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COMMUNITY ACQUIRED BACTERAEMIA IN THE ELDERLY

SUBMITTED FOR THE DEGREE OF MASTER OF MEDICINE PART III

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CHAPTER 1

INFECTION IN THE ELDERLY -

THEORETICAL CONSIDERATIONS.

INTRODUCTION:

Age affects the human frame at all levels - from the skin which is ravaged by exposure to ultraviolet light and toxic irritants to the immune system which becomes progressively less responsive to antigenic stimuli. Bacteraemia follows a focal infection and thus any change which results in increased infection will result in an increased chance of bacteraemia. Therefore any factors bearing on focal infection will, of necessity influence not only the possibility but also the severity of a bacteraemia.

It is the intention in this chapter to review these changes and gain perspective on their practical relevance as it affects the defence mechanisms in the elderly and their ability to respond and successfully combat bacterial infection.

CELLULAR & HUMORAL IMMUNITY:

Changes occur with age at all levels of the immune system. Stem cell reserves are diminished in certain mouse strains, associated with a reduced regenerative capacity and ability to clonal expansion[1]. The milieu in which the stem cell

functions also alters and young stem cells transplanted into an old animal have the kinetics of an "old stem cell"[1].

The thymus, which is intimately involved with the production and differentation of Thymic lymphocytes (T cells), involutes completely by the age of 50 years, and thymic hormones which are associated with the maturation of T cells are not detectable in the serum of individuals over 60 years of age[2]. The number of circulating T cells does not decrease with age[3]; but the percentage of circulating immature T cells increases, associated with an increase in the helper T cell subset at the expense of suppressor and cytotoxic T cells[2]. T cells from elderly patients have a decreased proliferative response to antigenic stimuli[3,4], and production of growth factors decreases with age[5].

B lymphocytes show similar qualitative changes. Thus antibody levels remain constant throughout life. However there is an increase in autoantibody and monoclonal antibody levels with age in humans[6]. In mice autoantiidiotypic antibodies which are associated with regulation of the immune response are increased[7]. These changes are reflected in the clinical situation by a progressive increase in the incidence of monoclonal gammopathy with age - <0,1% in individuals of under 50 years, rising to 19% in the over 90 year olds. Thymectomised mice have a marked increase in monoclonal gammopathy, implying that T cell function is involved in this process[7].

Evidence suggests that there is an inherent defect in the cellular responses of lymphocytes in the aged. T cell growth factor (Interleukin 2) production is reduced[5], while cytoplasmic factors involved in stimulation of DNA are less active[8]. The expression of antigenic determinants on the cell membrane also alters with age[2]. Ultrastructurally there is evidence of a decline in the organisation of organelles and an imbalance between cyclic AMP and GMP[1].

Macrophage function however does not appear to be influenced by age[8], although phagocytic function of polymorphonuclear cells does decline with age[3].

CLINICAL MANIFESTATIONS:

The changes described above do not result in a dramatic change in susceptibility to disease. However evidence is accumulating that reactivation of tuberculosis and varicella-zoster is increased in the aged and that this is associated with defective cellular immunity. The inability to mount a hypersensitivity reaction to tuberculin testing rises from 10% in culture positive patients under 55 years of age to 30% in those over 55years of age[9]. Similarly the percentage of non-responders to dinitrochlorobenzene rises with age[10]. These observations are associated with disease states and tuberculosis has been identified as a major health problem in the elderly, particularly in institutions[11,12].

Vaccination against influenza is less effective in the elderly[13]. Chronic disease renders pneumoccocal vaccine less efficient amongst the elderly[14,15].

These trials highlighted the problem of chronic disease in the elderly and the role which it plays in rendering the elderly more susceptible to infection. This is associated with alterations in the physical barriers to infection and these two aspects will be discussed in the next section.

PHYSICAL BARRIERS TO INFECTION, CHRONIC DISEASE AND INFECTION IN THE ELDERLY:

(i) The Respiratory System:

Changes in the respiratory system of the elderly which rendered them more vulnerable to pneumonia have been recognised for over 150 years[15]. Changes occur throughout the respiratory tree which increase the risk of infection.

The upper respiratory tract is more liable to colonisation by gram negative organisms. Alterations in the secretions of the pharynx and increased exposure to the organisms during hospitalisation facilitate this colonisation[18,19]. The possiblity of aspiration and subsequent gram negative pneumonia are increased where the cough reflex is diminished or there is a pseudobulbar palsy[18].

There are underlying physiological changes which predispose to infection, these include a loss of elastic recoil, decreased mucus production and impaired ciliary activity in the bronchi[2]. The presence of bacteria in the alveoli of the lung does not invariably result in pneumonia. Structural damage or pulmonary oedema is necessary before pneumonia ensues[16]. This damage may be due to viruses, physical agents or toxins but chronic lung disease is the most important predisposing factor[17].

(ii) Urinary Tract:

An impaired micturition reflex, obstruction due to prostatic hypertrophy in men or loss of muscle tone in the pelvic floor in women are common causes of residual urine in the bladder which results in bacterial colonisation[20]. In females senile vaginitis and the involution of the vaginal mucosa result in a loss of Doderleins bacilli and a rise in the pH. This and the reduction of cervical secretions are also associated with increased colonisation of the vagina by Gram negative organisms. Prostatic secretions which have antibacterial action are reduce in elderly men [20].

A variety of other causes render the elderly more susceptible to urinary tract infection. These range from poor personal hygiene, faecal and urinary

incontinence with indwelling catheters to renal calculi and diabetes[21].

(iii) Soft Tissues:

The skin is affected at all levels by ageing. Both elastin and collagen undergo changes in composition which result in a loss of elasticity, while blood flow to the skin diminishes. Secretions, which are under hormonal control are reduced. These secretions possess bacteriocidal or bacteriostatic properties[23]. Both apocrine and eccrine sweat glands are involved but with the loss of hormonal stimulation they become atrophic, however with appropriate stimulation normal function can be restored[22] .

The stratum corneum is reduced in thickness in the aged and permeability is increased[22]. Associated with this are an increased incidence of oedema and eczema. Eczematous skin has a significantly higher populations of potential pathogens[23], while the oedema, particularly if dependent further compromises circulation and these changes result in the stasis ulcers, so commonly encountered in the elderly. Similar conditions are encountered in bed ridden patients who often have the additional problems of hypoalbuminaemia, reduced sensation and in whom pressure sores are a common finding. Both stasis

ulcers and pressure sores are common sites of infection and subsequent bacteraemia[20].

(iv) General Factors:

The number of non specific factors which may predispose an elderly individual to infection is formidable; loss of cognitive function, diabetes, cardiovascular status, hydration, nutritional status and level of personal hygiene are but a few. The number of drugs which have been shown, at both the theoretical and practical level, to influence susceptibility to infection is vast and may well be a critical factor in determining the severity of an infection[24].

CONCLUSION:

A subtle decline in cellular immune mechanisms occurs with age, and probably results in a predisposition to certain infections, including tuberculosis. In addition these changes result in a poorer response to immunisation with the result that individuals who are most at risk receive less protection.

At the anatomical level the elderly individual is subject to numerous changes in the defence mechanisms of the respiratory, genito-urinary tracts and the soft tissues which render the individual more susceptible to infection.

CHAPTER 2

PATIENTS, METHODS AND DEFINITIONS.

During a two year period between the 1st of February 1986 and the 31st of January 1988 all positive blood cultures obtained from patients over the age of 65 years of age were reported to the investigators. These were prospectively analysed to determine patient profile, symptoms, risk factors, biochemical and haematological changes, treatment, and final outcome.

Blood Culture Techniques:

Blood cultures were performed by innoculating 3-5ml into 7D anaerobic and 6B aerobic BACTEC bottles. These contain 30ml of enriched tryptic soy broth, anticoagulant and ^{14}C labelled substrate. Aerobic bottles were incubated at $37^{o}C$ and tested daily from day 2 to day 7. A growth index of 35 or more for aerobic cultures or 20 or more for anaerobic cultures were considered positive. Identification testing and antibiotic sensitivity were carried out on positive cultures.

DEFINITIONS:

Community Acquired Bacteraemia:

Bacteraemia was considered to be community acquired if blood cultures, taken within 48 hours of admission, were positive, unless related to a procedure after admission. Blood

cultures considered to be contaminants on bacteriological or clinical grounds were disregarded. Patients who has suffered major trauma, or who recently (< 1 month) had had surgery were excluded. Patients with chronic indwelling catheters were included.

Source:

Source was based on clinical findings, if there was an obvious source of infection, or if the same organism was isolated from both the blood culture and a focal infection.

Antibiotic Treatment:

Treatment was considered appropriate if the organism was sensitive to the antibiotic used in standard in vitro testing, and the antibiotic was recognised as standard treatment for that organism. Treatment was considered inappropriate if the above conditions did not apply.

Prompt treatment was defined as appropriate antibiotics administered within 12 hours of admission, and delayed if commenced after this time.

Outcome:

A patient was considered to have survived if he/she was discharged and did not take account of deaths which occured after discharge.

CLINICAL FEATURES:

Signs and symptoms attributable to the infection were recorded either from the admission notes or direct questioning. Rarely the patient was discharged or died before the case was seen by the investigators and in some cases information was incomplete. Special attention was paid to fever, rigors, confusion, and depressed level of consciousness, vomiting and diarrhoea.

The highest temperature, the maximum pulse rate, lowest blood pressure in the first 24 hours of admission were recorded. Shock was defined as a systolic blood pressure of less than 90mm of mercury in a normovolaemic patient.

Haemoglobin, total white count (including differential count) and platelet count were recorded as well as parameters of liver and kidney function. A patient was considered to be in acute renal failure if there was a doubling of the creatine from baseline values.

Underlying Disease:

These were categorised as rapidly fatal (acute myeloid leukaemia or blastic transformation), ultimately fatal (likely to be fatal in less than 5 years), non fatal or none[26]. Alcoholism was accepted as an underlying condition if recorded in the notes. No distinction was made between insulin and non insulin dependent diabetes.

CHAPTER 3

PATIENT PROFILE, SYMPTOMS, AND UNDERLYING DISEASE

A total of 121 patients were identified as having a community acquired bacteraemia during the two year period. Sixty two patients were female and 59 male. Sex did not influence the mortality rate. Age range was 65 to 90 years. Forty six cases occurred in patients over seventy five. Overall mortality was 31%, with a 27% mortality in patients under 75 and 39% in the over 75year age group (p: n.s.; Fig. 1).

Approximately half of the patients were classified as "Coloured" (i.e. of mixed racial origins), one third were "White" (i.e. assumed to be of European extraction) and the remainder (15%) "Black" (i.e. of Negroid origin). These terms will be used for convenience in the following discussion. Mortality was not influenced by race, and although mortality was 59% in white patients over 75 year of age, this was not statistically significant ($p<0.11$).

Underlying Disease and Risk Factors:

Seventy seven percent of patients were recorded as having one or more underlying diseases. These ranged from scabies to dementia. There was no correlation between the number of underlying diseases and mortality (Table 1). Analysis using the disease categories of Rapidly fatal, Ultimately fatal and Non fatal[26], compared to patients with no underlying

disease also failed to produce significant differences in mortality rates, although the small numbers in the "Rapidly fatal" category prevents any conclusion being made in this regard (Table 2).

Diabetes, Hypertension, Ischaemia heart disease, Chronic Obstructive Airways Disease, and Cerebrovascular disease were the commonest underlying diseases. Ethanolism and smoking were commonly encountered risk factors. None of these conditions were associated with an increased mortality (Table 2), but the 3 patients with liver disease all died ($p< 0.02$). Two of the 9 patients with an indwelling urinary catheter died (20% p: n.s.).

Signs & Symptoms:

The non-specific symptoms traditionally associated with infections - sweating, fever, rigors, vomiting and diarrhoea were reported by varying numbers of patients, with no prognostic significance. However confusion occurred in 48 (40%) cases, with 26 (54%) deaths ($p<0.0003$). Additional symptoms did not affect mortality in this group (Table 3a and 3b).

Confusion was not confined to bacteraemia caused by a particular organism, nor related to a specific clinical parameter or metabolic disturbance. When tested against the parameters of temperature, blood pressure, acute renal failure, and hyperbilirubinaemia, only a temperature $< 36^{o}C$

was significantly associated with confusion ($p<0.001$;Table 4).

A pulse rate below 80/min. was uncommon but associated with a 60% mortality .

Twenty patients presented with a systolic pressure less than 100mm of mercury, 15 died (75% $p<0,0002$).

DISCUSSION:

In this chapter I have endeavoured to investigate features inherent in the patient "profile" which may have a bearing on the presentation of bacteraemia and its eventual outcome. This "profile" covers a wide variety of possibilities and the data presented above makes no pretence at covering all possible contributing factors.

Drugs are an obvious omission. A wide variety of drugs have been shown both *in vitro* and *in vivo* to have an effect on defence mechanisms[24].

Prospective trials have noted an association between non steroidal anti-inflammatories and pneumococcal pneumonia[30] but the clinical significance of this observation is not clear.

An attempt was made to investigate the effect of some categories of drugs on the outcome of bacteraemia; information on the use of antibiotics, non-steroidal anti-inflammatory agents, steroids and cytotoxics was extracted

from the clerking notes, and from questioning. However the number of patients falling into any one group was so small that no meaningful conclusions could be drawn from this data.

Age and Bacteraemia related Mortality:

Age has been identified by a number of workers as a poor prognostic factor in bacteraemia. Chattopadhyay and Al-Zahawi[27] in a study of community acquired and nosocomial infection found a mortality rate of 36% in elderly patients compared to 5% in the under 60 year old age group. A similar age related trend was found in both prospective[28] and retrospective[29] studies on pneumococcal bacteraemia. However a prospective study of this subject in 1984, failed to confirm these findings and the author concluded :

"Thus, the effects of advanced age on the manifestations and clinical course of community acquired bacteremic pneumococcal pneumonia appear less pronounced than has been reported previously"[30]. The present study supports this conclusion. In a parallel study of all ages in this institution, youth (< 30years) was a favourable prognostic factor[25], but overall mortality did not increase with age between 30 and 90 years.

There are few studies which allow direct comparison with the present one. Various authors have reported on different aspects of bacteraemia - either retrospectively[31,32], by combining nosocomial and community acquired[27] or by examining a single organism or group of organisms[28,29,30,33,34,37]. These studies reported mortality rates ranging from 4,5% for uncomplicated bacteraemia associated with urinary tract infections[34], to 36,6% for combined studies[27]. The present study found an overall mortality rate of 31% from all causes, but 21% related to the initial bacteraemia. Although mortality in patients over 75 years old was higher (39%) than in the younger age groups (27%), this difference was not statistically significant.

Because of the strict criteria applied in patient selection, this study is the first to publish mortality rates in English for community acquired bacteraemia in geriatric patients from prospective data.

UNDERLYING DISEASE AND MORTALITY:

Various studies have attempted to relate mortality to underlying conditions. These have been classified as rapidly fatal, ultimately fatal, non fatal and none by a number of authors[33,35,36,37]. This classification is unsatisfactory on a number of points:

(i) The classification is arbitary[26], and relies on the diagnosis of the disease and does not take severity into account.

(ii) The authors who have used this classification have relied on vague guidelines such as "Patients whose underlying disease was considered unlikely to be fatal within five years were all classified as having nonfatal underlying disease"[26].

(iii) There has been no uniformity in the use of these terms. Thus "rapidly fatal" was originally used to refer to acute leukaemia, blastic transformation and third degree burns[35]. Other authors have included dissecting aneurysms and selected malignancies in this group[36].

In the present study the terms were applied as stated in chapter 2. The term "Ultimately fatal disease" was applied to diagnoses and not attempt was made to judge severity. Using these criteria there was no correlation between underlying disease and mortality, although there were only 2 cases in the rapidly fatal category. The findings discussed here should deter doctors from using the mere diagnosis of malignancy, or multiple pathologies as criteria in attempting to determine prognosis especially in the acute stages of the illness.

It is often assumed that there is an increased prevalence of infection amongst diabetics, but objective evidence is sparse[67]. No studies to date have examined the role of diabetes or indwelling catheters in the morbidity associated with bacteraemia in the elderly but this study failed to show an association between either factor and mortality. Their role in the pathogenesis of the bacteraemia was not examined.

Confusion is a well documented feature of bacteraemia in the elderly[30,31,38,39]. It has been associated with gram positive organisms[30,31], pneumonia[39] and gram negative infection[38]. This study could not confirm any of the above observations, confusion being found throughout the range of organisms identified. Neither could it be ascribed to any metabolic derangement, and although a wide variety of complications of septicaemia were present in the confused patients there was no significant association with any one condition. Too few patients had arterial blood gases done to allow comment on the possible association between hypoxia or acidosis and confusion.

The association between confusion as a presenting symptom and mortality has not been reported before and is an important practical finding. Confusion is a non specific finding in the elderly[40] and bacteraemia is an eminently treatable condition if diagnosed early. Therefore a geriatric patient who becomes confused should be regarded as

having an infective process and treated as such until a bacteraemia has been excluded.

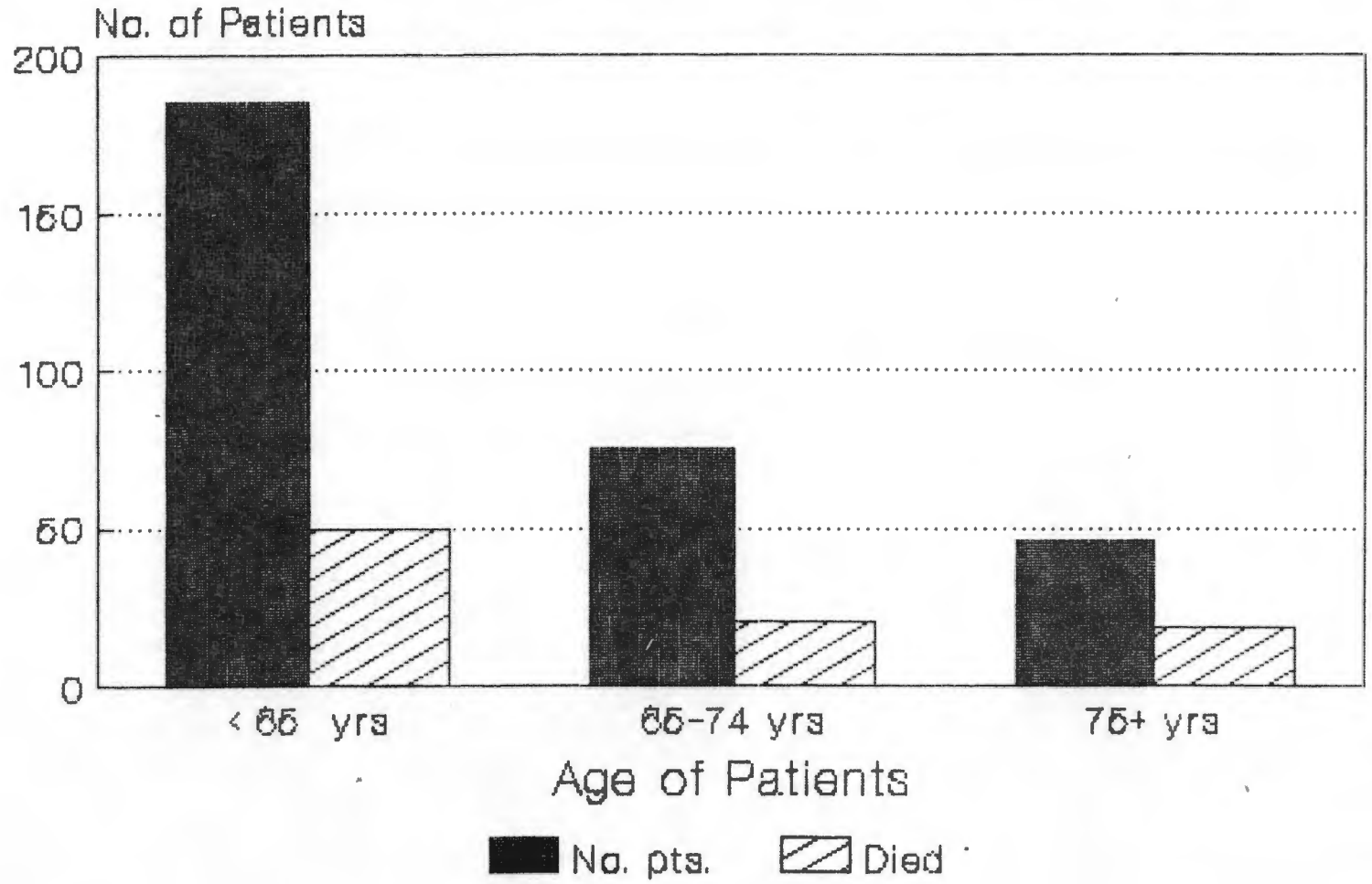
CONCLUSION:

In community acquired bacteraemia neither age nor race have prognostic importance, although individuals over 75 year of age may be at greater risk. Similarly the spectrum of chronic diseases to which the aged are prone in this community do not influence the outcome of the bacteraemia; liver disease may prove an exception but the number of cases in this study are too small to convincingly demonstrate this.

Confusion in the elderly which is due to bacteraemia is associated with a high mortality rate. This could not be associated with a particular metabolic derangement, although not all parameters were studied.

Comparison between this study and others which have included both community and nosocomial infection strongly suggest that significant differences exist between the two conditions and there can be no extrapolation from one to the other.

Fig 1 : Age vs Mortality



Data on Pts. < 65yrs from ref. 25.

TABLE 1 : Number of Underlying diseases and mortality.

No. Diseases	No. Patients	Mortality (%)		p
0	26	6	(23)	
1	38	16	(42)	
2	43	12	(28)	N.S.
3	12	4	(30)	
> 3	2	-		

TABLE 2 : Influence of Rapidly Fatal, Ultimately Fatal and Non Fatal Diseases on Mortality.

Category of Disease	No. Patients	Mortality (%)		p
Rapidly Fatal	2	1	(50)	
Ult. Fatal	21	9	(43)	
Non Fatal	72	22	(32)	N.S.
Nil	26	6	(23)	
All Malignancies	18	8	(47)	

TABLE 3(a) : Non Specific Symptoms of Bacteraemia as Prognositc Indicators.

Symptom	No. Patients	Mortality (%)	p
Sweating	15	1 (7)	
Fever	57	11 (19)	
Vomiting	37	10 (27)	
Rigors	43	7 (16)	
Confusion	48	26 (54)	<0,0003
Diarrhoea	19	8 (42)	

TABLE 3(b) Mortality in patients with confusion as only symptom versus those with confusion and other symptoms.

Symptoms	No. Patients	Mortality.(%)
Confusion/Others	25	13 (52)
Confusion alone	23	13 (57)

TABLE 4(a): Patients presenting with confusion as related to the responsible organism.

Organism	No. Patients	Mortality (%)	p
E. coli	18	6 (30)	
K. pneumoniae	7	6 (85)	
S. aureus	7	5 (72)	N.S.
S. pneumoniae	4	1 (25)	
Haem. Strep	5	5 (100)	
Mixed Orgs.	7	3 (43)	

TABLE 4(b): Relationship between temperature, blood pressure, metabolic disturbance and mortality in confused patients.

Parameter	No. Patients	Mortality(%)	p
Temp			
< 36°C	9	8 (89)	<0,001
36,1 - 37	8	2 (25)	
37,1 - 38,5	18	10 (55)	
> 38,5	13	6 (46)	
Syst. B.P			
< 90mmHg	7	7 (100)	
> 90mmHg	41	21 (51)	N.S.
Acute Renal F'lure	28	16 (57)	
No Renal Failure	20	10 (50)	
Hyperbilir'naemia*	11	7 (64)	
Ttl serum B'rubin < 34uMol/l	37	19 (51)	

* : All cases of hyperbilirubinaemia irrespective of underlying pathology.

CHAPTER 4

ORGANISMS AND SITE OF INFECTION

Sixty five episodes were due to gram negative (Gm-ve) organisms, 47 to gram positive (Gm+ve) organisms and nine cases were polymicrobial. Mortality was not significantly different in the three groups. E.coli, Klebsiella pneumoniae, Streptococcus pneumoniae, and Staphylococcus aureus were the most commonly isolated organisms (Table 5).

GRAM NEGATIVE ORGANISMS:

Eschericia coli (E.coli) was the commonest organism isolated, responsible for 47(39%) of all cases and 7 deaths (15% $P<0.04$). Thirty three cases resulted from urinary tract infection, with 4 deaths (12%). There were five males and 28 females in this subset; two of the males died (40% $p<.01$). In seven cases the source of infection could not be determined, gastro-intestinal and biliary tracts accounted for 6 cases and 2 deaths (Table 6).

Klebsiella pneumoniae: (Klebsiella) was isolated in 10 cases, with 7 deaths (70% $p<0.001$). In the majority of cases the focus could not be determined, the other cases originated from the lungs, gastro-intestinal or urinary tracts.

Other Pathogens: A wide variety of other gram negative were isolated, all in small numbers, these included Proteus (2), Neisseria (2), and Pseudomonas (1).

GRAM POSITIVE ORGANISMS:

Streptococcus pneumoniae (S. pneumoniae): Seventeen cases were due to this organism with 4 deaths (24%). Sixteen cases arose from the respiratory tract, and in one the focus of infection was not determined.

Staphylococcus aureus (S. aureus): Fourteen cases, with 9 deaths (64% $p<0,008$). Primary infection arose from a variety of sites including lungs and skin; in most cases the site could not be determined.

Haemolytic Streptococcus (Haemolytic Strep): Both a & b Streptococci are included in this group and were responsible for 9 cases with 6 deaths (67% $p<0,04$). Seven cases arose from skin sepsis, and diabetics appeared to be particularly susceptible (5 of the 6 fatal cases).

POLYMICROBIAL INFECTIONS:

The majority of cases involved Gm-ve organisms: E.coli (5 cases); Proteus mirabilis (3 cases) and Klebsiella (2 cases). Other Gm-ve organisms isolated included Bacteroides and Neisseria sp..

The commonest Gm+ve organism isolated in these cases was Streptococcus mitior (2 cases).

Gastrointestinal tract was the focus of infection in 4 cases, in 3 cases sites of infection was not known. The majority of cases had significant underlying pathology, 3 patients were severely debilitated with cerebrovascular accidents, while 2 others had liver disease, 1 presenting in delerium tremens and the other with a massive gastrointestinal haemorrhage.

MICROBIAL SENSITIVITIES:

E.coli :Twenty three (49%) of all isolates were sensitive to all antibiotics against which they were tested. In vitro resistance was commonly encountered, 43% of isolates were resistant to ampicillin, and 30% to cotrimoxazole. Multiple resistance was more common than resistance to a single agent. Thus 5 isolates (10%) were resistant to only ampicillin and 2 to cotrimoxazole. Fifteen were resistant to various combinations of antibiotics (Table 7).

Klebsiella: All isolates were resistant to ampicillin and 5 (50%) to cotrimoxazole. Two isolates (20%) were resistant to amikacin and 1 (10%) to cefotaxime. Fifty percent showed multiple resistance (Table 7).

Staph aureus: Nine (64%) were resistant to penicillin, 2 (14%) were resistant to methicillin and the same number to erythromycin (Table 7).

Streptococci: All streptococcal isolates were sensitive to penicillin.

PRIMARY SITE OF INFECTION:

Urinary Tract: Thirty nine (32%) episodes arose from the urinary tract, seven patients died (18% p<0.03). Females (30 cases, 77%) were more commonly affected than males (9 cases, 23%). However mortality was higher amongst the male cases - 4 deaths, (44%), compared to 3 deaths (10% p<0,03) in female patients.

All but 6 cases were due to E.coli; Klebsiella was isolated in 1 case and in 5 the bacteraemia was polymicrobial.

Neither indwelling urinary catheters nor diabetes had an effect on the mortality rate (Table 8).

Respiratory Tract:Twenty two cases of bacteraemia followed respiratory tract infection. Eight patients (36%) died.

S.pneumoniae was isolated in 16 cases, and four (20%) deaths resulted. Other cases were due to S.aureus, Klebsiella, and haemolytic Streptococcus each responsible for two cases.

Skin: Seven cases followed skin sepsis, S.aureus, and haemolytic Streptococcus were each responsible for 3 cases, and in one patient the bacteraemia was polymicrobial. All cases of Streptococcal infection died, a total of 5 of the 7 patients died (71% p< 0,05)

Gastrointestinal/Biliary Tracts: In 17 (14%) patients the portal of infection was via this route, and 7 patients (42%) died. Five patients has polymicrobial (gram -ve organisms)

with 3 deaths (60%). E.coli (6 patients, 2 deaths) and Klebsiella (2 patients, 2 deaths) were the commonest single organisms involved.

DISCUSSION:

The spectrum of organisms does not differ from those reported in other series on community acquired bacteraemias with E.coli the commonest pathogen and the urinary tract the commonest portal of entry[31,32,33,41]. The low mortality associated with E.coli bacteraemia particularly following a urinary tract infection is well documented[27,32,37,41]. Mortality was low even with an indwelling urinary catheter in situ, and diabetes mellitus is not a risk factor[31,36,41]. Urinary tract infections in males had a significantly higher mortality rate than females (10% vs 44% $p < 0.04$). The number of male patients was small however and this finding should be confirmed in a larger series which would also permit investigation of inapparent risk factors which might explain this observation.

High mortality rates in Klebsiella and S.aureus bacteraemias are well documented[37,42], although mortality rates attributed to Klebsiella sp. vary greatly [25,27,37,63]. The small sample in the present study does not permit any conclusions to be made as to possible risk factors in the elderly.

Both these organisms were isolated from a wide variety of foci and in a high percentage of cases (50% & 40% respectively) the focus of infection was not identified. It is therefore not possible to comment on possible poor prognostic factors.

The high mortality rate associated with haemolytic streptococci has been reported[59,64], and infectivity has been associated with host susceptibility[60]. In this series 5 of the 6 fatal cases were diabetic, another study of geriatric bacteraemia (also with small numbers) had similar findings[37]. Thus while diabetes was not associated with an overall increased mortality, in certain circumstances it may have a bearing on the final outcome. Recent reports of fulminant disease due to this organism may suggest more virulent strains of streptococci are emerging[66] and the elderly may become a major target for these organisms.

Reported mortality rates from pneumococcal bacteraemia vary widely. Chattopadhyaty and Al-Zahawi[27] reported a startingly high mortality of 65% in geriatric patients, while Finklestein and co workers found a 48% mortality[29]. Mortality rates ranging from 13% for children to 42% for elderly patients were reported from Birmingham[65], this included a group of 15 severely debilitated patients, who contracted nosocomial pneumonia, 10 died. Other series have reported figures of 23%[23] and 28%[28] from community based studies, which are in accord with the 24% of this study. The

reason for this wide range of results is not clear but mortality varies with polysaccharide typing; type 3 being particularly virulent[28,29], and this may account for the differences in reported in mortality rates.

The high incidence of resistance to the commonly used antibiotics, ampicillin and cotrimoxazole amongst the E.coli and Klebsiella strains is cause for concern. The occasional report of resistance to amikacin and cefotaxime may presage a lessening of the efficacy of these drugs in the near future. This study confirmed the high incidence of resistance to penicillin amongst S.aureus strains. A small number of isolates were resistant to erythromycin and cloxacillin which are widely used against the organism, particularly in community acquired infections. Resistance to cloxacillin may fluctuate and it would still be a drug of choice should a Staphycoccal bacteraemia be suspected[43].

The choice of antibiotics in a community acquired bacteraemia will be discussed in a later chapter.

CONCLUSION:

The spectrum of organisms and primary foci described in this study do not differ from those of similar studies. An E.coli bacteraemia secondary to a U.T.I. is by far the commonest form of bacteraemia in the elderly. Mortality from this occurrence (12%) is significantly lower than other forms of bacteraemia. The other major Gm-ve organism

Klebsiella sp. was associated with a variety of primary foci and a mortality of 70%. Gram negative organisms were responsible for the majority of polymicrobial infections, and usually occurred in compromised hosts.

S.pneumoniae was the commonest Gm+ve pathogen, 16 of the 17 cases were associated with pneumonia. Mortality was 24%. The other common Gm+ve pathogens were S.aureus and haemolytic streptococci, associated with various primary foci and with mortality rates of approxiamtely 70%. Resistance to commonly used antibiotics was encountered in a significant percentage of E.coli and Klebsiella sp. and S aureus isolates. The significance of this is discussed in a later chapter.

TABLE 5: Infecting Organism and Mortality.

Gram -ve	No. Patients(%)	Mortality(%)	p
E. coli	47 (39)	7 (18)	<0.004
Klebsiella sp	10 (8)	7 (70)	<0,001
Other	8 (7)	1 (12)	
TOTAL	65	15 (23)	
Gram Positive			
S. pneumoniae	17 (14)	4 (24)	
S. aureus	14 (12)	9 (64)	<0,008
Haem. Strep	9 (7)	6 (66)	<0,04
Other	7 (6)	0 -	
TOTAL	47 (39)	19 (41)	
Polymicrobial	9 (7)	4 (44)	
GRAND TOTAL	121 (100)	38 (31)	

TABLE 6: Primary Sites of the E. coli Bacteraemias.

Site Infection	No. Patients(%)	Mortality (%)
Urinary Tract	33 (70)	4 (12)
Biliary Tract	2 (4)	0
Gastro/Intestine	4 (8)	2 (50)
Skin	1 (2)	0
Undetermined	7 (15)	1 (14)
TOTAL	47 (100)	7 (15)

TABLE 7 : Microbial Resistance to in vitro testing.

A/biotic	Organism			
	E.coli	Klebs	S. aureus	S.pn'iae*
Penicillin	-	-	64	0
Ampicillin	45	100	-	0
Cloxacillin	-	-	14	-
Cotrimoxazole	28	40	-	-
Cefotaxime	2	10	-	-
Amikacin	-	20	-	-

*: S. pneumoniae

TABLE 8 : Urinary Tract Infections as a source of bacteraemia.

Organism	Episodes(%)	Mortality(%)	
E. coli	33 (85)	5 (15)	
Klebsiella sp	1 (2)	1	
Polymicrobial	5 (13)	1 (20)	
TOTAL	39 (100)	7 (18)	
Sex			
Females	30	3 (10)	
Males	9	4 (44)	p<0,04
Catheterised Pt	9	2 (20)	
Diabetics	18	3 (17)	

CHAPTER 5

BIOCHEMICAL AND HAEMATOLOGICAL PARAMETERS AND THEIR SIGNIFICANCE.

INTRODUCTION:

In this chapter I shall detail the results of routine biochemical and haematological investigations, their relationship to bacteraemia and their prognostic significance.

LIVER FUNCTION TESTS:

These investigations were carried out on 101 patients. In the other cases the patient died shortly after arriving at hospital or the attending doctor elected not to perform the investigation. This may have introduced an element of bias into the results which should be borne in mind in their interpretation.

Results were divided into those from patients in whom there was no history of liver disease, those with ethanol abuse, underlying liver disease or biliary tract infection. Numbers in the latter three categories were too small to permit conclusions to be drawn and the results and discussion which follow refer only to patients with no history of liver disease.

RESULTS:

There were 87 patients in whom there was no history or signs of liver disease.

Eight patients had bilirubin levels greater than twice normal (34umol/l). Three of these patients died.

Small numbers of patients had increased levels of the liver enzymes (Aspartate transaminase (AST); Alanine transaminase(ALT); Glutamyl transaminase (GGT); and Alkaline phosphatase (AP) (Table 9a).

In 18 patients serum albumin concentration was less than 25g/l., 9 patients died (50% $p<0.01$). Forty six patients had albumin concentrations of between 25 and 34g/l. 10 died (22%). Two of the 19 patients (11%) died in whom the serum albumin concentration was 35g/l or more (Table 9b).

ELECTROLYTE AND RENAL FAILURE:

Urea and Creatinine estimations were done on all but 4 patients. There were four cases of chronic renal failure and these will not be considered. Thus data on 113 cases will be discussed.

Urea and Creatinine: Data are presented in Table 10. There is no association between these values and mortality until there is evidence of established renal failure. A creatinine

more than twice the upper limit of normal (ie 230uMol/l) was associated with a 50% mortality rate ($p<0,003$).

Electrolyte Disturbances: Potassium values varied between 2,6mM/l and greater than 6mM/l. Neither hyper nor hypokalaemia was associated with increased mortality. Nor was there a prognositc trend with hyper or hyponatraemia.

HAEMATOLOGICAL PARAMETERS:

A full blood count was performed in 110 patients, four patients with chronic renal failure were excluded from this analysis.

Haemoglobin (Hb): In male patients an Hb of less than 10g/dl was associated with a poor prognosis, 8 of 15 patients died (53% $p< 0,02$). This association was not present in females. (Table 11).

White Cell count: There was no association between either high or low counts and mortality (Table 11).

Platelet Count: Thrombocytopaenia was associated with a poor prognosis. Eleven of 17 patients presenting with a platelet count of less than 100^9/l died (65% $p< 0,006$, Table 11).

DISCUSSION:

Liver Functions: The association between serum albumin concentration and mortality is striking. Hypoalbuminaemia is not a marker of malnutrition but an index of the severity of

disease[44] . The decline in serum albumin concentration during acute illness may be rapid, and is associated with falls in serum transferrin and iron levels, and a rise in the acute phase reactants[44,45]. The serum CRP level has prognostic significance in infection in the elderly, and is an early sensitive index of response to therapy[46]; and it would seem that a low serum albumin is an index of the severity of the infection.

Hyperbilirubinaemia is a common feature of bacteraemia in neonates and infants, but is an uncommon but well described feature of bacteraemia in adults[47]. In a retrospective series, 7 patients of 1150 were found to have jaundice[48]. Other reports in the literature centre round small series of patients with jaundice and do not comment on the incidence of the phenomenon. Intrahepatic cholestasis, conjugated hyperbilirubinaemia and minimally raised liver enzymes are common findings[47,49,50]. There does not appear to be a consistent relationship between jaundice and infection and reported mortality rates vary from 12% to 86%[48,49]. All these series contained small numbers and referred to patients of all ages. It is therefore difficult to extrapolate the results to the aged, but it would seem that hyperbilirubinaemia is an uncommon finding and has uncertain prognostic significance. Its importance lies in its possible diagnostic role, any patient with conjugated

hyperbilirubinaemia and normal or minimally elevated enzymes may have an underlying infection.

Renal Aspects: The relationship between sepsis and acute renal failure (ARF) is controversial. Reports in the literature of sepsis causing ARF range from 5%[68] to 58%[69]. However Rasmussen & Ibels[70] in a multivariate analysis of causes of ARF could not incriminate sepsis as the sole cause. They proposed that renal failure in this setting was due to an additive effect with sepsis an important predisposing factor. These authors found that age was not of prognostic significance in patients with ARF. Treatment of renal failure should proceed with caution particularly if aminoglycosides are used, injudicious use of these drugs may lead to a toxic nephritis and residual scarring[71], an important consideration in the aged where renal function may have declined. It is of interest to note that age does not influence the mortality rate from ARF from any cause[74].

Haematological Aspects: The association between anaemia and mortality is of interest. It is unfortunate that no provision was made in the protocol for monitoring the type of anaemia. It is not possible therefore to state whether the anaemia was due to chronic disease, a deficiency or bone marrow dysfunction; nor whether the poor prognosis is associated with a particular type of anaemia.

There is mounting evidence however that iron is crucial in the immune mechanism and in bacterial killing by neutrophils. Cytochrome activity and the "respiratory burst" as well as the production of oxidised halogens from oxygen radicals is dependent on the presence of iron as a co-enzyme[52]. Bacteria are also dependent on iron for their function and, to ensure availability, have developed a variety of siderophores to chelate iron from the environment[53]. In the elderly haemopoeitic function is significantly influenced by nutrition[54], and may be more sensitive to marginal deficiencies than in the young adult[55]. Iron deficiency may be an underlying reason for the observed association.

No studies in the elderly have examined the relationship between anaemia and mortality in bacteraemia, and this is the first reported association between the two. There is obviously scope for investigation in this field.

The absence of prognostic significance in the white count is surprising, as this has been reported by a number of other authors[25,33]. This may be due to the lack of data on patients who died before the investigation could be done, the absence of these data may have biased the results.

Thrombocytopaenia was a poor prognostic indicator, as noted in other studies[25]. One patient was proven to have disseminated intravascular coagulation (DIC). This is an

uncommon cause of thrombocytopaenia in bacteraemia[56]; common causes include platelet adherence to damaged endothelium, direct interaction between bacteria and platelets and possibly a toxic effect[56]. The adherence of bacteria to platelets results in an increased sequestration in the reticuloendothelial system[57].

CONCLUSION:

Hyperbilirubinaemia was noted in a small number of patients and was not associated with a concomitant rise in enzmyes. In the elderly where atypical presentations may be more common than in the young adult, this may be a clue to a bacteraemic process, when the other more classical signs of infection are missing. The strong association between serum albumin concentration and mortality is probably a reflection of the severity of the infection than a separate process.

The presence of acute renal failure is a poor prognostic feature.

This survey revealed an association between anaemia and a poor prognosis. The precise nature of this relationship was not explored and may prove an important area for further research.

TABLE 9: Liver Function Abnormalities vs mortality in patients with no history of liver disease or ethanol abuse and in whom the site of infection was not the biliary tract.

Parameter	No. Patients(%)	No. Deaths(%)	p
Albumin g/l (N: 35-50g/l)			
< 25	18 (22)	9 (50)	<0,01
25 - 34	46 (56)	10 (22)	
> 34	19 (22)	2 (11)	
Ttl B/rubin uMol/l (N: < 17uMol/l)			
< 17	58 (67)	11 (19)	
17 - 34	17 (19)	7 (41)	
> 34	8 (9)	3 (38)	
A.S.T. (N: < 40U/l)			
< 40	55 (66)	9 (16)	<0,01
40 - 100	20 (24)	7 (35)	
> 100	8 (10)	5 (63)	
A.L.T. (N: < 40U/l)			
< 40	55 (66)	13 (24)	
40 - 200	27 (32)	8 (30)	
> 200	1 (1)	0 -	
G.G.T. (N: < 50U/l)			
< 50	60 (72)	12 (20)	
50 - 200	16 (19)	8 (50)	
> 200	7 (8)	1 (14)	
A.P. (N: < 120U/l)			
< 120	36 (43)	10 (28)	
120 - 400	47 (57)	11 (23)	

TABLE 10: Serum Urea and Creatinine Concentrations and Mortality.

Urea Conc.(mMol/l)	No. Cases	Mortality(%)	p
< 7,5	43	10 (23)	
7,5 - 10,0	16	4 (24)	
10,0 - 12,5	15	6 (38)	
12,5 - 15,0	8	4 (50)	
15,0 - 20,0	11	2 (15)	
> 20,0	20	11 (50)	0,003
Creatinine Conc.(uMol/l)			
< 115	34	7 (20)	
115 - 150	13	2 (14)	
150 - 175	17	3 (17)	
175 - 200	8	3 (38)	
200 - 230	8	3 (38)	
> 230	33	19 (54)	0,0006

CHAPTER 6.

TREATMENT, PROGNOSIS AND OUTCOME.

In this chapter I shall present details of treatment and correlate this with outcome and prognostic factors, some of which have been been discussed in the preceding chapters.

RESULTS:

The complications of septicaemia (acute renal failure, respiratory failure, shock and disseminated intravascular coagulation) were associated with a significantly higher mortality rate compared to patients with none of these complications (Table 12).

Mortality was also strongly associated with prompt and appropriate treatment. In six patients (5%) treatment was delayed, four (66%) died. In three no treatment was given, all died. Twenty four patients received inappropriate antibiotics, 14 (58%) died ($p<0,003$). Antibiotic administration was not influenced by age (Table 13).

Thirteen patients died within 24 hours of admission. Three were discharged the same day after having blood cultures taken and oral antibiotics prescribed; all survived (including a case of Klebsiella bacteraemia). Twenty of the 38 fatalities occurred within 72 hours of admission ($p<0,00001$). Sixty four of the 83 survivors were discharged within 14 days of admission.

Twenty six deaths (69%) were due to initial sepsis, and 2 cases to nosocomial infection. Underlying disease was responsible for six deaths (5 had terminal malignancy); miscellaneous events caused a further 4 deaths (Table 14).

DISCUSSION:

The high mortality rate within 24 hours of admission suggests than the patients or their carers are not aware of the importance of seeking medical help early in the course of an illness. This delay in reaching hospital makes the prompt administration of antibiotics in hospital even more critical. Four of the 6 patients in whom treatment was delayed died, while the three patients who received no treatment all died. (Two of these patients were known to have disseminated malignancies and the notes do not indicate whether the decision to withold treatment was deliberate).

The high mortality rate associated with inappropriate antibiotic treatment emphasises the need for the correct choice of antibiotic.

Common sense would suggest that antibiotics commenced immediately after blood cultures taken would have a beneficial effect on prognosis. This is a common[25,27,31] but not universal finding[29]. Choice of antibiotic should be dictated by the sensitivity of organisms at the hospital concerned, and also the clinical findings. There was a low level of resistance to amikacin and cefotaxime amongst the

common gram negative organisms, while S.pneumoniae and haemolytic Streptococci are still sensitive to penicillin. A logical choice of antibiotic would therefore be either cefotaxime (or other third generation cephalosporin) or penicillin and an aminoglycoside. Use of multiple agents does not improve survival in the case of gram negative organisms[73] .This would provide limited cover against Staphylococcus aureus. Addition of anti-Staphylococcal agents should be determined by clinical indications. Although there is a significant incidence of resistance to cloxacillin it is still regarded as the drug of choice by some authorities[43]. MARSA (Methicillin-aminoglycoside-resistant Staphylococcus aureus) have not emerged in this country but may well do so in the forseeable future[58].

The high incidence of resistance to ampicillin and cotrimoxazole amongst the gram negative organisms isolated, makes these agents unsuitable for patients with a suspected bacteraemia.

Confusion is a common presenting feature of bacteraemia in the elderly[27,30,31,62] and may be the only presenting feature (possibly as the patient is not able to describe other symptoms). Consequently any elderly individual who presents with confusion and no obvious cause should be treated as having a bacteraemia until this is disproved.

No record was kept of the number of patients who presented from old age homes. It is possible that greater awareness of the signs and symptoms of bacteraemia at institutions of this nature may result in patients presenting earlier[41]. Consideration should be given to incorporating information on bacteraemia into teaching updates presented to staff at these centres.

CONCLUSION:

Prompt and appropriate antibiotic therapy is essential in an elderly patient with a bacteraemia.

Choice of antibiotic should be determined by local sensitivities and by clinical findings. At this institution at present penicillin and an aminoglycoside or a third generation cephalosporin should be used until culture results become available. Clinical findings would dictate whether anti-Staphylococcal should be added.

TABLE 11: Haematological Parameters and Mortality.

Haemoglobin (g/dl)	No. Cases	Mortality (%)	p
Males			
<10	15	8 (53)	<0,02
10 - 11	7	4 (57)	<0,06
11 - 12	8	3 (38)	
>12	24	4 (16)	
Females			
<10	14	6 (43)	
10 - 11	13	1 (8)	
11 - 12	9	3 (33)	
>12	16	3 (19)	
White Cell Count (10^3/ml)			
<2,5	3	1 (33)	
2,5 - 10	21	7 (33)	
10 - 20	48	13 (27)	
20 - 30	21	9 (43)	
>30	11	4 (33)	
Platelet Ct. (10^3/ml)			
<100	17	11 (65)	<0,006
>100	87	23 (26)	

TABLE 12: Complications of Bacteraemia and Mortality.

Complication	Episodes(%)	Mortality(%)	p
Nil	51 (42)	9 (18)	
Shock	20 (17)	15 (75)	<0,0002
A.R.F.	42 (35)	22 (52)	<0,001
Resp. Failure	7 (6)	4 (57)	<0,008
Disseminated I/vasc Coagulation	1	1	

TABLE 13: Mortality associated with choice of antibiotic and the speed of administration.

Antibiotic Treatment	65 - 75 yrs	>75 yrs
	No./Deaths(%)	No./Deaths(%)
Appropriate	56/10 (18)	32/7 (22)
Inappropriate	14/7 (50)*	10/7 (70)#
Delayed	4/2 (50)	2/2 (100)
Nil	1/1	2/2

* p< 0,02 # p< 0,002

TABLE 14: Cause of Death.

Aetiology	No. of Cases(%)
Sepsis	26 (69)
Nosocomial Sepsis	2 (5)
Underlying Disease	6 (16)
Miscellaneous	4 (10)

CHAPTER 7.

CONCLUSIONS AND RECOMMENDATIONS.

INTRODUCTION:

In this chapter I shall endeavour to place the current study in perspective with other work done in this field and summarise what has be presented in the preceding chapters.

Comparison with other Work:

Despite the difficulty of comparing reports which are based on a variety of populations, or confined to a single or a group of organisms there are a number of constant findings which were confirmed by the present work. These include :

(i) E. coli is the commonest pathogen[27,31,32,37,41], but has the lowest mortality rate.

(ii) Other common pathogens include Klebsiella sp, S.aureus, S.pneumoniae and haemolytic Streptococci.

(iii) Although gram negative organisms were more commonly involved, bacteraemia due to gram positive organisms resulted in a higher mortality rate[27,31,37,41].

(iv) The urinary tract is the commonest site of primary infection[27,31,32,37,41].

(v) Other common sites of infection resulting in bacteraemia include the respiratory, gastrointestinal and biliary tracts. Bacteraemia resulting from skin sepsis carries a poor prognosis.

In addition to these findings, the following observations could be drawn from the present study and which have not been clearly documented before:

(vi) Increasing age is not a poor prognostic factor in community acquired bacteraemia, compared to the situation which exists in nosocomial infections where there is a strong correlation between age and mortality[71].

(vii) Confusion is an important prognostic symptom and any elderly patient with confusion and no obvious cause should be regarded as being bacteraemic until this has been excluded.

(viii) Haemoglobin concentration in males and serum albumin were found to be important prognostic factors. A low serum albumin concentration is probably an index of the severity of the infection and not a preexisting state.The nature of the anaemia and its cause were not investigated.

(ix) Resistance to ampicillin and cotrimoxazole is common in community acquired strains of E.coli and Klebsiella and should not be used as first line antibiotics.

(x) Major complications of septicaemia are poor prognostic factors.

(xi) A major factor in ensuring a favourable outcome was the prompt administration of appropriate antibiotics.

(xii) Initial antibiotic therapy should consist of penicillin and an aminoglycoside or third generation cephalosporin, until results of blood cultures are known.

Anti-Staphyococcal therapy should be added if clinically indicated.

(xiii) A significant proportion of patients demised within 24 hours of admission, suggesting that they or their carers delayed seeking medical help. This suggests that ignorance exists both at the individual level and in institutions as to the symptoms of bacteraemia. Schemes should be investigated whereby individuals and those who care for the aged could be informed of these symptoms.

In this study I have investigated the problems relating to bacteraemic illness in the elderly and to furnish clinicians with clinical and prognostic features which may be of importance in treating this group of patients; and delineating guidelines in managing individuals who are at risk not only from the current sepsis and underlying disease but also from the changes wrought by age.

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