Septic shock in the Intensive Care Unit, Hillbrow Hospital, Johannesburg

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Summary

The records of all patients with septic shock admitted to an intensive care unit during a 15-month period were analysed retrospectively. The main purpose of the study was to describe the aetiology and clinical features of illness, and to determine the outcome of the patients, including those factors influencing prognosis. Thirty-five patients (46% medical, 54% surgical) fulfilling the criteria for the diagnosis of septic shock were admitted to the study. There were 21 male and 14 female patients. Most infections were community-acquired (69%). The two most common sources of infection were the respiratory tract and the abdomen. All patients required inotropic blood pressure support. Most patients (94%) were mechanically ventilated and 7 required dialysis. Organisms, sometimes multiple, were isolated in 18 patients. Fifty per cent of the isolates (12 of 24) were Gram-negative, 10 were Gram-positive and there were 2 associated *Candida albicans* bacteraemias. The overall mortality rate was 40%. There was no difference in outcome between community or hospital-acquired infections, infections with Gram-positive or Gram-negative organisms, or in patients with differing sources of sepsis. Features associated with a poorer prognosis were older age and higher bilirubin value.

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Septic shock is an important, potentially reversible, cause of admission to an intensive care unit (ICU). This condition is a complex entity, of which the salient features are inadequate tissue perfusion causally related to sepsis. Important aspects in the pathophysiology include the uncontrolled release of inflammatory mediators and a maldistribution of blood flow.[1] The mortality rate remains high (often approaching 50%[2]), despite advances in antimicrobial chemotherapy and modern ICU facilities.[3,4]

The records of all patients with septic shock admitted to Hillbrow Hospital ICU over a 15-month period were analysed retrospectively. The aim of the study was to describe the aetiology and clinical features of the illness, and to determine the outcome, defining those features associated with a poorer prognosis.

Patients and methods

This was a retrospective study of the records of all patients with septic shock admitted to Hillbrow Hospital ICU between 1 December 1987 and 28 February 1989. Hillbrow Hospital is an adult general hospital admitting mainly black patients from urban Johannesburg. The ICU is a multidisciplinary 8-bedded respiratory unit, admitting all critically ill medical and surgical patients from the hospital.

Septic shock was defined as the presence in a patient of a hyperdynamic circulation (pulse $\geq$ 120/min), systolic hypotension (blood pressure $\leq$ 90 mmHg after adequate fluid replacement), decreased organ perfusion (as evidenced by either decreased cerebral, renal or hepatic function) and a well-documented source of infection (according to clinical and laboratory features). Patients with any other possible cause of shock, not due to sepsis itself, were excluded.

The following data were analysed in the first 24 hours of septic shock. The severity of illness was recorded using the APACHE II scoring index.[5] Demographic data included the age and sex of the patients and whether the infection was community acquired (infection acquired outside hospital) or nosocomial (infection developing more than 48 hours after admission to hospital). Clinical features analysed included the blood pressure, pulse, temperature, respiratory rate and the primary site of infection. Laboratory investigations included haematological tests (haemoglobin value, white cell count and platelet count), biochemical measurements (serum urea and creatinine values) and liver function tests (total bilirubin and serum albumin levels). Additional data recorded were those parameters needed to determine the APACHE II score.[5]

The treatment in all patients was recorded, including the need for surgery, use of inotropic agents, dialysis and mechanical ventilation.

The outcome of all patients was documented, and features predictive of a poor prognosis were determined. Statistical analysis was performed using the Mann-Whitney *U*-test and Student's unpaired *t*-test for continuous variables, and the χ^2 and Fisher's exact (two-tailed) tests for categorical variables. This analysis was used to compare survivors and non-survivors, and patients with nosocomial and community acquired sepsis, medical and surgical causes of illness, and Gram-negative and Gram-positive infections.

Results

All results are expressed as a mean ± standard error of the mean (SEM) and a range of values. Thirty-five patients with septic shock were admitted to the ICU during the study period, constituting 7% of all admissions. There were 21 male (60%) and 14 female (40%) patients. The mean age was 39,9 ± 2,5 years (range 12 - 68 years). Twenty-four infections were community acquired (69%) and 11 were nosocomial (31%). Nineteen patients had sepsis related to surgery (54%) and 16 had medical illnesses (46%).

The primary site of infection, together with the associated mortality, are shown in Table I. Pneumonia and intra-abdominal sepsis were the most common infections.

Factors predisposing to infection are shown in Table II. Seventeen patients had prior surgery and 9 patients had medical factors possibly predisposing to infection. The most common surgical procedure was a laparotomy, usually for blunt abdominal trauma or perforated viscus (4 patients each). Preceding gynaecological surgery was performed in 6 patients,

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TABLE I. PRIMARY SITES OF INFECTION IN 35 PATIENTS WITH SEPTIC SHOCK AND THE ASSOCIATED MORTALITY

	Patients		Deaths	
Site	No.	%	No.	%
Respiratory	18	51	7	39
Intra-abdominal	14	40	5	36
Nervous system	1	3	1	100
Skin	1	3	1	100
Endocarditis	1	3	0	0

TABLE II. FACTORS PREDISPOSING TO INFECTION IN 35 PATIENTS WITH SEPTIC SHOCK*

Factor	No. of patients
Surgical	17
Laparotomy	
Trauma	4
Perforated viscus	4†
Pancreatitis	2
Cancer	1‡
Gynaecological	6
Medical	9
Chronic chest disease	4†
Diabetes mellitus	3
Malignant disease	1
Otitis media	1
Nil	9

* Sometimes multiple.
† Including alcoholism in 1 patient each.
‡ One surgical patient undergoing a Whipple's procedure.

4 of whom had septic incomplete abortions. Chronic chest disease and diabetes mellitus were the most common medical predisposing factors to infection.

The mean pulse rate was 150 ± 3,7/min (range 120 - 190/min), systolic blood pressure 73 ± 3,6 mmHg (range 0 - 90 mmHg), respiratory rate 31 ± 1,5 breaths/min (range 18 - 44 breaths/min), and temperature 38,2 ± 0,2°C (range 33 - 41,2°C). Four patients presented with hypothermia (rectal temperature ≤ 35,5°C), of whom 2 remained apyrexial (1 died) and 2 developed pyrexia (1 died). All other patients manifested pyrexia.

Of the laboratory data, the mean haemoglobin value was 11,6 ± 0,5 g/dl (range 5,8 - 17,7 g/dl) and the white cell count 17 × 10^9 ± 1,7/l (range 4,9 - 34,3 × 10^9/l). No patient had leucopenia and 14 patients did not manifest leucocytosis initially. One of these patients, who survived, never manifested leucocytosis. The remaining patients all developed leucocytosis and there was no association with the initial lack of leucocytosis and mortality (only 2 of these patients died). The mean platelet count was 159 ± 16 × 10^9/l (range 12 - 248 × 10^9/l). The mean serum urea value was 12,9 ± 1,9 mmol/l (range 2,5 - 47,3 mmol/l) and the mean serum creatinine level was 207 ± 24,7 µmol/l (range 63 - 580 µmol/l). Eighteen patients had a serum creatinine level of > 150 µmol/l on admission. The mean serum bilirubin level was 44,2 ± 11,5 mmol/l (range 3 - 306 mmol/l).

Table III summarises the initial microbiological data. A total of 24 organisms were isolated in 18 patients, causally related to the septic shock. These organisms were Gram-positive in 10 patients, Gram-negative in 12 and *Candida albicans* was isolated in 2 blood cultures. Table IV correlates the clinical diagnoses with the microbiological data, the complications, and the outcome of the 15 patients from whom organisms were isolated. Sixteen of these isolates were from the blood, 7 from sputum, and 1 from abdominal pus.

The antibiotic susceptibilities of the isolates, where documented, were as follows: all *Streptococcus pneumoniae* isolates (blood) were sensitive to penicillin/erythromycin and all other antibiotics tested; 1 isolate of *Staphylococcus epidermidis* from blood was resistant to cloxacillin; two *Acinetobacter* spp. isolated from sputum were sensitive only to ciprofloxacin and tobramycin; 1 blood isolate of *Escherichia coli* was resistant to piperacillin; and 1 blood isolate of *Klebsiella ozaenae* was sensitive only to ciprofloxacin.

All patients received aggressive initial resuscitation with fluids. Broad-spectrum antibiotics were empirically administered to all patients with appropriate changes made in every case according to microbiological data. Fourteen patients

TABLE III. MICROBIOLOGICAL DATA (24 ISOLATES FROM 18 PATIENTS)

	No. of patients	H/C	Deaths	
			No.	%
Gram-positive cocci				
Streptococcus pneumoniae	2	0/2	1	50
Staphylococcus epidermidis	2	1/1	0	0
S. aureus	2	0/2	0	0
Staphylococcus spp.	1	1/0	1	100
Enterococcus faecalis	1	1/0	1	100
Not identified	2	0/2	2	100
Gram-negative bacilli				
***Klebsiella* species**	3	2/1	1	33
Acinetobacter	3	1/2	0	0
Escherichia coli	2	0/2	0	0
***Enterobacter* species**	1	1/0	0	0
Proteus mirabilis	1	0/1	0	0
Pseudomonas aeruginosa	1	0/1	1	100
Haemophilus influenzae	1	0/1	0	0
Fungi				
Candida albicans	2	2/0	1	50

There was no statistical difference in the outcome between the patients infected with Gram-positive and Gram-negative organisms.
H/C = hospital/community acquired sepsis.

TABLE IV. CORRELATION OF CLINICAL AND MICROBIOLOGICAL DATA IN 18 PATIENTS IN WHOM MICRO-ORGANISMS WERE ISOLATED

	Diagnosis	No. of patients	Isolate	Sensitivity	Site	Complic.	Outcome
Medical							
Community acquired	**Pneumonia**	**10**	***S. pneumoniae***	**Y**	**B**	**Meningitis SIADH**	**Died**
			S. pneumoniae	**Y**	**B**	**ARF**	**Lived**
			G+ve cocci	**–**	**S**	**–**	**Died**
			G+ve cocci	**–**	**S**	**ARF**	**Died**
			***Acinetobacter* spp.**	**N**	**S**	**–**	**Lived**
			***Acinetobacter* spp.**	**N**	**S**	**–**	**Lived**
			S. aureus	**Y**	**S**	**ARF**	**Lived**
			H. influenzae	**–**	**S**	**ARF TED**	**Lived**
			K. pneumoniae	**–**	**B**	**ARF Arrhythmia**	**Died**
			S. epidermidis	**–**	**B**	**–**	**Lived**
	Skin sepsis	**1**	***P. aeruginosa***	**–**	**B**	**ARF Pneumonia**	**Died**
Hospital acquired	**Pneumonia**	**2**	***K. oxytoca***	**Y**	**B**	**–**	**Lived**
			***Acinetobacter* spp.**	**–**	**S**	**–**	**Lived**
	SBE	**1**	***S. epidermidis***	**N**	**B**	**–**	**Lived**
			***Enterobacter* spp.**	**–**	**B**	**–**	
			K. ozaenae	**N**	**B**	**–**	
			C. albicans	**–**	**B**	**–**	
Surgical							
Community acquired	**Abdominal sepsis**	**3**	***E. coli****	**N**	**B**	**Pneumonia**	**Lived**
			E. coli	**–**	**P**	**ARF**	**Lived**
			S. aureus	**–**	**B**	**Chest sepsis**	**Lived**
			P. mirabilis*	**Y**	**B**	**Pneumonia**	**Lived**
Hospital acquired	**Abdominal sepsis**	**1**	***S. faecalis**†**	**–**	**B**	**–**	**Died**
			***C. albicans**†**	**–**	**B**	**–**	**Died**
			***Staphylococcus* spp.†**	**–**	**B**	**–**	**Died**

* 2 organisms from the same patient.
† 3 organisms from the same patient.
Sensitivity = sensitivity to 'usual' antibiotics (Y = yes; N = no); Site = site of isolation (B = blood; S = sputum; P = pus); Complic. = complications; SIADH = syndrome of inappropriate anti-diuretic hormone secretion; ARF = acute renal failure; G+ve cocci = organisms demonstrated on sputum Gram stain, which was culture-negative; TED = thrombo-embolism; SBE = endocarditis, all organisms isolated from the same patient at the diagnosis of septic shock.

underwent surgery for abdominal sepsis. All patients received inotropic agents, including dopamine (2 - 5 μg/kg/min) and dobutamine and/or adrenaline. Mechanical ventilation was required in 33 patients (94%).

Complications, and the associated mortality, are noted in Table V. Of the 18 patients with renal dysfunction, 7 eventually required dialysis, but 1 patient died before this could be instituted. Nosocomial chest infections developing in the ICU were documented in 4 patients (11%), and a similar number of patients showed disseminated intravascular coagulation.

The mean APACHE II score was 17,7 ± 1 (range 9 - 34) with a predicted mortality of 23%. Fourteen patients died, resulting in a mortality rate of 40%. Of the patients who died, 8 had medical reasons for admission to ICU. There was no statistically significant difference in mortality between the medical and surgical patients.

There was no significant difference in outcome between patients with community acquired and nosocomial infections. Twenty-four infections were community acquired, 13 being respiratory, 9 being intra-abdominal, and 1 each from the nervous system and skin. Seven of these community acquired

TABLE V. COMPLICATIONS IN 35 PATIENTS AND ASSOCIATED MORTALITY

	Patients		Deaths	
Complication*	No.	%	No.	%
Renal dysfunction†	**18**	**51**	**10**	**56**
Chest infection	**4**	**11**	**2**	**50**
DIC	**4**	**11**	**2**	**50**
ARDS	**3**	**9**	**1**	**33**
Hepatitis	**2**	**6**	**1**	**50**
SIADH	**2**	**6**	**2**	**100**
Arrhythmia	**1**	**3**	**1**	**100**
Thrombo-embolism	**1**	**3**	**0**	**0**
Pneumothorax	**1**	**3**	**1**	**100**
Haematemesis	**1**	**3**	**1**	**100**

* Sometimes multiple.
† 7 patients required dialysis.
DIC = disseminated intravascular coagulation; ARDS = adult respiratory distress syndrome; SIADH = syndrome of inappropriate anti-diuretic hormone secretion.

infections were due to Gram-positive organisms and 8 to Gram-negative organisms, with no difference in the mortality between the two groups. Of the 11 hospital-acquired infections, micro-organisms were found in 6, of which 4 were Gram-negative bacteria. The site of infection was respiratory in 6 patients, intra-abdominal in 4 and cardiovascular system in 1. Only 1 patient developed nosocomial septic shock in the ICU, and subsequently died.

Features associated with a poorer prognosis were a higher mean age (non-survivors 47,2 ± 2,6 years compared with 35 ± 2,2 years in survivors; $P = 0,02$) and a higher serum bilirubin level (81 ± 16,4 mmol/l compared with 20 ± 2,9 mmol/l, respectively; $P = 0,04$). None of the other parameters tested were associated with a higher mortality, including the haemoglobin value, white cell count, respiratory rate and serum albumin level. While the mean APACHE II score and serum urea value were higher, and the mean platelet count lower in non-survivors, these values did not reach statistical significance. Mortality was also not related to the sex of the patients, the isolation or not of an organism (including the presence/absence of bacteraemia), or the organism type (Gram-positive or Gram-negative isolates). The mortality of patients with acute renal failure was 55,6% compared with 23,5% in patients without this complication. This difference did not quite reach statistical significance ($P = 0,055$). Neither the need for dialysis, nor the presence of any other complication, could be shown to be associated with an increased mortality.

Discussion

Septic shock is an important cause of admission of both medical and surgical patients to ICUs. It is often the commonest cause of death in these units[2] and may be associated with multi-organ failure (including adult respiratory distress syndrome (ARDS)) and a high mortality rate.[6,7] The syndrome of septic shock has been increasing in incidence since the 1930s.[8]

Septic shock is usually defined as inadequate tissue perfusion in a patient with severe sepsis, described in both Gram-positive and Gram-negative infections. It is a syndrome resulting from a systemic response to serious infection; other causes of shock (cardiac, oligaemic, toxic, anaphylactic, neurogenic and endocrinological) need to be excluded on clinical and laboratory grounds.

Manifestations of septic shock, both clinical and laboratory, are protean, and certain classic features of sepsis itself, such as fever or leucocytosis, may be absent.[9] In fact, an absent temperature response or even the presence of hypothermia and/or neutropenia with infections are said to be features associated with a poorer prognosis.[9,10] In the present study, while some patients who presented were apyrexial (4) and others were without an elevated initial white cell count (14), all had other definitive evidence of infection. In addition, neither feature was associated with a poorer prognosis.

In this retrospective study of ICU patients in Hillbrow Hospital over a 15-month period, 35 patients had septic shock accounting for 7% of admissions to the unit. A number of features indicating a poor prognosis have been documented in patients with bacteraemia.[10,11] These include among others, the presence of shock itself as well as thrombocytopenia, leucopenia, renal and respiratory failure, type of organism, and site of sepsis. Features that we found to be associated with an adverse prognosis in patients with a clinical syndrome of septic shock were an older age and hyperbilirubinaemia. Jaundice is a relatively common concomitant of severe infections, particularly Gram-negative ones, and is said to be due to intrahepatic cholestasis possibly related to endotoxin or other bacterial toxins.[10,12,13] While certain of the above features, including a higher mean serum urea value and/or acute renal failure and a lower mean platelet count, tended to be associated with a higher mortality rate among the present patients, as did a higher mean APACHE II score, these values did not quite reach statistical significance, possibly due to low patient numbers.

In the present study, mortality was not related to the site of sepsis or to whether it was community or hospital acquired. This is despite the equal distribution of medical and surgical patients, and the wide range of pathogens. The 1 patient who developed nosocomial septic shock while in the ICU did not survive. Mortality could also not be accurately related to individual pathogens, possibly owing to the small numbers.

The overall mortality rate of 40% was higher than that predicted by the APACHE II score, but similar to that found in several other studies.[2,3,14,15] This outcome was achieved with a policy of aggressive early resuscitation followed by careful clinical management. While early aggressive resuscitation and careful medical management are major factors in the management of these patients,[2] modern concepts advocate the early use of pulmonary artery catheters in order to optimise haemodynamic variables.[16,17]

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The aetiology of severe community-acquired pneumonia and its impact on initial, empiric, antimicrobial chemotherapy

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Of 259 patients admitted to an intensive care unit with severe acute community-acquired pneumonia, 173 had primary infections and 86 had secondary infections. The commonest organism isolated in each group was *Streptococcus pneumoniae* (51·3 and 36·6% of known isolates in each group respectively). *Klebsiella pneumoniae* was the next most common isolate (31·9 and 29·3% respectively). A variety of other Gram-negative organisms and *Staphylococcus aureus* accounted for most of the remaining pathogens.

Based on retrospective analysis of data, there appeared to be no difference in the alcohol consumption of patients with infection due to *S. pneumoniae* and *K. pneumoniae*. The overall mortality rate for the primary infections was 47·4%, with 68·4% of these infections due to *K. pneumoniae* and 33·9% due to the pneumococcus ($P<0·002$). Among the secondary infections, the overall mortality rate was 40·8% (not significantly different to that of primary infections) with 45·5% due to *K. pneumoniae* and 23·1% due to the pneumococcus (not significantly different on statistical analysis, probably due to low patient numbers). Our investigation confirms that severe community-acquired pneumonia due to *K. pneumoniae* is extremely common, even in patients without obvious risk factors for Gram-negative colonization. This organism is contributing to the high mortality rate seen in our intensive care unit among patients with pneumonia, and our empiric therapy for such cases routinely includes a combination of agents active against this organism (e.g. a cephalosporin and an aminoglycoside).

Introduction

Community-acquired pneumonia continues to be associated with significant morbidity and mortality in patients world-wide (1–3). Not all factors associated with this ongoing mortality are completely understood, but it is recognized that critically-ill patients (4,5), and cases with certain initial clinical and laboratory features of illness, noted at the time of presentation to hospital, have a worse prognosis (4–8). There is indirect evidence, based on experimental and human studies, that delayed or incorrect empiric antibiotic therapy may be associated with a poorer prognosis in patients with pneumonia (6,9). In addition, two recent publications have suggested that the initial antibiotic therapy used in patients with severe community-acquired pneumonia may have an impact on patient survival (7,8).

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Initial antibiotic therapy in pneumonia is, of necessity, empiric and is based on a consideration of several factors, including an appreciation of the common causes of such infections in the different areas (10–12). Importantly, and influencing the choice of initial therapy, is the ongoing debate as to the usual bacterial causes of pneumonia, particularly among cases of severe community-acquired pneumonia (SCAP), and with special reference to the prevalence of Gram-negative organisms (other than *Haemophilus influenzae*). Thus, while some studies have shown Gram-negative organisms to be relatively more common causes of SCAP (5,7,13–15), others have not confirmed these findings (6,9,16,17). It has been suggested that those studies showing a high prevalence of Gram-negative organisms may be due to a high intake of alcohol in patient populations (17). Others have suggested that the prevalence of Gram-negative organisms in any particular study may relate to the invasiveness of the diagnostic approach; those studies using more aggressive approaches to diagnosis uncovering a larger group of

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Gram-negative infections (18). From our own unit, we have published data showing Gram-negative organisms, in particular *K. pneumoniae*, to be important causes of SCAP (5,19).

The aim of the present investigation was to document the causes of SCAP among patients admitted to our intensive care unit (ICU) over an 11-yr period. In particular, we wished to determine (a) whether *K. pneumoniae* remained an important cause of SCAP when extending our initial observations over a much longer period of time, (b) to document whether such infections occurred as frequently when only patients with pure primary community-acquired infections (community-acquired cases without any underlying disorder whatsoever) were included and (c) to investigate the possible association of an increased prevalence of such infections with regular alcohol consumption.

Patients and Methods

This was a retrospective view of the records of all patients with an admission diagnosis of acute SCAP treated in the Hillbrow Hospital ICU in Johannesburg, between January 1982 and December 1992. Approval to conduct the study was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand.

Acute community-acquired pneumonia was defined as an acute lower respiratory tract infection associated with clinical and radiological evidence of pulmonary consolidation. All cases entered into the study had been admitted to the Hospital from the community, and were taken into the ICU within 24 h of admission to the Hospital. In order to study cases without apparent specific predisposing factors to Gram-negative infections, the patient population was divided into primary infections (defined as those cases with no apparent predisposing factors to illness whatsoever, aside perhaps from a history of regular ingestion of alcohol), and secondary infections (defined as those cases with known underlying disorders including diabetes mellitus, asthma and chronic obstructive airways disease, immunosuppression, malignancies, and evidence from clinical or laboratory investigations of other chronic disorders) as described previously (20). Patients were admitted to the ICU usually for mechanical ventilation, or because they were critically-ill and expected to need intensive medical and nursing care, multiple changes in therapy, and possible mechanical ventilation.

The data recorded included age and gender, history of alcohol ingestion, results of microbiological investigation and outcome. In cases with primary infections we also recorded the presence or absence of those features noted in previous studies to be associated with SCAP (i.e. the need for ICU admission), as well as the treatment received in ICU, including mechanical ventilation, inotropic support of the blood pressure and dialysis. In this group of patients, once APACHE II scoring became routinely used in the unit, these results were documented as well (21). In the secondary group of patients we recorded, additionally, the reasons for the characterization of cases within this group.

The microbiological data were based primarily on the results of blood cultures and/or on Gram stain and/or culture of expectorated sputum or endotracheal secretions, taken from patients within 24 h of admission to hospital. Serological testing for *Legionella* and *Mycoplasma* infections and for the various respiratory viruses had been performed only in some cases, usually based on clinical suspicion of an 'atypical' infection.

Statistical analysis, using the Fisher's exact (2-tail) test, was undertaken to compare the mortality of patients with primary and with secondary infections, to compare mortality in patients with infections due to the pneumococcus and due to *K. pneumoniae*, and to compare alcohol consumption in patients with these two infections.

Results

A total of 280 patients with acute community-acquired pneumonia were admitted to our ICU over the 11-yr period. In 21 cases, *Mycobacterium tuberculosis* was isolated from sputum (with or without the presence of co-existent bacteria in blood and/or sputum) and these cases were excluded from further analysis. Thus, there were 173 primary, and 86 secondary infections.

Of the patients with primary infections, 134 were males and 39 females. The mean age was 43·6 years (range 14–74 years), and the mean ($\pm$ SD) Apache II score was 15·8 ($\pm$ 8·9). The microbiological data of these patients are shown in Table 1. A positive diagnosis was made in 119 cases (68·8%), no organisms being isolated in the remainder. The commonest organism isolated was *S. pneumoniae*, accounting for 51·3% of the isolates, and the second commonest organism isolated was *K. pneumoniae*, accounting for 31·9% of the isolates. A variety of other Gram-negative organisms (9·2%) and *Staphylococcus aureus* (3·4%) accounted for most of the remaining isolates. In 26 patients, serological testing had been undertaken and demonstrated two infections with *Mycoplasma pneumoniae* and one with *Legionella*

Table 1 The aetiology of primary acute severe community-acquired pneumonia in 173 patients

Micro-organisms	Total no. of isolates	% of positive cultures	Blood and sputum	Blood	Sputum	Serology
Streptococcus pneumoniae	61*	51·3	11	38†‡	10†	—
Klebsiella pneumoniae	38	31·9	2	27	9	—
Other Gram negative	8§	6·7	1	3	4	—
Staphylococcus aureus	4‖	3·4	—	—	3	—
Mixed Gram negative	3	2·5	—	1	2	—
Mycoplasma pneumoniae	2	1·7	—	—	—	2
Legionella pneumophila	1	0·8	—	—	—	1
Viral¶	2	1·7	—	—	—	2

*, site of isolation in two cases not documented.
†, the isolate in each case from cerebrospinal fluid as well.
‡, one bactec positive, culture negative, blood positive countercurrent immunoelectrophoresis.
§, *Escherichia coli* (2 cases), *Haemophilus influenzae* (2), *Serratia marcescens* (2), *Proteus mirabilis* (1) and *Acinetobacter anitratus* (1).
‖, site of isolation in one case not documented.
¶Parainfluenza virus infection diagnosed on serology and influenza virus infection diagnosed on lung biopsy and serology.

Table 2 The frequency of admission features found in patients with primary community-acquired pneumonia associated with severe infection*

Feature	Number present/total number of cases in whom feature was documented (%)
Respiratory rate >30 breaths min^{-1}	94/145 (64·8)
Confusion	42/76 (55·3)
Absent chest pain	3/41 (7·3)
Diastolic blood pressure <60 mmHg	22/100 (22)
P_aO_2 <8 kPa	40/100 (40)
Leucocytes <4 or >20 × 10^9 l^{-1}	85/170 (50)
Lymphocytes <1 × 10^9 l^{-1}	2/81 (2·5)
Sodium <130 mmol l^{-1}	44/169 (26)
Urea >7 mmol l^{-1}	108/170 (63·2)
Albumin <30 g l^{-1}	94/132 (71·2)
Abnormal liver function†	77/121 (63·6)

*Modified after the British Thoracic Society publication in *Respiratory Medicine* (17), reproduced with permission.
†At least one value twice the upper limit of normal.

pneumophila. Forty-one patients, according to the history recorded, consumed alcoholic beverages on a regular basis. There was no significant difference in the alcohol consumption of patients with pneumococcal and *K. pneumoniae* infections (72·7 *vs.* 65·4% respectively).

The frequency of features associated with the need for ICU admission in patients with pneumonia [British Thoracic Society (17)] noted in our patients, are demonstrated in Table 2. Confusion, tachypnoea, raised urea and liver enzymes, low albumin, extremes of leucocyte count, and hypoxia were among the most important features. Treatment of these patients included mechanical ventilation in 85·9%, use of inotropic agents in 69·2% and dialysis in 22·2%.

The overall mortality rate was 47·4%, this being 68·4% in patients with documented *K. pneumoniae* infection and 33·9% in documented pneumococcal infections ($P<0·002$). The mortality rate in patients in whom no microbiological diagnosis was made was 46·3%.

Of the 86 patients with secondary infections, 66 were males and 20 females, with a mean age of 45·0 years (range 20–75 years). The reasons for the classification of these infections as secondary are shown in Table 3. The most common reasons for inclusion were the presence of underlying lung disorders, and diabetes mellitus. The microbiological results are shown in Table 4; in 40 cases a specific diagnosis was made (47·7%). The common organisms documented

Table 3 Features present in 86 patients classified as having secondary acute severe community-acquired pneumonia

Feature	Number of patients
Respiratory diseases	49
Old fibrocavitatory TB	19
Chronic obstructive airways disease/corpulmonale	15
Asthma on systemic corticosteroids	6
Bronchiectasis	4
Pneumothorax (recurrent)	2
Carcinoma of the lung	1
Tracheo-oesophageal fistula	1
Pneumoconiosis	1
Diabetes mellitus	20
Presentation in coma	5
General disorders	16
Severe malnutrition	5
Neurological	3
Connective tissue disorder	2
HIV positive	1
Poisoning	1
Malignancy (4)	
Chronic lymphatic leukaemia	2
Myeloma	2
Renal disease	4
Chronic renal failure	2
Other	2
Cardiovascular disease	3
Congestive cardiac failure/ cardiomyopathy	3

in this group were the pneumococcus (36·6%), *K. pneumoniae* (29·3%), other Gram-negative organisms (22·0%) and *S. aureus* (9·8%). In 10 cases, serological testing for *Legionella, Mycoplasma* or viral infections had been undertaken and no cases identified. No microbiological diagnosis was made in 52·3% of patients.

The overall mortality for this group was 40·8%, which was not significantly different from that found in the group of patients with primary infections. The mortality was 45·5% for the *K. pneumoniae* group and 23·1% for the pneumococcal group of infections (not significantly different). The mortality rate in patients with negative microbiological testing was 42·1%.

Discussion

This study documents the aetiology of acute SCAP among a large number of patients admitted to the ICU of an urban general hospital in Johannesburg, South Africa. While the pneumococcus was the commonest isolate, the study confirms that Gram-negative isolates, and in particular *K. pneumoniae*, account for a significant proportion of the remaining cases (Tables 1 and 4). In our study we recorded, but subsequently excluded from further analysis, patients with infection due to *M. tuberculosis* (of which there were 21 cases). The reason for drawing attention to these cases is that this study and several previous investigations, in both ICU and non-ICU settings (13,15,22,23), have shown that infection with this organism may commonly present as an apparent acute community-acquired pneumonia in countries with a high prevalence of tuberculosis.

A number of studies in recent years have investigated the aetiology of community-acquired pneumonia in different countries. Previous studies in critically-ill cases, particularly from Spain (7,14,15) have suggested that Gram-negative infections are common. This has also been true in studies among critically-ill cases in South Africa (5,13). However, this is in contradiction to several studies from the U.K. in which Gram-negative organisms have not featured as important pathogens even among severely-ill patients (6,9,16,17).

Table 4 The aetiology of secondary acute severe community-acquired pneumonia in 86 patients

Micro-organisms	Total number of isolates	% of positive cultures	Blood and sputum	Blood	Sputum	Serology
Streptococcus pneumoniae	15	36·6	3	5	7	—
*Klebsiella pneumoniae**	12	29·3	—	5	6	—
Other Gram negative	5	12·2	—	2	3	—
Staphylococcus aureus	4	9·8	—	2	2	—
Mixed Gram negative	4	9·8	—	—	4	—
Viruses†	1	2·4	—	—	—	1

*, Site of isolation in one case not documented.
†, *Escherichia coli* (three cases), *Haemophilus influenzae* (1), *Pseudomonas aeruginosa* (1).
‡, Influenza virus infection documented on serology.

The reasons for the differences in aetiology noted in the various studies is uncertain. One possibility is that some studies showing many Gram-negative organisms have included patients with underlying disorders, known to be associated with increased colonization and/or invasive disease with Gram-negative organisms (5,13). The present study included a group of patients with so-called primary infections, specifically excluding cases with any such underlying disorders, and still found this high prevalence of *K. pneumoniae* infections.

Another possibility suggested is that the high prevalence of Gram-negative infections may be associated with greater alcohol consumption by the patients (17). In the present study, we attempted to address this possibility, and although acknowledging that the data are based on a retrospective analysis of records, we were unable to show a significant difference in alcohol consumption in the patients with pneumococcal and *K. pneumoniae* infections.

A third possibility suggested by one author was that the method of diagnosis may make a difference, and that the use of more invasive techniques for the diagnosis of pneumonia may be associated with the documentation of more Gram-negative infections, even among non-critically ill patients (18). In the present study invasive techniques were not routinely used for diagnosis, yet the prevalence of Gram-negative infections was high. However, of these Gram-negative infections, 76% of the isolates in primary infections and 45·5% of the isolates of secondary infections (69·4% for the group as a whole) were from blood culture, one of the gold standards of microbiological diagnosis.

Thus, the exact reason(s) for our high prevalence of infection with *K. pneumoniae* still need to be elucidated. Our study population does differ somewhat from patients from some of the other studies, in that the overwhelming majority of our cases are male, almost two-thirds have no underlying disorders, and in those cases with underlying illnesses, cardiovascular disease is not common. Nevertheless, we would suggest that many of these features should possibly be associated with a lower prevalence of Gram-negative infection, rather than be contributory.

This high prevalence of *K. pneumoniae* infection has persisted in our ICU over several years, and is not a reflection of an outbreak of infection at any one particular time. The current study merely complements our previous publication in 1989, documenting the high prevalence of *K. pneumoniae* infection during the initial 42 months since the establishment of our ICU (5).

Although certain clinical features of illness are said to be characteristic of infection with *K. pneumoniae*, it is recognized that these features are not consistent enough to be of diagnostic value, and the clinical picture is often indistinguishable from that with pneumococcal infection (24). In an attempt to document clinical and laboratory features which would specifically alert one to the possibility of an ICU case being infected with a Gram-negative organism, we recently compared clinical, radiological and laboratory features between patients with severe pneumococcal and *K. pneumoniae* infections, and found that a lower white cell and particularly a lower platelet count are more commonly found in the latter group of infections (19).

Having identified the possibility of a patient being infected with a Gram-negative organism, raises the question as to the most appropriate therapy to institute while awaiting the microbiological results. In a further study we conducted among patients with *K. pneumoniae* bacteraemia at our hospital, we clearly demonstrated that empiric therapy with the combination of a β-lactam and an aminoglycoside antibiotic to which the organism was susceptible was associated with a significantly better prognosis than any other form of therapy (25). The importance of aminoglycosides in the therapy of Gram-negative infections has been noted previously, and one study using multivariate analysis of factors associated with outcome demonstrated adequate peak concentrations of these agents to be of paramount importance (26).

Our suggested empiric choice of antibiotics for critically-ill patients with pneumonia, particularly in cases with a low white cell and platelet count, would therefore include a cephalosporin and an aminoglycoside. To this we would add erythromycin which would cover atypical infections such as with *Legionella* and *Mycoplasma* sp. which are a varying (and sometimes important) cause of infection even in the ICU (8,15–17). The choice of cephalosporin would depend on local susceptibility patterns of Gram-negative organisms. *S. aureus* is also a prominent cause of SCAP and should this organism be strongly suspected, based on the clinical features, more specific therapy should be added. In our experience, with a low incidence of methicillin resistant *S. aureus*, we would usually consider cloxacillin.

In conclusion, we recommend that empiric antibiotic therapy for SCAP should include a second or third generation cephalosporin, erythromycin, and an aminoglycoside. The former two are recommended by both the British Thoracic Society (17), and the American Thoracic Society (27), and

experience in South Africa and elsewhere, makes a good case for the addition of the latter (25–28).

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