenge. Q J Med 1984; L111:259-270.

241. Marrie TJ. Bacteraemic pneumoccocal pneumonia: a continiously evolving disease. J Infect 1992; 24:247-256.

242. Banks RA, George RC, McNicol MW. Pneumococcal pneumonia with bacteraemia. Br J Dis Chest 1984; 78:352-357.

243. Ortqvist A, Kalin M, Julander, I, Mufson MA. Deaths in Bacteraemic Pneumococcal Pneumonia. Chest 1993; 103:710-716.

244. Bruyn GAW, van der Meer JWM, Hermans J, Knoppert W. Pneumoccocal bacteraemic over a 10-year period at University Hospital, Leiden.. Rev Infect Dis 1988; 10:446-450.

245. Breiman RF, Spika JS, Navarro VJ, Darden PM, Darby CP. Pneumococcal bacteraemia in Charleston County, South Carolina: a decade later. Arch Intern Med 1990; 150:1401-1405.

246. Chase RA, Trenholme GM. Overwhelming Pneumonia. Med Clin NA 1986; 70:945-959.

247. Bryan CS, Reynolds KL. Bacteraemic nosocomial pneumonia.. Am Rev Respir Dis 1984; 70:945-959.

248. Keene AR, Cullen DJ. Therapeutic Intervention Scoring System: Update 1983. Crit Care Med 1984; 11:1-3.

249. Schonell ME, Gray W, Moffat MAJ, Calder MA, Stewart SM. The Relationship between the Aetiology of Pneumonia in Adults and Certain Clinical and Radiographic Findings. Brit J Dis Chest 1969; 63:140-149.

250. Harrison BDW, Farr BM, Connolly GK, Macfarlane JT, Selkon JB, Bartlett CLR. The hospital management of community-acquired pneumonia. Journal of the Royal College of Physicians of London 1987; 21:267-269.

251. Rosendaal R, Bakker-Wondenberg IAJM. Therapeutic efficacy of continuous versus intermittant administration of ceftazidime in an experimental Klebsiella pneumoniae pneumonia in rats. J Infect Dis 1885; 152:373-378.

252. Klatersky J. Concept of empiric therapy with antibiotic combinations. Indications and limits.. Am J Med 1986; 80(supp 5c):2-12.

253. Weber DM, Pellecchia JA. Varicella Pneumonia. JAMA 1965; 192:228-229.

254. Garcia QA, Alegre MJ, Falco, V, Fernandes de Sevilla T, Martinez Vazquez JM. Neumonia varicelosa en el adulto. Estudio de trece casos.. Revista Clinica Espanola 1992; 191:314-316.

255. Vukmirovits G, Ferencz A, Csomor J, Antony A. Varicella pneumonia felnottkorban. Orvosi Hetilap 1992; 133:3135-3140.

256. Mermelstein RH, Friereich AW. Varicella pneumonia. Ann Intern Med 1961; 55:456-463.

257. Davidson RN, Lynn W, Savage P, Wansbrough-Jones mh. Chickenpox pneumonia:experience with antiviral treatment.. Thorax 1988; 43:627-630.

258. Esmonde TF, Herdman G, Anderson G. Chickenpox pneumonia: an association with pregnancy. Thorax 1989; 44:812-815.

259. Bryer A, Potgieter PD, Moodie J. Acyclovir and varicella pneumonia.. S Afr Med J 1984; 66:515

260. Smego RA, Asperills MO. Use of Acyclovir for Varicella Pneumonia During Pregnancy. Obstet Gynecol 1991; 78:1112-1116.

261. Pillans P. Chickenpox pneumonia. S Afr Med J 1983; 63:861-862.

262. Dunkle LM, Arvin AM, Whitley RJ, et al. A controlled trial of acyclovir for chickenpox in normal children. N Engl J Med 1991; 325:1539-1544.

263. Balfour HH, Rotbart HA, Feldman S, et al. Acyclovir treatment of varicella in otherwise healthy adolescents. J Pediatr 1992; 120:627-633.

264. Anonymous. Controversy about chickenpox. Lancet 1992; 340:639-640.

265. Brown ZA, Baker DA. Acyclovir therapy during pregnancy. Obstet Gynecol 1989; 73:526-531.

APPENDIX 1

RICU Computer Data Collection Form.

PD 633

1

RESPIRATORY UNIT

SUMMARY SHEET

NAME: _____

FOLDER NO: _____

DATE OF BIRTH: _____/_____/19_____ AGE: [ ]

RACE/SEX: 1.WM 2.WF 3.CM 4.CF 5.BM 6.BF [ ]

WARD: 1.A10 2.A1 3.F3 [ ]

SPECIALITY: _____

(Key to speciality) [ ]

1. Medical
2. General surgery
3. Trauma
4. Thoracic surgery
5. Cardiac surgery
6. Obstets & Gynae
7. Orthopaedics
8. Other surgery

APACHE SCORE ON ADMISSION (1st 24 hours) [ ]

DATE OF ADMISSION TO UNIT: _____/_____/19_____

DATE OF DISCHARGE/DEATH: _____/_____/19_____

ADMITTED FROM: _____ [ ]

DISCHARGED TO: _____ [ ]

(Key to Admitted from and Discharged to)

1. Cas.
2. Acc Unit
3. Resp.Clinic
4. Theatre
5. Other hosp
6. Gen. ward
7. Home
8. Died
9. Other ICU

RESPIRATORY SYSTEM

1. Pneumonia. (Primary diagnosis)
   Type of pneumonia (in assoc diagnosis)
2. Primary pneumonia
3. Secondary pneumonia - Hospital acquired
4. " " - Immuno compromised
5. " " - Aspiration
6. " " - Pre-existing lung disease
7. " " - Other (specify)
8. Other lung infection (specify)
9. COAD
10. Asthma
11. Active TB/Pulmonary
12. " "/Disseminated
13. CA lung
14. Interstitial Fibrosis
15. Kyphoscoliosis
16. Bronchiectasis
17. Other Restrictive LD
18. Bullous lung disease
19. Post TB LD
20. Pulmonary embolism - bland
21. " " - septic
22. Upper a/w obstruction
23. Atelectasis
24. Pneumothorax
25. ARDS - Primary diagnosis

CAUSES OF ARDS (in associated diagnosis)

26. Septicaemia
27. Fat embolism
28. Amniotic fluid embolism
29. Aspiration
30. Pancreatitis
31. Inhaled toxic agent
32. Resp. burns
33. Secondary drowning
34. Tauma/shock
35. Other (specify)
36. Obesity
37. Sleep apnoea/hypoventilation
38. Other lung disease (specify)

CARDIOVASCULAR SYSTEM

39. Myocardial infarct
40. Valvular disease
41. Ischaemic heart disease
42. Cardiomyopathy
43. Cardiac failure
44. Septicaemic shock (SBP<80 off inotropes)

NEUROLOGICAL/NEUROMUSCULAR

45. Status epilepticus
46. Autonomic dysfunction
47. Coma CNS
48. " cardiac arrest
49. " anaesthetic asso
50. " drowning
51. Hypothermia
52. Guillan Barre
53. Transverse myelitis
54. Polyneuritis - any cause
55. Myasthenia gravis
56. Myopathy
57. Tetanus mild
58. " moderate/severe (in associated disease)
59. Porphyria

OTHER DISEASE/UNKNOWN

60. Septicaemia
61. Other disease (specify)
62. Unknown (specify)
63. Psychiatric disease

METABOLIC

64. Diabetes
65. " with Hyperosmolar coma
66. " with Keto acidotic coma
67. Liver failure/coma
68. Renal disease - acute
69. " " - chronic
70. Poisoning - accidental
71. " - suicide
72. Organophosphate (Ass.Dis.)
73. Paraquat (" ")
74. Other substances (" ") - specify
75. Overdose - accidental
76. " - suicide
77. Benzodiazepine (Ass.Dis)
78. Tricyclic/antidepressants (Ass.Dis)
79. Salicylates (Ass.Dis)
80. Other drugs (specify) (Ass.Dis)
81. Haematological diseases (specify)
82. DIC

SURGICAL

83. Post-op, elective admission to ICU
84. " emergency admission to ICU (in ass.dis. only)

ANAESTHETIC ASSOCIATED

85. Anaesthetic complication (prim Diag)
86. Muscle relaxants non-depolarisor
87. " " depolarisors
88. " " both
89. Drugs opiates
90. anaesthetic gases
91. local anaesthetics
92. Aspiration

93. TRAUMA (Ass.dis only)
94. Blunt chest # ribs (flail chest) (Prim.diag only)
95. " " ruptured diaphragm
96. " " pneumotherax
97. " " haemotherax
98. " " vascular injury
100. " " myocardial contusion
101. " " laryngeal/bronchial injury
102. Abdominal injury
103. Head "
104. Spinal "
105. Multiple fractures
106. Penetrating chest - pulmonary
107. heart
108. - both

109. Eclampsia
110. Fluid overload
111. HIV
112. Meningitis
113. Encephalitis

PRIMARY DIAGNOSIS

(main indication for admission to unit)

ASSOCIATED DISEASES

SURGICAL DETAILS

Type of Surgery

1. General - major vascular
2. " - bowel resection - small
3. " - bowel resection - large
4. " - gastrectomy/gastric surgery/vagotomy etc.
5. " - cholecystectomy
6. " - hepatectomy
7. " - pancreatectomy
8. " - hernia repair
9. " - varices
10. " - oesophagectomy
11. " - laparotomy
12. Thoracic - lobectomy
13. " - pneumonectomy
14. " - decortication
15. " - bullectomy
16. " - open lung biopsy
17. " - other (specify)
18. Cardiac
19. Urological
20. Orthopaedic
21. Neurosurgical
22. ENT
23. Ophthamology
24. Gynaecology
25. Obstetric
26. Other surgery (specify)
27. **Emergency surgery**
28. **Elective surgery**

NO. OF ORGANS FAILED (Day 1) ☐

NO. OF ORGANS FAILED (Day 2) ☐

NO. OF ORGANS FAILED (Day 3) ☐

NO. OF ORGANS FAILED (Day 4) ☐

NO. OF ORGANS FAILED (Day 5) ☐

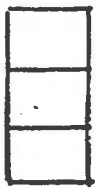
DEFINITION OF ORGAN FAILURE (only 1 criteria in each system necessary)

Renal	1.	Urine output $\leq$ 479 ml/24 hours or $\leq$ 159 ml/8 hours
	2.	S.creatinine > 300 mm/l
	3.	S.urea > 20 mmol/l
CVS	1.	MBP $\leq$ 49 mmHg
	2.	HR $\leq$ 54/min
	3.	VF or VT
	4.	pH $\leq$ 7.24 $PCO_2 \leq 6$
Haematological	1.	WCC < 1000 mm^3
	2.	Platelets < 20000 mm^3
	3.	HCT $\leq$ 20%
Respiratory	1.	RR $\leq$ 5/min or $\geq$ 49/min
	2.	$PaCO_2 \geq 6$ kPa
	3.	$AaDO_2 \geq 46$ kPa (FIO_2 - PaO_2 - $PaCO_2$)
	4.	Dependent on ventilator for $\geq$ 4 days
Neurologic	1.	Unconscious GCS $\leq$ 6 (no sedatives for 24 hours)

BACTERIOLOGY

INFECTIONS PRESENT ON ADMISSION
(how diagnosis is made)

01. Sputum
02. Tracheal aspirate
03. Bronchoscopy
04. Blood culture
05. Serology
06. Wound swab
07. Aspirate - pleural
08. " - peritoneal
09. Transtracheal aspirate
10. CSF
11. Tissue biopsy
12. Lung biopsy
13. Other (specify)



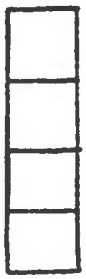
14. Community acquired
15. Nosocomial

Admission Infection Only

Bacteriological diagnosis

01. Streptococcus pneumoniae
02. Staphylococcus aureus
03. Staph.epidermidis
04. H.Influenzae
05. E.Coli
06. Klebsiella sp.
07. Serratia sp.
08. Proteus sp.
09. Pseudomonas sp.
10. Acinetobacter sp.
11. Anaerobes (specify)
12. TB
13. Mycoplasma
14. Legionella
15. Viruses
16. Rickettsia
17. Malaria
18. Candida
19. Aspergillus
20. Strep milleri
21. Other strep
22. Enterobacter
23. Enterococcus
24. Unknown
25. Other organism
26. Branhamella catarrhalis
27. Neisseria meningitidis
28. Pneumocystic carinii

Secondary "Significant" organism isolated in ICU (ie required Rx)



SPECAL INVESTIGATION

01. FOB
02. Brushings
03. Trans Bronchial Biopsy
04. Open Lung Biopsy
05. Echo cardiography
06. Lung scan
07. MUGA
08. CAT
09. (Ultra sound) ABD
10. Angiography
11. Cardiac catheterization (fluroscopy)
12. I.cranial pressure monitoring
13. Intra-arterial pressure monitoring
14. Bone marrow
15. Liver biopsy
16. Renal biopsy
17. Lumbar puncture
18. Gallium scan
19. Indium oxide scan
20. Cardiac biopsy
21. Bone scan
22. Other (specify)

S.G. Catheter Yes 1 No 0

Route: 11. J.V.P. (R) 12. J.V.P. (L) 13. Subclavian (L)
14. Subclavian (R) 15. Peripheral arm 16. Leg

COMPLICATIONS OF THE SWAN GANZ CATHETER

21. Multiple stabs at vein (>3) unilateral
22. Bilateral attempts
23. Failed attempt
24. Arterial puncture
25. Pneumothorax
26. Arrhythmias (required treatment)
27. Failed placement
" equipment
28. " balloon
29. " transducers
30. " C.O. computer/thermistor
31. Ruptured pulmonary artery/haemoptysis
32. Knot in catheter
33. Catheter embolism
34. Pulmonary infarction
35. Inability to wedge
36. Other (specify)

VENTILATORY THERAPY (Tick)

CONSERVATIVE (ONLY) (Only if not ventilated)	☐
CPAP - Mask (Only if not ventilated)	☐
- Tube (Only if not ventilated)	☐
ETT	☐
IPPV without PEEP	☐
IPPV with PEEP	☐
> 15 cms	☐
Tracheostomy	☐
Minitrac	☐
HFPPV	☐
Double lumen tube	☐
Indep lung vent.	☐

DURATION IN DAYS

ETT	☐
Tracheostomy	☐
CPAP	☐
IPPV	☐
Maximum PEEP (CMS)	☐
INDICATION FOR ETT	☐
INDICATION FOR TRACHEOSTOMY	☐

1. Obstructed airway
2. Secretion retention
3. Respiratory failure
4. Other (specify)
5. Prolonged intubation
6. To assist weaning
7. Elective ventilation

OTHER THERAPY (Tick)

1. Dialysis PD	☐
2. Dialysis Haemo	☐
3. Dialysis PD + Haemo	☐
4. Haemoperfusion	☐
5. Enteral feeding	☐
6. IV nutrition	☐
7. Epidural lumbar	☐
8. Epidural thoracic	☐
9. Plasmapharesis	☐
10. Difibrillation (planned)	☐

PROCEDURES

1. Peripheral IV	☐
2. Central IV Internal jugular	☐
3. Central IV subclavian	☐
4. Central IV peripheral vein	☐
5. Arterial line	☐
6. Resuscitation (successful)	☐
7. Chest drain	☐
8. Other	☐

DRUGS

ANTIBIOTICS
01 Penicillin
02 Gentamicin
03 Tobramycin
04 Cephamandole
05 Cefotaxime
06 Cloxacillin
07 Fucidin
08 Erythromycin
09 Clindamycin
10 Chloromycetin
11 Amoxil/Ampicillin
12 Tetracycline
13 Cotrimoxazole
14 Piperacillin
15 Amikacin
16 Anti TB Therapy
17 Rifampicin (not for TB)
18 Steptomycin (not for TB)
19 Amphotericin B
20 5 Flucytosine
21 Other (specify)
22 Ceftriaxone
23 Netilmicin
24 Metronidazole

CARDIAC INOTROPES
25 Adrenaline
26 Dopamine
27 Dobutamine
28 Isuprel
29 Glucagon

30 Heparin
31 Streptokinase

SEDATIVES
32 Benzodiazepines
33 Midazolam
34 Pentothal
35 Heminevrin
36 Barbiturates
37 Epanutin
38 Rivatrol
39 Human tetanus immunoglobulin
40 Etomine

DIURETICS
41 Furosemide
42 Thiazides
43 Other diuretics

MUSCLE RELAXANTS
54 Scoline
55 Non-depolarisors

EPIDURAL
56 LA
57 Opiates
58 Both

RESPIRATORY
59 Aminophylline
60 B-2 agonists inhalation
61 B-2 agonists IV
62 Ipratropium bromide

VASODILATORS/ ANTIHYPERTENSIVES
63 SNP
64 TNT
65 MgS04
66 Minipress
67 Hydralazine

OTHER DRUGS
68 Antacids
69 Cimetidine
70 Insulin
71 Oral antidiabetics
72 Sterolds
73 Immunosupressants
74 Cholinesterase Inhibitors
75 2 PAM or toxogonin
76 Amphotericin bladder wash
77 Other drugs
78 Ranitidine

NEW DRUGS
79 Imipenem
80 Ceftazadime
81 Perfloxacin
82 ACE inhibitors
83 Urokinase
84
85
86 Anexate
87

ANALGESICS
88 Morphine
89 Fentanyl
90 Other opiates
91 Non-steroidals
92

COMPLICATIONS (Developed in ICU)

01 G.I.T. Bleed
02 Hepatic failure
03 Cardiac failure
04 Renal failure (without dialysis)
05 Renal failure (peritoneal)
06 Renal failure (haemo)
07 Renal failure (both)
08 Pulmonary infection
09 Pulmonary embolism
10 Pulmonary haemoptysis

COMPLICATIONS OF VENTILATION

11 Blocked endotracheal tube
12 Accidental disconnection
13 Ruptured cuff
14 Ventilator failure
15 Accidental extubation
16 Tracheal perforation/dilation
17 T.O.F.
18 Tracheal bleed
19 Pneumothorax/BPF
20 CVA on CPPV
21 Atelectasis

OTHER

22 Septicaemia
23 U.T.I.
24 Endocarditis
25 Infection with a second organism (Superinfection on antibiotics)
26 Other infection
27 DIC
28 Diarrhoea
29 Arrhythmias
30 DTs
31 Any other complication (specify)
32 Diarrhoea due to enteral feeds
33 DVT

COMPLICATIONS OF IV LINES

34 Complication of IV lines
35 Phlebitis
36 Septicaemia
37 Other (specify)
38 Thrombosis
39

COMPLICATIONS OF DRUGS

40 Complication of drugs (specify drug)
41 Anaphylaxis
42 Allergy
43 Skin reaction
44 Diarrhoea
45 Renal failure
46 Other (specify)

CAUSE OF DEATH
(One only)

01	Does not apply (patient survived)	
02	Arrhythmia (primary)	
03	Brain damage following arrest	
04	Head injury/stroke	
05	Complication of procedure	
06	Dissecting aneurysm	
07	Drug induced death	
08	Hepatic failure	
09	Respiratory failure	
10	Renal failure	
11	Shock (cardiogenic) and/or CCF	
12	Hypovolaemia	
13	Septicaemia	
14	Pulmonary embolus	
15	Mechanical failure	
16	Multiple organ failure	
17	Surgical death	
18	Active treatment discontinued/specify reason _____	
19	Brain death - specify	
20	Other - specify	

Autopsy: 1. Yes
2. No

If no, must specify why not

1. **ADMISSION DIAGNOSTIC CATEGORY :** ☐

Post emergency surgery Y / N
From the lists below, indicate the one primary admission diagnosis that necessitated ICU admission.

2. **NON OPERATIVE**

Respiratory failure from :

1. Asthma/allergy
2. COPD
3. ARDS
4. Aspiration/poison/toxic
5. Pulmonary embolus
6. Respiratory infection
7. Respiratory neoplasm
8. Post respiratory arrest (only)

Cardiovascular failure from :

9. Hypertension
10. Rhythm disturbance
11. Congestive heart failure
12. Haemorrhagic shock/hypovolemia
13. Coronary artery disease
14. Sepsis
15. Post cardiac arrest (only)
16. Cardiogenic shock
17. Dissecting aneurysm

Trauma :

18. Multiple trauma
19. Head trauma

Neurologic :

20. Seizure disorder
21. ICH/SDH/SAH

Other :

22. Drug OD
23. Diabetic ketoacidosis
24. GI bleeding

If not in the above specific groups, then which organ system was the principal reason for admission ?

25. Metabolic/renal
26. Respiratory
27. Neurologic
28. CVS
29. GIT

POSTOPERATIVE ☐☐

30. Multiple trauma
31. Chronic CVS disease
32. Peripheral vascular surgery
33. Heart valve surgery
34. Craniotomy for neoplasm
35. Renal surgery for neoplasm
36. Renal transplant
37. Head trauma
38. Thoracic surgery for neoplasm
39. Craniotomy for ICH/SDH/SAH
40. Laminectomy/cord surgery
41. Haemorrhagic shock
42. GI bleeding
43. GI surgery for neoplasm
44. Respiratory failure post surgery
45. GI perforation/obstruction

If sepsis or postarrest, use corresponding non-operative category.
If not in the above specific groups, then which organ system was the principal reason for admission?

46. Neurologic
47. CVS
48. Respiratory
49. GIT
50. Metabolic/renal

3. Injury Severity Score (ISS) ☐☐

INJURY SEVERITY SCORE

Severity category 1 - minor

General :Aches all over.
Minor lacerations,contusion,abrasions(first aid, simple closure)
All first or small second or small third degree burns.
Head and neck :Cerebral injury with headache, dizzyness but no loss of consciousness
Whiplash complaint with no anatomical or radiological evidence
Abrasions and contusions of occular apparatus (lid-, conjunctival-, corneal-, uveal- injuries.) Vitreous or retinal haemorrhage.
Fracture and /or dislocation of tooth
Chest :Muscle ache or chest wall stiffness
Abdominal :Muscle ache,minor abrasions etc.
Extremities :Minor sprains,fracture and/or dislocation of digits.

Severity category 2 - moderate

General :Extensive contusions, abrasions, large lacerations, avulsions(less than 7,5 cm wide)
10- 20% body surface second or third degree burns.
Head and neck :Cerebral injury with or withoout skull fracture, less than 15 minutes unconsciousness, no post traumatic amnesia.
Undisplaced skull or facial bone fractures or compound fracture of nose.
Lacerations of the eye and appendages: Retinal detachment.
Disfiguring lacerations.
Whiplash - severe complaint with anatomical or radiological evidence.
Chest :Simple rib or sternal fractures
Major contusion of chest wall without haemothorax or pneumothorax or respiratory embarassment.
Abdominal :Major contusion of abdominal wall.
Extremities and/or pelvic girdle :Compound fractures of digits.
Undisplaced long bone or pelvic fracture
Major sprains of major joints.

Severity category 3 - critical (survival uncertain)

General :Over 50% body surface second or third degree burns.
Head and neck : Cerebral injury with or without skull fracture with unconsciousness of more than 24 hours, post traumatic amnesia more than 12 hours, intracranial haemorrhage. Signs of increased intracranial pressure(decreasing state of consciousness, bradycardia under 60, ,progressive rise in blood pressure or progressive pupil inequality)
Cervical spine injury with quadraplegia.
Major airway obstruction.
Chest :Chest injuries with major respiratory embarassment(laceration of trachea, haemomediastinum etc)
Aortic laceration.
Myocardial rupture or contusion with circulatory embarassment.
Abdominal :Rupture, avulsion or severe laceration of intra abdominal vessels or organs, except kidneys, spleen, ureter.
Extremities :Multiple open limb fractures.

General :Extensive contusions., abrasions, large lacerations involving more than 2 extremities, or large avulsions(greater than 7,5 cm wide)
20-30% body surface second or third degree burns.
Head and neck :Cerebral injury with or without skull fracture with unconsciousness lasting more than 15 minutes, without svere neurological signs. Brief post traumatic amnesia(less than 3 hours).
Displaced closed skull fracture without unconsciousness or other signs of intracranial injury.
Loss of eye or avulsion of optic nerve.
Displaced facial bone fractures or those with antral or orbital involvement.
Cervical spine fractures without cord damage.
Chest :Multiple rib fractures without respiratory embarassment.
Haemothorax or pneumothorax.
Rupture of diaphragm.
Lung contusion.
Abdominal :Contusion of abdominal organs.
Extraperitoneal bladder rupture.
Retroperitoneal haemorrhage.
Avulsion of ureter.
Laceration of urethra.
Thoracic or lumbar spine fractures, without neurological involvement.
Extremities and/or pelvic girdle :Displaced simple long bone fractures and/ or multiple hand and foot fractures.
Single open long bone fractures.
Pelvic fractures with displacement.
Dislocation of major joint.
Multiple amputations of digits.
Lacerations of the major nerves or vessels of extremities.

Severity category 4 - severe(life threatening,survival probable)

General :Severe laceration and/or avulsions with dangerous haemorrhage.
30-50% body surface second or third degree burns
Head and neck :Cerebral injury with or without skull fracture, with unconsciousness of more than fifteen minutes,with definite abnormal neurological signs. Post traumatic amnesia of 3-12 hours.
Compound skull fracture
Chest :Open chest wounds, flail chest, pneumomediastinum,myocardial contusion without circulatory embarassment; pericardial injuries.
Abdominal :Minor laceration of intra abdominal contents(to include ruptured spleen, kidney,and injuries to tail of pancreas)
Intraperitoneal bladder rupture.
Avulsion of the genitals.
Thoracic and/or lumbar spine fractures with paraplegia
Extremities :Multiple closed long bone fractuires.
Amputation of limbs.

Calculation of ISS = addition of the squares of the 3 severest scores.

ISS= 1st( )^2 +2nd( )^2 +3rd( )^2 =

APPENDIX 2

APACHE II Data Form.

DATE ___/___/___ (da / mo / yr)

APACHE SCORE

Physiologic Variable	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)	○ ≥ 41°	○ 39° - 40.9°		○ 38.5° - 38.9°	○ 36° - 38.4°	○ 34° - 35.9°	○ 32° - 33.9°	○ 30° - 31.9°	○ ≤ 29.9°
Mean Arterial Pressure - mm Hg	○ ≥ 160	○ 130 - 159	○ 110 - 129		○ 70 - 109		○ 50 - 69		○ ≤ 49
Heart Rate (ventricular response)	○ ≥ 180	○ 140 - 179	○ 110 - 139		○ 70 - 109		○ 55 - 69	○ 40 - 54	○ ≤ 39
Respiratory Rate - (non-ventilated or ventilated)	○ ≥ 50	○ 35 - 49		○ 25 - 34	○ 12 - 24	○ 10 - 11	○ 6 - 9		○ ≤ 5
Oxygenation: $AaDO_2$ or PaO_2 (kPa) a $FIO_2 \geq 0.5$ record $AaDO_2$	○ ≥ 65	○ 46-64	○ 26-45		○ ≤ 25				
b $FIO_2 < 0.5$ record only PaO_2					○ > 9.3	○ 8.1-9.2		○ 7.3-8.0	○ ≤ 7.2
Arterial pH	○ ≥ 7.7	○ 7.6 - 7.69		○ 7.5 - 7.59	○ 7.33 - 7.49		○ 7.25 - 7.32	○ 7.15 - 7.24	○ < 7.15
Serum Sodium (mMol/L)	○ ≥ 180	○ 160 - 179	○ 155 - 159	○ 150 - 154	○ 130 - 149		○ 120 - 129	○ 111 - 119	○ ≤ 110
Serum Potassium (mMol/L)	○ ≥ 7	○ 6 - 6.9		○ 5.5 - 5.9	○ 3.5 - 5.4	○ 3 - 3.4	○ 2.5 - 2.9		○ < 2.5
Serum Creatinine (mMol/L) (Double point score for acute renal failure)	○ ≥ 301	○ 177-300	○ 136-176		○ 76-135		○ ≤ 75		
Hematocrit (%)	○ ≥ 60		○ 50 - 59.9	○ 46 - 49.9	○ 30 - 45.9		○ 20 - 29.9		○ < 20
White Blood Count (total/mm3) (in 1.000_3)	○ ≥ 40		○ 20 - 39.9	○ 15 - 19.9	○ 3 - 14.9		○ 1 - 2.9		○ < 1
Glasgow Coma Score (GCS): Score = 15 minus actual GCS ☐☐									

(Circle appropriate score for each category)

Eye	Verbal Non-Intubated	Verbal Intubated	Motor
4 Spontaneously	5 Oriented & Talks	5 Seems Able To Talk	6 Verbal Command
3 Verbal Command	4 Disoriented & Talks	3 Questionable Ability To Talk	5 Localizes To Pain
2 Painful Stimuli	3 Inappropriate Words	1 Generally Unresponsive	4 Withdraws To Pain
1 No Response	2 Incomprehensible Sounds		3 Decoriticate
	1 No Response		2 Decerbrate
			1 No Response

A Total Acute Physiology Score (APS): Sum of the 12 individual variable points ☐☐									
Serum HCO_3 (venous mMol/L) (Not preferred, use if no ABGs)	○ ≥ 52	○ 41 - 51.9		○ 32 - 40.9	○ 22 - 31.9		○ 18 - 21.9	○ 15 - 17.9	○ < 15

B Age Points: Assign points to age as follows:

Age(yrs)	Points
≤ 44	0
45 - 54	2
55 - 64	3
65 - 74	5
≥ 75	6

C Chronic Health Points

If the patient has a history of severe organ system insufficiency or is immuno-compromised, assign points as follows:

a. for nonoperative or emergency postoperative patients - 5 points

b. for elective postoperative patients - 2 points

Apache II Score

Sum of A + B + C

A APS Points _____

B AGE Points _____

C Chronic Health Points _____

Total Apache II _____

APPENDIX 3

Pneumonia : Predictors of Severity

Folder Number _____.

Name_____

Age _____.

Survived <Y>

Duration ICU _____. (days)

Duration Symptoms_____. (days)

Chronic Health <Y> Specify _____,_____

APACHE 11 _____.

Confused <Y>

Temp. _____ ^{o}C

Resp. Rate _____.

Shock <Y>

WCC _____ ({Polys} ____% {lymphos}____% {Eosinophils} ____%)

Platelets _____. Cells/ml

DIC <Y> (Platelets < 80000/mm3, PTT prolonged, D-dimer +ve.)

Microbiology{Organism 1}_____

{Organism 2}_____

{Organism 3}_____

High Risk Organism <Y>

1Sputum _____(Mucoid,Purulent,Bloody)

2Sputum _____(Minimal,Copious)

Bacteraemia _____(S.pneumoniae,Staph.Aureus etc)

Biochemistry{Na+} :_____.

{K+} :_____.

{PO4} :_____.

{Mg++} :_____.

{Urea} :_____

{Cr-} :_____

{ALT} :_____

{AST} :_____

{LDH} :_____

{Alk Phos}:_____

{CBilirubin}:_____

{TBilirubin}:_____

{ALB}:_____

{Total Pr-}:_____

Blood gas D1{PaO2}:_____ Day2 :_____ Day3:_____

{PCO2}:_____ Day2 :_____ Day3:_____

{PH}:_____ Day2 :_____ Day3:_____

{Base+}:_____ Day2 :_____ Day3:_____

{Base-}:_____ Day2 :_____ Day3:_____

{FiO2}:_____ Day2 :_____ Day3:_____

{PaO2/FiO2}:_____ Day2 :_____ Day3:_____

{PEEP}:_____ Day2 :_____ Day3:_____

{XRAY Quadrants}(1-4):_____ Day2 :_____ Day3:_____

{Lung Injury Score}:_____ Day2 :_____ Day3:_____

Xray1 _____ (Lobar/segmental;Lobular;Broncho;Interstitial)

Xray2 _____ (Improved,same,worse on day 2)

Xray3 _____ (Improved,same,worse on day 3)

ARDS <Y>

Effusion <Y>

Bilateral <Y>

Xray diagnosis _____(S pneumoniae, S. aureus,

H.influenzae, K pneumoniae, Atypical).

APPENDIX 4

Lung Injury Score.

1. Chest Xray Score

Component	Value	Score
No alveolar consolidation	(0)	0
Alveolar consolidation	(1 quadrant)	1
Alveolar consolidation	(2 quadrant)	2
Alveolar consolidation	(3 quadrant)	3
Alveolar consolidation	(4 quadrant)	4

2. Hypoxaemia Score

PaO^2/FiO^2	>300	0
PaO^2/FiO^2	225-299	0
PaO^2/FiO^2	175-224	0
PaO^2/FiO^2	100-174	0
PaO^2/FiO^2	<100	0

3. PEEP Score

PEEP	<= 5 cm H_20	0
PEEP	6-8 cm H_20	0
PEEP	9-11 cm H_20	0
PEEP	12-14 cm H_20	0
PEEP	>= 15 cm H_20	0

4. Compliance Score(when available)

Compliance	>= 80 ml/cm H_20	0
Compliance	60-79 ml/cm H_20	0
Compliance	40-59 ml/cm H_20	0
Compliance	20-39 ml/cm H_20	0
Compliance	<20 ml/cm H_20	0

Score = aggregate sum / number of components used.

APPENDIX 5

Prognosis of Severe Community-Acquired Pneumonia

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Keywords: community-acquired pneumonia, outcome, severity of illness score, intensive care.

Abstract:

Study Objective: To determine the predictive value of clinical prognostic factors and scoring systems in severe community acquired pneumonia.

Design: Prospective non-concurrent clinical study.

Setting: Medical intensive care unit in a 1200 bed university hospital.

Patients: 237 consecutive patients admitted from January 1987 through December 1993. Immunocompromised patients, those with a history of aspiration or with pulmonary tuberculosis were excluded.

Measurements and Results: 82% required mechanical ventilation; the mean age was 45.2 years and 59% were male. The duration of ICU stay was 11.45 ± 11 days and the overall mortality was 24.8%.

All severity of illness scoring systems were highly predictive of outcome: organ failure ($p<0.0001$), APACHE II ($p<0.0001$), lung injury ($p=0.0007$). However, in the individual patient their predictive value , and the prognostic score of the British Thoracic Society and of Fine were poor. Organ failure performed best for the individual patient (>2 organs: overall accuracy 80%, sensitivity 37%, specificity 94%). Individually significant parameters included age ($p=0.041$), shock (Systolic blood pressure <=80 mm Hg ($p<0.001$), WCC <4000 cells/ml ($p=0.036$), platelets < 80,000 cells/ml ($p=0.003$), > 2 lobe involvement on chest radiograph ($p=0.035$), ARDS ($p=0.0001$), urea ($p=0.004$), inorganic phosphate ($p=0.004$), conjugated bilirubin ($p=0.041$), albumin ($p=0.027$) and co-morbid disease ($p=0.026$).

Etiological microorganisms with percentage incidence and odds of death were: *S. pneumoniae* (23.2%, odds 0.6), *S. aureus* (8.4%, odds 2.17), *K. pneumoniae* (8%, odds 1.86), *H. influenzae* (5.9%, odds 0.49), other Gram negatives (3%, odds 1.21), mixed infection (11%, odds 1.39), unknown (28.3%, odds 1.16).

Conclusions: Conventional ICU scoring systems accurately predict the severity of disease in severe community acquired pneumonia, however their sensitivity and specificity for the individual patient are poor.

Introduction

Community-acquired pneumonia requiring intensive care admission has been shown in recent, well-designed, prospective studies to demonstrate differences in aetiology and clinical features from less severe disease.[1-4] While *S. pneumoniae* remains the most common pathogen, the increased incidence of Gram negative and staphylococcal infections and relative paucity of Mycoplasma and Chlamydia pneumonia have become evident in most studies. [2-4] The mortality of these severe cases is high, ranging between 24% to over 50%; with the cause of this higher mortality not being evident from the descriptions of the clinical features or severity of illness of the different cohorts.[2,4-6]

There are still discrepancies in the definitions and classification of community-acquired pneumonia which make comparisons difficult, as the criteria for inclusion affect the interpretation of both the incidence and outcome of differing etiologies .[3] Older studies have for example, in some instances, selected only lobar pneumonia, or included aspiration pneumonia and pneumonia in immunocompromised patients, while others have included infections caused by *Mycobacterium tuberculosis.* [6-9] The ability to predict accurately the outcome for an individual with severe community-acquired pneumonia requiring intensive care unit (ICU) admission has, thus far, eluded severity of illness scoring systems.[6,10-13] At least part of the reason for the ongoing difficulty in assessing the likelihood of death in severe pneumonia is that adverse prognostic factors have not been evaluated in sufficient numbers of patients with severe pneumonia requiring admission to the ICU.

A number of outpatient and hospital-based studies have developed and validated various rules to determine prognosis based on predictive clinical parameters found to be significant on multivariate analysis. These rules have proved useful in groups of patients where the likelihood of an adverse outcome is low.[14-18] Other studies have identified clinical criteria that can accurately determine low risk patients who can be successfully treated as outpatients.[19-21]

The ability to define the severity of disease is essential to make therapeutic decisions regarding the choice of empirical antibiotics, and the need for hospitalisation or ICU admission. While outcome prediction in severe pneumonia is not as crucial, it is useful to allow clinicians to communicate accurate information to the patients and their families, to determine the most cost effective management strategies, and to evaluate current or new therapies.

We report here a prospective clinical audit designed to assess whether the aetiology, clinical features, and the use of general ICU scoring systems were able to assist in the prediction of outcomes of consecutive patients with severe community acquired pneumonia admitted to our respiratory ICU over a 7 year period. We have also attempted to define more accurately possible significant adverse prognostic features, and to assess the specificity and sensitivity of several newer methods of predicting outcome in severe pneumonia which have been published subsequent to the initiation of this audit.[14,15,17,20]

Patients and Methods

Two hundred and thirty-seven adult patients with a diagnosis of community-acquired pneumonia presenting to our respiratory ICU between January 1987 and December 1993 were included in this analysis. Criteria for the diagnosis included a clinical history of an infective illness suggestive of pneumonia; pyrexia or hypothermia; clinical signs of lung consolidation including crackles or bronchial breathing; an elevated white cell count or a left shift in the morphology of the neutrophils, and evidence of an infiltrate on the chest radiograph. Patients with a history of aspiration, those severely immunocompromised by disease or drugs (e.g. haematological malignancy or AIDS, transplant patients or cancer chemotherapy) were excluded. All patients with pulmonary (88 patients), or disseminated tuberculosis (28 patients) were excluded from this analysis, except for two patients in whom other micro-organisms were also present on blood culture.

There were no strict entry criteria for ICU admission, and all patients who were considered likely to benefit from ICU care on the basis of clinical judgement were admitted; specifically old age and clinical features suggestive of a poor outcome were not exclusion criteria.

Initial antibiotic therapy usually consisted of penicillin and an aminoglycoside until culture results were available. A third generation cephalosporin was substituted in the elderly and in renal failure; in cases of suspected staphylococcal infection cloxacillin was added, and where a Gram negative aetiology was suspected combination Gram negative cover was provided.

The majority (81%) of patients needed intubation and mechanical ventilation, however a few were able to be treated with continuous positive airway pressure (CPAP) by face mask or by oxygen alone. The inability to maintain adequate respiratory function and any evidence of septic shock (systolic blood pressure <90 mm Hg despite adequate volume replacement), were used as independent indicators of the need for immediate intubation. No routine stress ulcer prophylaxis was used.

The causative organisms were determined using microscopic and culture evaluation of acceptable sputum specimens (<5 squamous epithelial cells/LPF and >25 leucocytes/LPF), tracheal aspirates taken immediately after intubation, and routine blood cultures in all cases; serological and protected specimens were taken in patients where no diagnosis was evident or when clinically indicated. Immunofluorescent staining for *Legionella spp* was more recently performed on the protected brush specimens. The pneumonia was attributed to the microorganism if it was present on blood culture, present in significant numbers on microscopy and in culture, or if the antibody titre showed a fourfold rise over time, or was very high on initial serological testing.

Patient demographics and all associated diseases present on admission were recorded. The severity of illness was calculated using the APACHE II scoring system with the worst physiological parameters in the first 24 hours being used .[10] The organ failure

score was assessed daily for the first 5 days following admission using the following criteria for defining organ failure :

Respiratory:-

Respiratory rate <6 breaths/minute or >49 /minute or

$PaCO_2$ >5.9 kPa or

$AaDO_2$ >46 kPa (FiO_2 - PaO_2 - $PaCO_2$) or

Dependent on ventilator for >3 days.

Renal -

Urine output <480 ml/24 hours or <160 ml/12 hr or

Serum creatinine >300 µmol/l or

Serum urea >20 mmol/l.

CVS -

Mean blood pressure <50 mm Hg or

Heart rate <55 beats/minute or

pH <7.25 with $PaCO_2$ <6 kPa.

Haematological -

WCC <1000 /ml or

Platelets <20,000 /ml or

Haematocrit <21%

Neurologic

Unconcious with a Glasgow Coma Score <7 (no sedatives for 24 hr)

The lung injury score excluding compliance was retrospectively applied to these patients.[13] A score of 0 to 4 was given for the extent of radiological involvement of the lung, PaO_2/FiO_2 ratio, compliance and PEEP, with the total being divided by the number of parameters scored.

Additional clinical parameters which could possibly predict a poor outcome (age, confusion, tachypnoea, renal function, serum chemistry and haematology, as well as 3 parameters of the lung injury score (PaO_2/FiO_2 ratio, chest radiograph, and PEEP

level) were carefully documented on admission. The chest radiographs were subsequently recalled and read by a pulmonologist who was blinded to the causative organism and outcome, and the pneumonia was classified as lobar or segmental, bronchopneumonia, interstitial or lobular, and the presence of radiological changes compatible with ARDS ocurring over the first 3 days of admission were noted.

The scoring systems for pneumonia proposed by the British Thoracic Society[14] and Fine et al [15] were retrospectively calculated from these clinical parameters.

All data were collected by junior medical staff during the patients stay in the ICU and recorded on a prescribed form which was reviewed weekly to ensure the accuracy of the data (by the author or a deputy when not available). Data was stored on a DBase 4 programme specifically designed for this ICU information.

Numerical data is reported as mean and standard deviation. Comparison between data was done by Student's t for continuous variables, Chi square testing (with Yates or Fishers exact correction if indicated), relative risk and odds ratio for categorical variables using Epi-Info Version 6 and Epistat statistical packages.[22]

Results

Clinical features

During the seven year study period 237 patients were admitted with community-acquired pneumonia: 82 were black, 20 white and 135 of mixed race, there were 141 males and 96 females, with a mean age of 45.2 years (median 46 range 13-84 , S.D. 17.07). All patients were in respiratory failure: 17 required O2 by facemask, 27 received CPAP via face mask ,and 193 IPPV of whom 172 were ventilated with PEEP. Tracheostomy was performed in 70 patients while the remainder were treated by nasotracheal or orotracheal intubation. 59 patients died in the ICU (24.8% mortality, 30.6% for those requiring IPPV), with the mean time to death being 7.62 days (range <1 - 35 days) following admission. The mean duration of ICU admission was 11.45 ±11.01 days.

The patient demographics, co-morbid disease, and clinical features on presentation and haematology, are shown in tables 1 and 2 for survivors and non-survivors. Bacteraemia was present in 69 patients (29.1%) with 18 (26%) deaths compared with 41 (24%) deaths in 168 non-bacteraemic patients (p = 0.9)

The relationship between age and mortality and the odds ratio for death in the different age groups are shown in figure 1. Twenty-eight patients were over 65 years of age of whom 12 died (p = 0.019) and of 82 over the age of 55, 24 died (p = 0.257). Sixty patients were 30 years of age or younger of whom 9 (15%) died, and this, compared with 50 (28.2%) deaths in 177 patients aged 31 years or older, showed no significant difference in mortality (p = 0.06). The demographic features of these young patients were similar but APACHE II was 11.47 +- 4.95 in survivors and 16.56 +- 5.48 in non-survivors (p=0.007) and the organ failure scores were 0.78 +- 0.64 - and 1.89 +- 1.05 respectively (p= 0.01). The causes of death were brain damage following cardiac arrest 1, respiratory failure 1, shock 1, and multiple organ failure in 6. There was severe underlying disease in 3 patients who died, including a presumed collagen vascular syndrome, a subarachnoid haemorrhage and a patient with end-stage Prader-Willi syndrome and in 2 further deaths there was over a week's delay in seeking medical attention. The organisms that caused death included *S. Pneumoniae* in 2, *S. Aureus* (3), *K. Pneumoniae* (1), and there were dual infections in 3.

The initial biochemical indices for survivors and non-survivors are shown in table 2 (data on 7 patients incomplete) and those that were significantly different in survivors and non-survivors are illustrated in figure 2.

There were no significant differences for outcome for the different causative organisms although the odds of death was increased with *S. aureus, K. pneumoniae* and other Gram -ve infections (figure 3). Infections caused by a single organism only were included in each category and 26 patients had pneumonia caused by multiple microorganisms (25 were caused by 2 microorganisms and 1 by three) and are classified as a mixed group. The most common microorganisms in this mixed group were *S. pneumoniae* (18 isolates), *H. influenzae* (14), *S. aureus* (5), anaerobes (5),

Gram negative organisms (8), other Gram positive microorganisms (1), and 2 had what was considered clinically to be *Mycobacterium tuberculosis* in addition to a blood culture positive bacterial pathogen. Patients in whom no microorganisms were identified were designated "unknown".

Severity of Illness Scoring

The APACHE II score determined from the worst physiological abnormality in the first 24 hours of ICU admission showed a significant difference between survivors (15.3 ± 6.69), and non-survivors (22.36 ± 9.27 p = <0.001). The APACHE II scores and mortality are related in figure 4. Seven of 76 patients with APACHE II scores of 12 or less died. The microorganisms causing pneumonia in the patients with low APACHE II scores were similar to the overall spectrum of pathogens, and deaths were due to *S. pneumoniae* in 2, *S. aureus* (1), *Candida spp* (1), unknown (3), and one had dual infection with *S. pneumoniae* and *H. influenzae.* In those with a low APACHE II score, 2 deaths were in patients with extensive malignancy and 1 with a collagen vascular syndrome; death was due to unremitting sepsis and multiple organ failure in all cases other than one who died of shock.

The number of organs in failure on day one in survivors was 1.08 ± 0.8, and non-survivors 2.17 ± 1.28 (P= <0.0001). The number of organs in failure related to mortality showed a significant increase in mortality if more than 2 organ failure was present on day 1 of ICU admission (see figure 5). Organ failure was assessed daily for the first five days of ICU admission in patients admitted from 1988. The overall relationship of organ failure to mortality from day 1 to 5 is shown in figure 6. (available in 168 patients only).

There was a significant difference in lung injury score between 126 survivors, mean score of 1.6 ± 0.64 and in 32 non-survivors 2.04 ± 0.69 (p = 0.0007).(Figure 7) The lung injury score showed minimal change over the first 3 days of admission being 1.6, 1.64 and 1.56 in survivors and 2.04, 2.12 and 2.03 in non-survivors respectively.

The chest radiographs were available for review in 165 patients: 93 (56.4%) had lobar or segmental opacification, 23 (13.9%) bronchopneumonia, 24 (14.5%) interstitial, and 25 (15.2%) lobular changes. There was no statistical differences in mortality but the odds ratio for death in bronchopneumonia and lobular pneumonia were 2.17 and 1.88 respectively. 47 patients had changes compatible with ARDS with a significantly higher mortality (p=0.0001 and odds ratio 4.58)

Rules for predicting outcome

It was possible to test 2 modified predictive BTS rules (Rule 1; any 2 of hypotension (SBP <80 mm Hg), renal failure (urea > 7 mmol/l) or respiratory rate of >29 breaths/min; Rule 2: BTS rule 1 +- confusion instead of urea to make it immediately applicable) in 230 patients .(table 3) [14]

The predictors of outcome defined by Fine et al including a vital sign abnormality, age >65 years, confusion, high risk organism and neoplasia with the exclusion of pleuritic pain scored as 2 points for each positive function are shown in table 3 and 4.[15]

Discussion

While the conventional general ICU severity of illness scoring systems are able to predict mortality in cohorts of patients with severe pneumonia, we have been unable to show that either they or any other specific system for predicting outcome in pneumonia are accurate predictors for the individual patient. We found that the organ failure score was the most reliable and yielded the most reproducible results, but even this was only able to predict certain death in three patients with five organ failure on day 1, and in all patients with 4 organ failure on subsequent days. When applied as a prognostic rule, taking more than 2 organ failure as the index on day 1, it had a positive predictive value of only 69%, sensitivity of 37% and an overall accuracy of 80%. The high specificity (94%), would make it of some use in individualising

decisions; but its low sensitivity would limit its use for decisions regarding resource allocation.

The APACHE II system showed significantly higher scores for non-survivors, but considerable overlap occurred. When a score of more than 21 was applied as a cut-off, the predictive value was generally worse than using >2 organ failure, although the sensitivity was slightly better. Other more recently developed scoring systems for pneumonia were also of lesser predictive value overall, than the organ failure score (Table 3).

Age as previously reported, predicted an adverse outcome in those over the age of 65 years. The average age of our patients was much lower than in most other series and only 28 patients were over the age of 65 years which may partially explain the lower mortality in this series.[14,15] In the 9 deaths that occurred in patients under 31 years of age, a terminal illness was present in 3, and in 2 others there was considerable delay in obtaining medical treatment.

Because the general ICU scoring systems perform relatively poorly in lung disease, a lung injury score has been proposed for scoring ARDS more accurately.[10] We applied a modified lung injury score (excluding compliance) and tested a score of >2 for predicting death. This performed worse than either the APACHE II or organ failure scores, and selecting a higher score would have proved no better.(Table 3)

The modified rules 1 and 2 of the British Thoracic Society also performed poorly and both were less accurate than shock alone.[14] The rules were modified by using a systolic blood pressure of <= 80 mmHg rather than a diastolic pressure of <60 mmHg, as we considered the systolic pressure to be more easily detected, particularly in septic patients, and therefore a more reliable measurement. However in a previous multicenter study of 60 patients requiring ICU admission, the unmodified rule 1 identified only 75% of patients requiring ICU admission, and the positive predictive value was only 19%. Furthermore, no individual clinical or laboratory parameters were found to be significantly associated with death.[5]

While Fine's scoring system using a score of >4 points achieved a specificity of 95% in our population, the sensitivity was only 20%. In a study validating this system using the MedisGroups comparative hospital database with a mortality of 11.1%, the benefits of this system for classifying low risk patients were confirmed[20]; however the classification of "high risk aetiology" in the absence of definitive microbiology may have contributed to their successful validation. In our study, we found a relative risk of death of 2.4 in patients with more than 4 points and a similar positive predictive value to that achieved with the other scoring systems, suggesting that this score may not contribute additional information.

In the cohort of patients with low APACHE scores (<13) who died, end stage, co-existing disease may have contributed to death in a number of cases, and this is a factor which needs more weight in pneumonia than it is currently accorded by the chronic health component of the APACHE II score. There were no other striking differences between the patients with low APACHE II scores who survived and those who died, although three of the five patients who died were admitted from a general ward or referred from another hospital, with treatment already having been started. This suggests that there may have been failure to respond, and that the prior admission may have stabilised these patients resulting in a falsely low APACHE II score. However, only 67 patients (35%) were admitted directly from the emergency unit, making it unlikely that the low scores in those who died could be attributed only to prior stabilisation.

More careful evaluation of patients with both low APACHE II scores and younger age who died against prediction suggests that severe co-morbid disease and delay in antibiotic therapy may both increase the risk of dying. It is well accepted that outcome in severe infection is related to timely and appropriate antibiotic therapy.[7,23] If a measure of delay in treatment, as well as the appropriateness of therapy and the initial response, could be included, prognostication might be improved as these factors are not identified by the standard scoring systems.

The microbiological aetiology of severe community-acquired pneumonia reported here is similar to recent reports from France [2,4] A high incidence of Gram negative and *S. aureus* infections which are asscociated with a high mortality, suggest that these pathogens may produce a more severe form of disease. The mortality rates for *K. pneumoniae* (36.8%, odds ratio 1.86), and *S. aureus* (40%, odds ratio 2.17) are considerably higher than for *S. pneumoniae* (15.4%, odds ratio 0.6), *H. influenzae* (14.3%, odds ratio 0.49) or Legionella and Varicella infections, where no deaths occurred. Leroy has included *H Influenzae* and *Moraxella catarrhalis* with Gram negative infections and while this is theoretically correct, it is conventional in community-acquired pneumonia to classify high risk organisms such as *K. pneumoniae*, *E. coli, Pseudomonas spp, Acinetobacter spp* and *Proteus spp* as Gram negative infections, while *H. influenzae* and *M. catarrhalis* are grouped separately because of the difference in mortality and their association with chronic lung disease.[4].

We have previously reported a significant increase in mortality associated with Klebsiella pneumonia requiring ICU admission, and other community based studies have documented the high mortality associated with *S. aureus* infections.[24,25] Previous studies of community-acquired pneumonia both from the general hospital and the intensive care units have failed to take into consideration the important influence and prognostic value of the aetiological agent on the severity of disease, possibly because of the relatively small numbers of patients with infections caused by high risk organisms.[2,4,14,18,26,27]

The importance of *L. pneumophila* as a cause of community-acquired pneumonia requiring hospitalisation, and also ICU care, has recently been described.[3,5,19,28] Infection with these agents with a high mortality should alert the clinician to the need for early ICU admission with appropriate antibiotic therapy. Of interest, the majority of patients with *L pneumophila* pneumonia treated in our hospital during this period required ICU admission; howevever, there were no fatalities suggesting that, with appropriate therapy, these patients do well. *Mycoplasma pneumoniae,* as in other

series of community-acquired pneumonia seldom requires ICU admission or causes death. [2-4]

A number of biochemical tests in this study were associated with death on univariate analysis including serum urea, inorganic phosphate , conjugated bilirubin and albumin. Only gross derangement of these parameters was a significant predictor of mortality. None of these parameters was highly discriminating and no combinations proved of value as a discriminant rule to predict outcome. The high serum phosphate was not invariably associated with renal failure and the mechanism of this derangement is unclear, although another study has identified it as a poor prognostic indicator in lobar pneumonia.[6]

The outcome of individuals with severe pneumonia continues to defy accurate prediction; however both APACHE II and organ failure are useful to predict mortality of a cohort. We have demonstrated that individual outcome can only be predicted with certainty if more than 4 organ failure is present on day 1 of admission or more than 3 organ failure on day 2, but the sensitivity of this prediction is less than 10%. A more sensitive clinical decision could be made by considering both APACHE II, organ failure score and other individual discriminant factors, such as the type of microorganism, shock, the presence of ARDS, a low white cell and platelet count serum urea > 30m mol/l, serum albumin <20 m mol/l, conjugated bilirubin >30 m mol/l, associated disease and age >65 years, mechanical ventilation, pre-existing disease and the failure to respond, all factors which were found to be relevant in this cohort of patients.

Similar factors, differing only in the significance of bacteraemia and lack of inclusion of high risk organisms, high conjugated bilirubin, and inorganic phosphate, which were found in this study, have been identified and validated by Leroy, who developed a scoring system with a score for individual parameters proportional to the the magnitude of its coefficient in a multivariate mortality model. Of the 16 parameters, the most heavily weighted were a high simplified acute physiologic score (>11), multiple organ failure score (>2), low neutrophil count (3500 cells/ml), delayed need

for mechanical ventilation(>12hr), immunosuppression and ineffective initial antibiotic therapy and, when validated in 125 patients with 36 deaths, a sensitivity of 61% and specificity of 97% was found.[29,30] With the maximum weight in this scoring system being applied to measures of failed antibiotic therapy, this system would be of greatest use only after the response to therapy could already have been assessed by other means.

While scoring systems have become an integral part of the assessment of the severity of disease and are valuable in the planning of therapy, this does not necessarily mean that they are accurate predictors of outcome for the individual patient, particularly in the intensive care unit. It seems unlikely that the development of further scoring systems for pneumonia will be able to contribute more than we are already able to achieve with good clinical judgement. The large variety of schemes currently available does, however, serve to emphasise the urgent need for a general consensus on accepted standard management strategies, in order that new and different methods of therapy can be accurately compared and evaluated.

Legends.

Figure 1: Correlation between age and mortality in CAP

Figure 2: Serum albumin, urea, PO_4 andconjugated bilirubin in survivors and non-survivors.

Figure 3: Mortality related to CAP of different etiologies.

Figure 4: APACHE II severity of illness score related to mortality.

Figure 5: Organ failure on day one related to mortality.

Figure 6: Organ failure on day 1 to 5 related to outcome

Figure 7. Lung Injury Score related to mortality

Table 1. Differences in demographics and other potential clinical prognostic features between survivors and non-survivors.

Table 2. Clinical features, haematology, and serum biochemistry related to mortality

Table 3. The predictive value of the modified rules of British Thoracic Society and Fine et al, APACHE II, organ failure, and lung injury scoring systems and shock in determining individual outcome in severe community-acquired pneumonia.

Table 4. The prognostic index for patients hospitalised with community-acquired pneumonia described by Fine et al. [15]

Table 1. Differences in demographics and other potential clinical prognostic features between survivors and non-survivors

	Survivors	Non-survivors	p=	Odds	RR
n=	178	59			
Age	43.93 ±16.9	49.15±17.03	0.041		
Race: Black	61	21	0.978	1.06	1.04
Caucasian	15	5	0.587	1.01	1.01
Other*	102	33	0.973	0.95	0.98
Male/Female	102/76	39/20	0.298	1.45	1.15
Co-morbid disease	89	19	0.026	0.47	0.64
COPD	41	11	0.599	0.77	0.81
Diabetes	24	8	0.837	1.01	1.01
Bacteraemia	51	18	0.914	1.09	1.06
APACHE II	15.3 +- 6.69	22.36 +- 9.27	<0.0001		
Organ failure	1.08 +- 0.8	2.17 +- 1.28	<0.0001		
Lung injury	(n=126)1.6 ± 0.64	(n=32)2.04 ± 0.69	0.0007		
X-ray >2 lobes (n=158)	66	24	0.035	2.73	1.43
Xray >3 lobes	42	13	0.571	1.37	1.22
ARDS (n=162)	27	20	0.0001	4.58	2.59

Table 2. Clinical features, haematology, and serum biochemistry related to mortality

	n	Survivors	n	Non-survivors	p =
Clinical Features					
Temp.^{O}C	173	37.6 ± 1.311	55	37.36 ± 1.68	0.34
Respiratory Rate	169	30.882 ± 12.769	51	32.26 ± 11.28	0.488
Confused	146	26	41	16	0.007
Shock (SBP<80 mmHg)	151	28	47	27	<0.001
WCC cells/ml	172	19867.6 ± 3618	50	17730 ± 40392	0.777
WCC <4,000 cells/ml	172	19	50	12	0.036
WCC >30,000 cells/ml	172	16	50	7	0.45
Platelets cells/ml	172	231459.9±120973	50	201268±170077	0.25
Platelets <80,000 cells/ml	172	11	50	11	0.002
Biochemistry					
Na^{+} m mol/l	174	136.8± 6.7	54	136.5 ± 6.8	0.77
K^{+} m mol/l	173	3.9 ± .7	51	4.13 ± 1.1	0.18
$PO4^{-}$ m mol/l	144	0.972 ± 0.6	40	1.597 ± 1.3	0.004
Mg+	34	0.959±1.1	7	0.843±0.2	0.57
Urea m mol/l	174	10.97± 12.5	54	16.62 ± 13.8	0.004
Cr^{-} u mol/l	173	178.89 ± 493.3	54	251.8 ± 219.5	0.16
ALT units/l	137	58.445 ± 104.4	39	39.41 ± 40.1	0.086
AST units/l	139	91.87 ± 123.7	38	88.66 ± 137.8	0.89
LDH units/l	128	620.016 ± 973.6	36	655.36 ±517.3	0.77
Alk. Phos. IU/l	140	114.886 ± 82.5	38	112.132 ± 86.6	0.84
Bilirubin Conj. u mol/l	141	8.9 ± 13.1	41	14.88 ± 16.9	0.041
Bilirubin Total u mol/l	155	16.85 ± 15.1	44	22.36 ± 21	0.11
S albumin g/l	156	28.88 ± 6.5	46	26.44 ± 6.7	0.027

Table 3: . The predictive value of the modified rules of British Thoracic Society and Fine et al, APACHE II, organ failure, and lung injury scoring systems and shock in determining individual outcome in severe community-acquired pneumonia.

	Positive predictive value %	**Overall accuracy %**	**Sensitivity %**	**Specificity %**	**Youden's Index**	**Relative Risk**
*Rule 1	37	64	64	64	.29	2.4
*Rule 2	42	73	39	83	.22	2.2
**Fine	52	80	20	95	.15	2.4
Shock	49	76	57	81	.39	3.5
APACHE II >21	52	76	48	85	.33	3.1
Organ failure >2	69	80	37	94	.31	3.8
Lung Inj. >2	30	70	38	78	.16	1.78

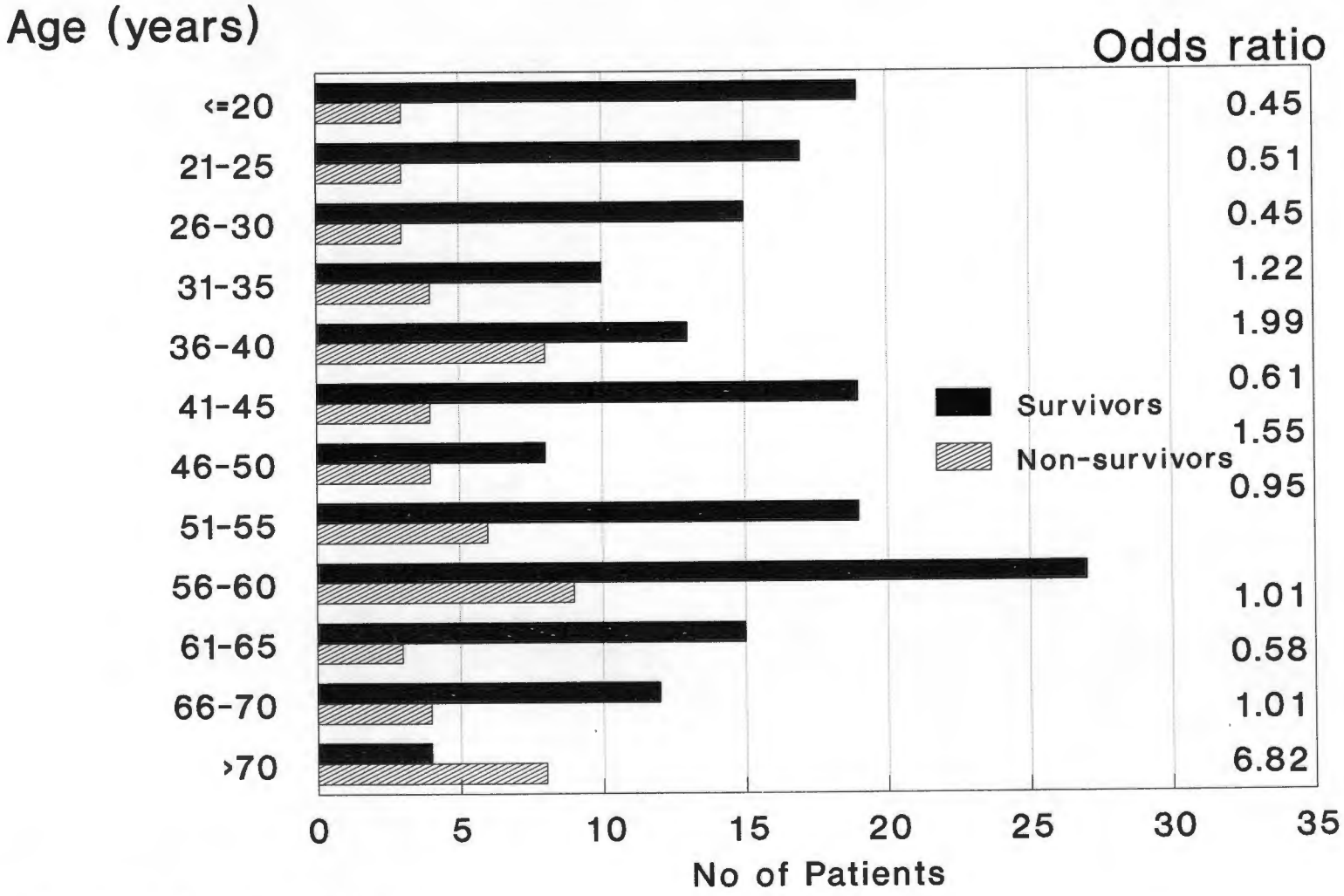
Positive predictive value = no. with positive function who died / no. with positive function. Overall accuracy = no. outcomes correctly identified / no tested with function. Sensitivity = no. with positive function who died / no. tested who died. Specificity = no with negative function who survived / no. tested who survived. Youden's index = specificity + sensitivity - 1. Relative risk = proportion who died with positive function / proportion who died with negative function.
** British Thoracic Society*[14]*; **>4 points as described by Fine et al* [15].

Table 4. The prognostic index for patients hospitalised with community-acquired pneumonia described by Fine et al. [15]

Points*	no of patients	Survivors	Non-survivors	X^2	Odds ratio (95% CI)
2	146	123	23	0.0001	0.29 (0.15<or>0.56)
4	63	42	21	0.07	1.89 (0.94<or>3.76)
6	19	8	11	0.001	5.07 (1.76<or>14.8)
8	2	1	1	0.42	3.15 (00<or>117)

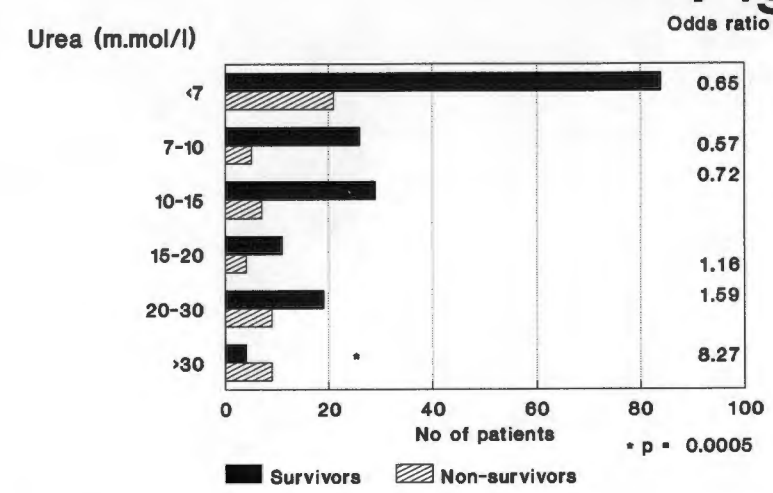
* 2 points given for the presence of each prognostic factor including a vital sign abnormality, age >65 years, confusion or mental abnormality, a high risk micro-organism, and neoplasia.

Figure 1

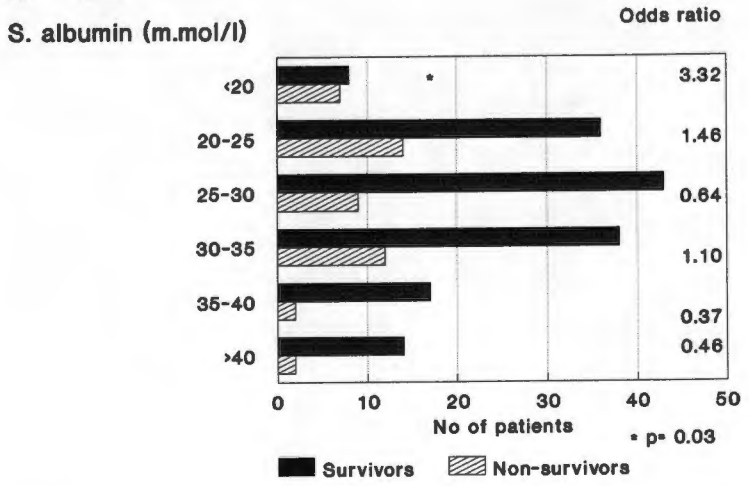


237 patients Age vs mortality

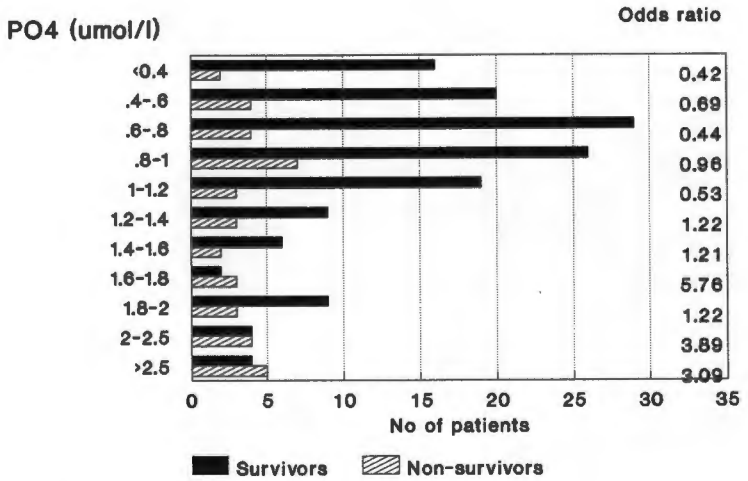
Figure 2



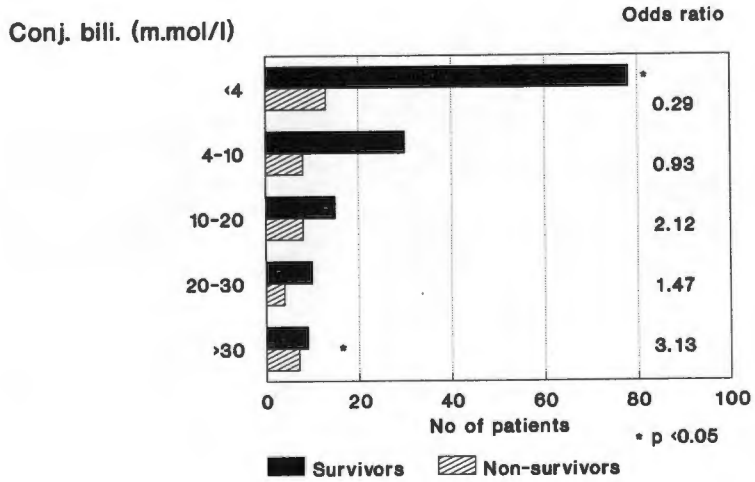
228 patients



202 patients

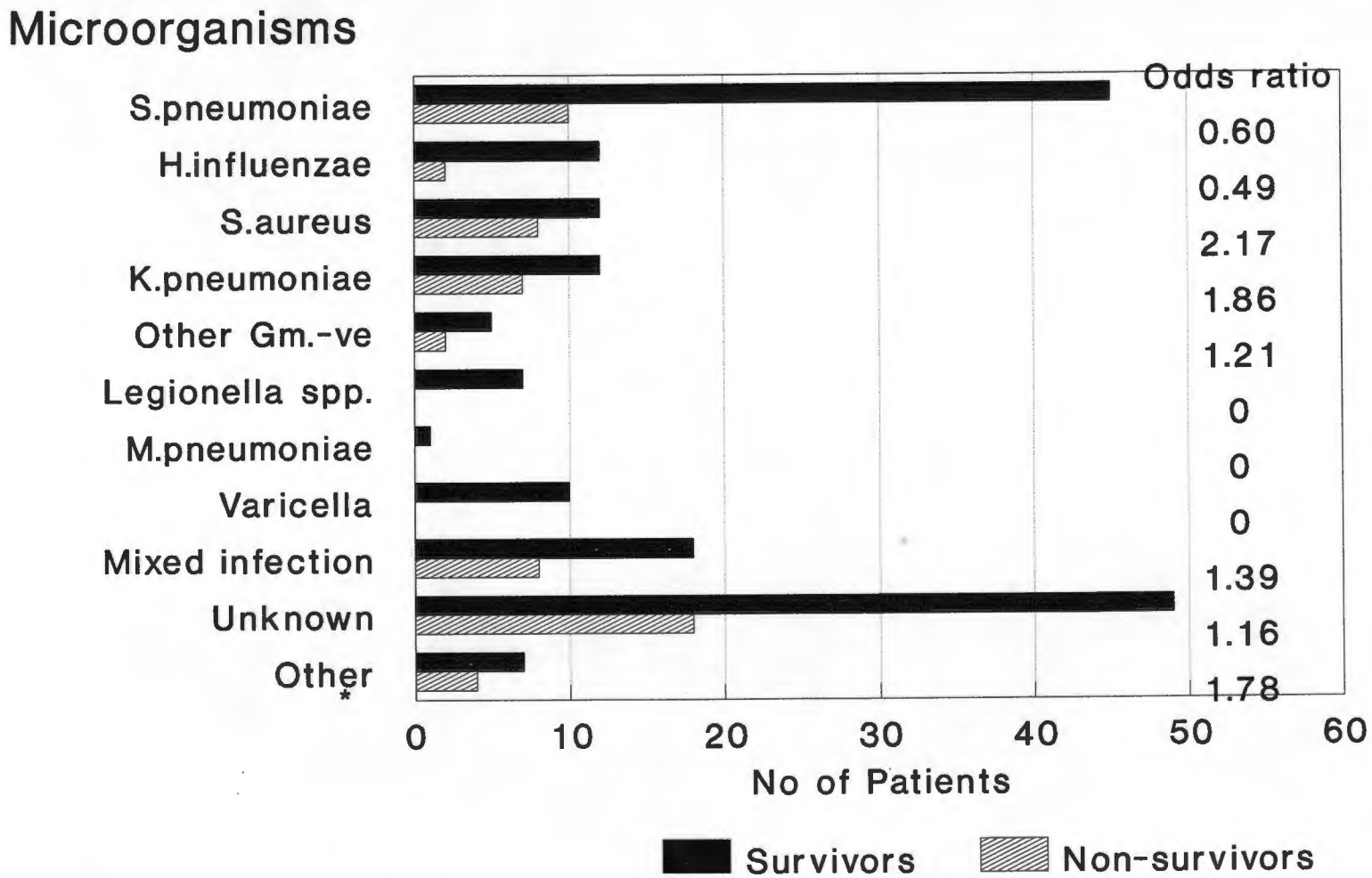


184 patients



182 patients

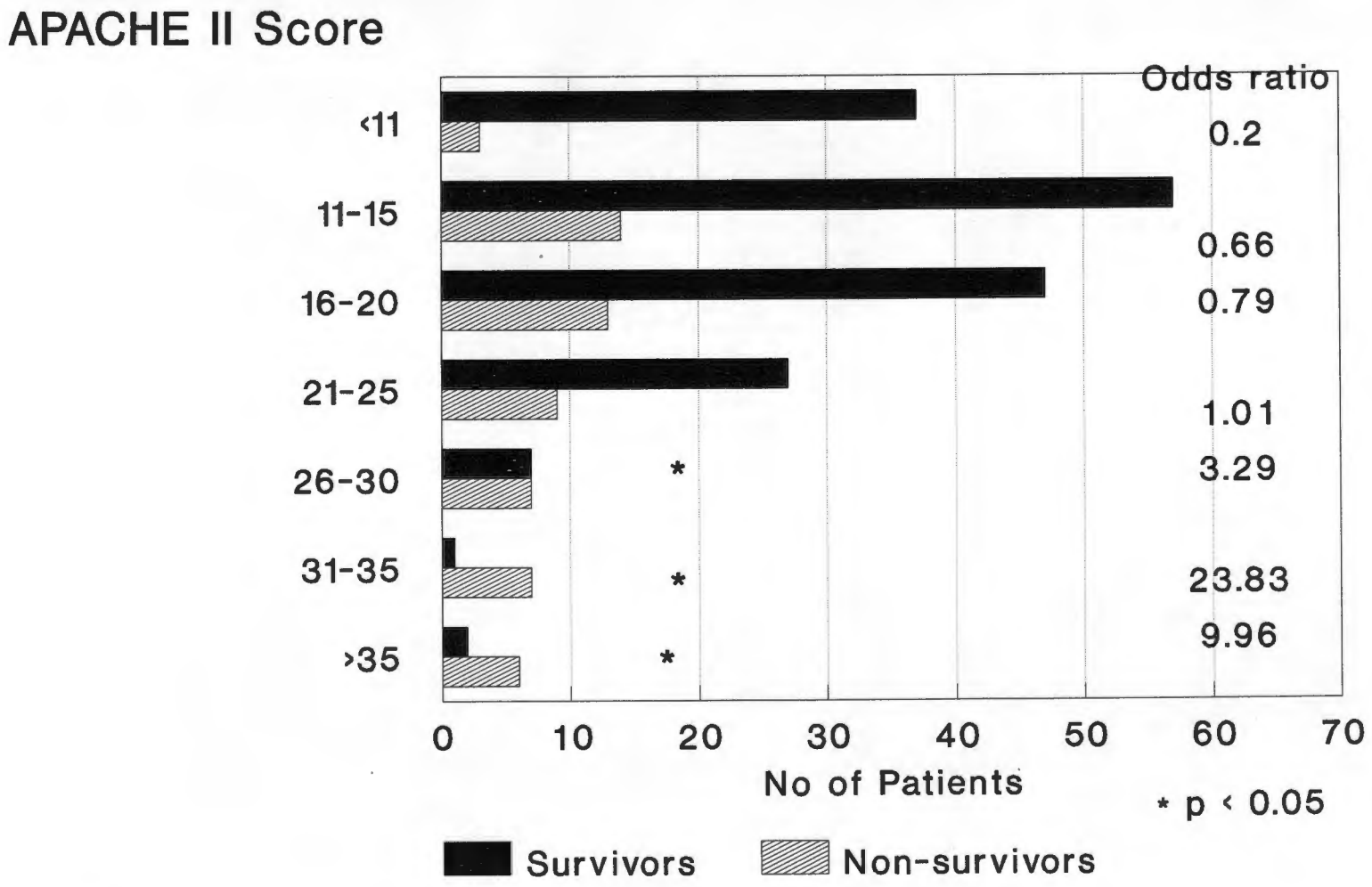
Figure 3 - Mortality vs micro-organism



237 patients

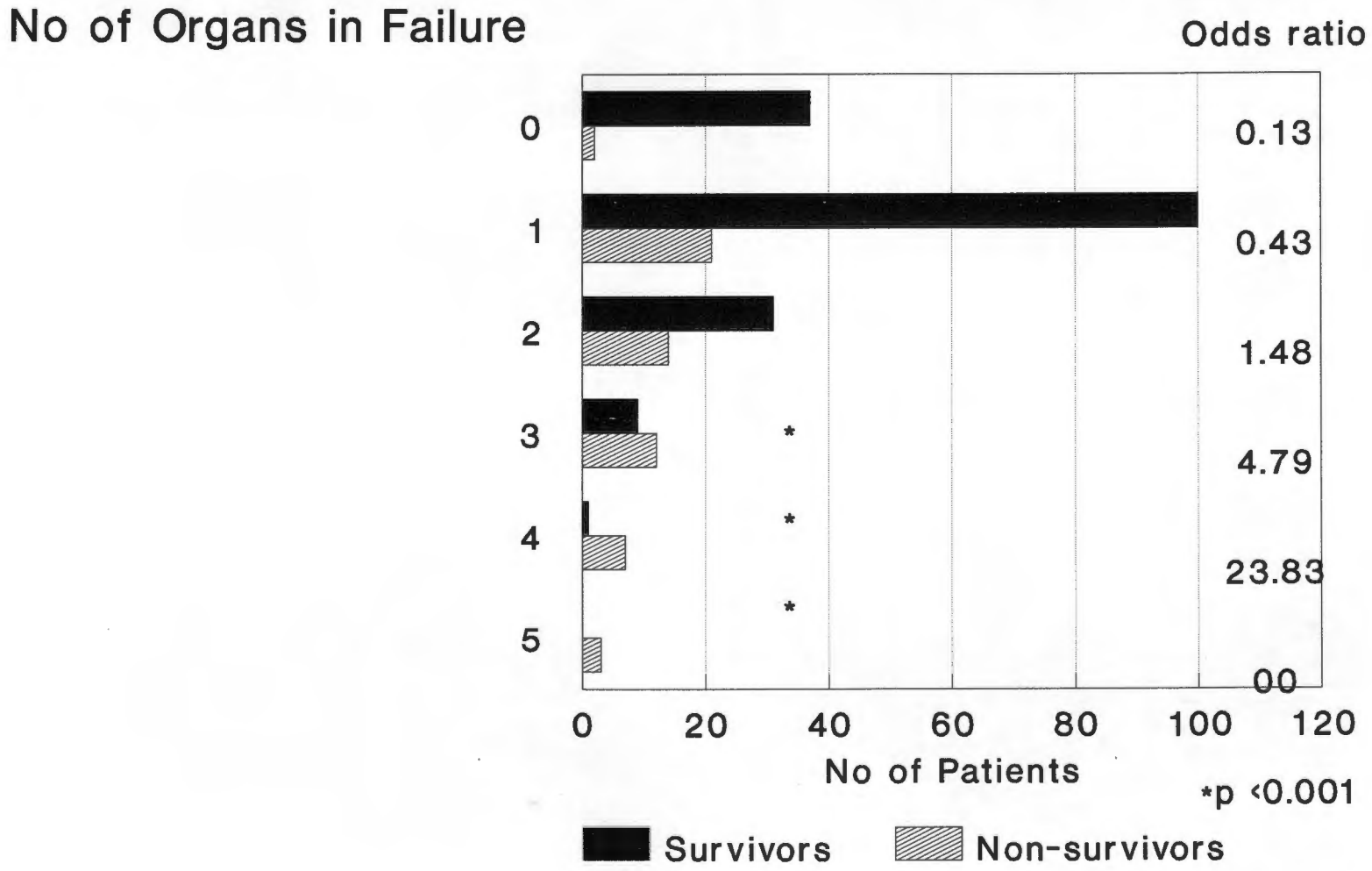
* M. catarrhalis (4), B Haem. strep. (3), S. epid. (1), Candida spp. (2), S. milleri (1).

Figure 4 Mortality related to APACHE II



237 patients

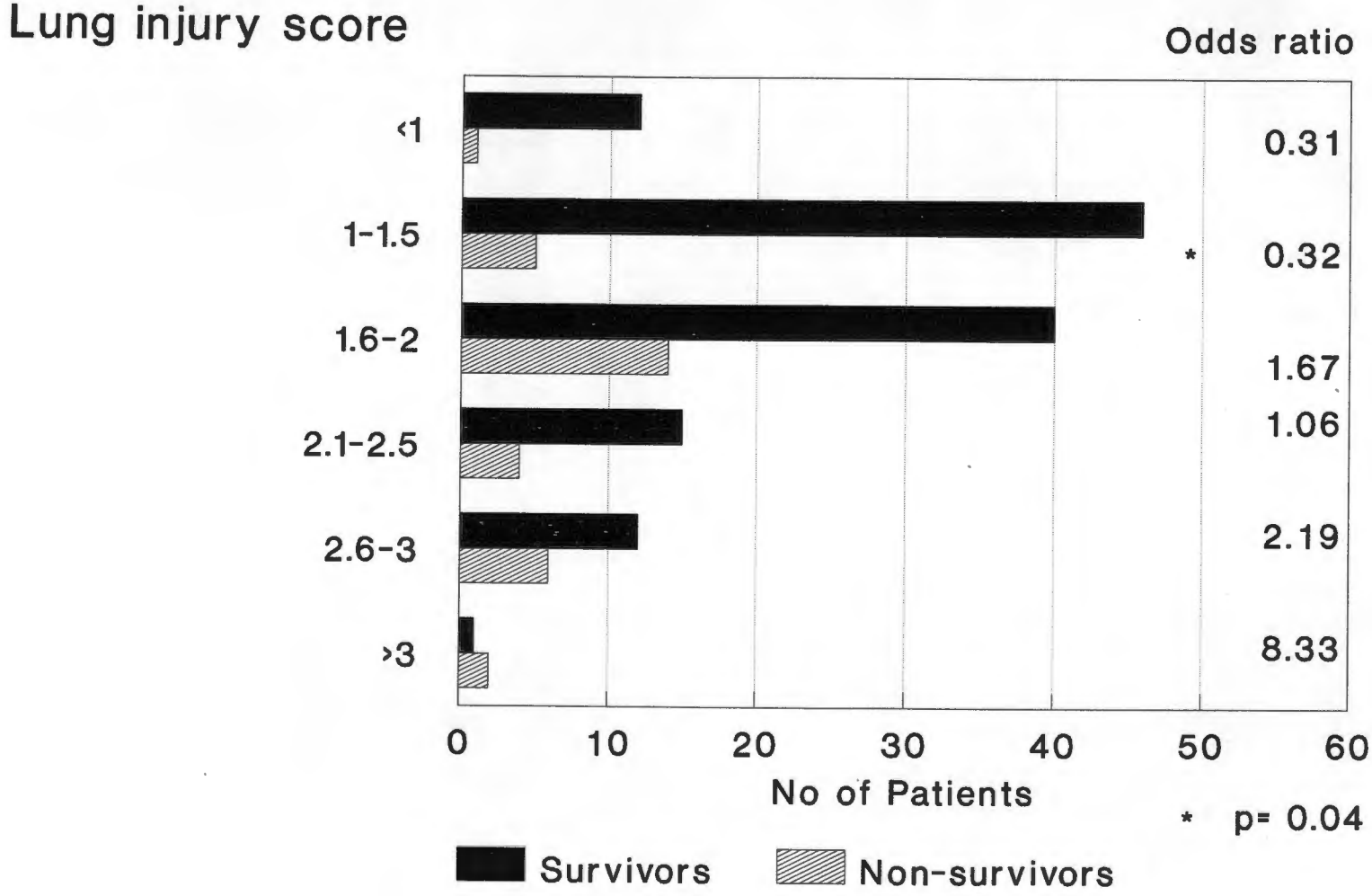
Figure 5 Mortality vs organ failure



237 patients

Organ Failure	Day 1	Day 2	Day 3	Day 4	Day 5
0	37 / 2	63 / 21	65 / 24	61 / 23	64 / 24
1	100 / 21	82 / 14	80 / 12	75 / 10	64 / 7
2	31 / 14	22 / 12	16 / 9	14 / 9	13 / 8
3	9 / 12	4 / 9	2 / 5	2 / 3	2 / 4
4	1 / 7	0 / 3	0 / 3	0 / 3	0 / 2
5	0 / 3	/	/	/	Alive / Died

Figure 7 Mortality vs Lung Injury Score



158 patients