Streptococcus pneumoniae

A major cause of adult infections in Malawi

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Abstract

***Streptococcus pneumoniae* is one of the principle infections of adults in Malawi. In recent studies in Blantyre we have described the frequency and severity of infections due to these bacteria among adults presenting to QECH with bacteraemia, meningitis and pneumonia. We also studied the patterns of antibiotic resistance in pneumococcal isolates. The results of these Blantyre studies of bacteraemia and meningitis are reviewed here. In addition, we review an important study of pneumonia from Kenya in order to complement the local data and serve as a reminder that pneumonia remains the most common severe disease presentation caused by Streptococcus pneumoniae. Finally, we outline ongoing and planned future studies of pneumococcal disease in Blantyre.**

Introduction

Streptococcus pneumoniae is an organism found in the nasopharynx of up to 20% of healthy adults.[1] These bacteria may remain merely colonising commensals, causing no symptoms, or they may invade the host to cause severe disease. They have no other host than humans and rely on droplet infection and contact for transmission. Infection of the respiratory tract can cause acute sinusitis, otitis media and bronchitis as well the classic pneumococcal infection, lobar pneumonia.[2] Invasion from inflamed respiratory mucosa leads to bacteraemia and meningitis, as well as rarer presentations such as peritonitis, endocarditis and myositis in immunocompromised patients. The more invasive forms of pneumococcal disease have a high mortality. They also cause much morbidity, and one-third of patients surviving an episode of pneumococcal meningitis experience substantial neurological damage.

Pneumococcus and HIV

Patients infected with the human immunodeficiency virus (HIV) have more than 20 times increased risk of infection and re-infection with *S.pneumoniae* compared to matched HIV negative patients[3]. These infections are of the invasive types and the relationship with HIV increases as the CD4 count falls. The association between invasive pneumococcal disease and HIV infection has been recognised world-wide[4] and the prevalence of pneumococcal infection in adults has even been used as a surrogate marker of HIV prevalence.[5] The mechanisms for the increased susceptibility of HIV infected adults to pneumococcal infection are only partly understood, and prophylactic vaccination with pneumococcal polysaccharide vaccine has been shown to be ineffective.[6]

The problem in Malawi

Pneumococcal disease is an important problem among adults in Malawi, especially as an HIV-associated disease.[7, 8] There is no immediate prospect of an effective vaccine. We hope that this review of locally relevant clinical information will be of use to clinicians.

Bacteraemia study design

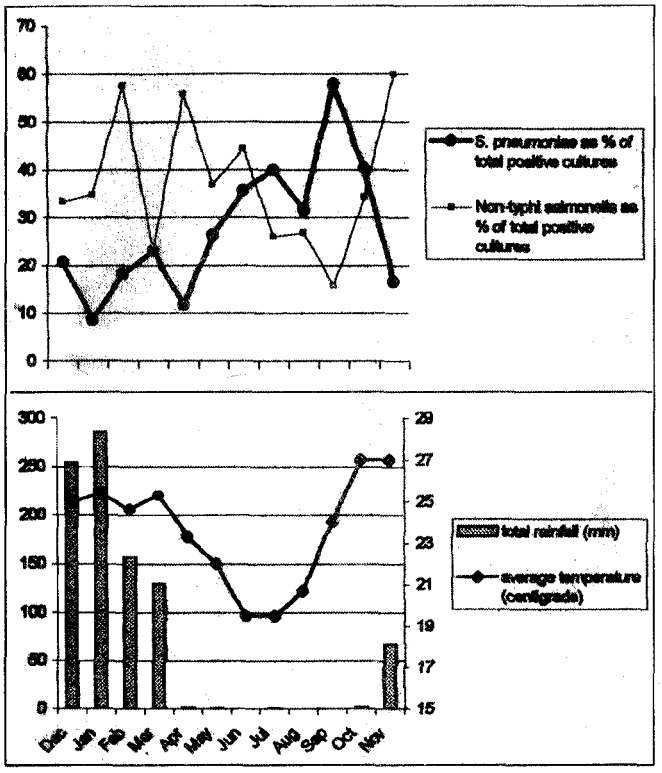
From 1 December 1997 to 30 November 1998, patients newly admitted to the QECH medical wards with fever over 37.5(C had blood culture performed using standard methods.[7] The skin was wiped with an alcohol swab and 5mls of venous blood taken. This was inoculated into a single aerobic culture bottle containing 50mls brain heart infusion broth (E&O Laboratories, UK). Standard antibiotic treatment for patients with a clinical diagnosis of bacteraemia was intravenous benzyl-penicillin 4MU and intravenous chloramphenicol 500mg, both given 6 hourly. Antibiotic treatment was subsequently modified according to antibiotic susceptibility testing of isolates from blood cultures. The outcomes for patients with positive blood cultures were determined from patient files and ward records, and were then confirmed by searching mortuary records. No HIV testing was carried out as part of this study, but HIV seroprevalence data were available for a sub-group of patients with invasive pneumococcal infections, recruited to another study approved by the College of Medicine Research Committee of the University of Malawi.

Results

During the study year, there were 9298 adult medical admissions, with equal numbers of admissions to the male and female wards (4649 to each). Recorded patients' ages (135 cases) ranged from 14 to 76 years (median 30 years). The overall mortality on the wards during this period was 17.9%, and the mortality among men was slightly higher than that among women (916 men and 746 women died = 19.7% vs 16.1%: $p<0.00001$). 2789 patients (29.9%) had blood taken for culture and 449 samples (16.1%) grew significant pathogens. The total numbers of each pathogen isolated and the patient mortality by pathogen are summarised in table 1. Non-typhi salmonellae (NTS) (36.5%) and S. pneumoniae (30.3%) were the two most commonly isolated pathogens. Mortality among patients with a positive blood culture was 37.9% overall. In 27 patients, the same organism was isolated from both blood and CSF. These isolates comprised 16 *S. pneumoniae, 6 Neisseria meningitidis, 3 Cryptococcus neoformans, 1 Escherichia coli and 1 Streptococcus spp.* A seasonal distribution of cases of S. pneumoniae was noted and is shown in figure 1. There was an increase in the number of isolates of S. pneumoniae obtained in the cold season from June to September. HIV testing was requested in 124 sequential patients with *S. pneumoniae* bacteraemia. 102 gave

consent to HIV testing, and 95 (95%) of these patients were HIV positive.

Figure 1. Seasonal pattern of major bacterial isolates from blood cultures



Antibiotic resistance was measured using disk sensitivity testing. This screening test for penicillin resistance showed altered sensitivity to penicillin in 16% of pneumococcal isolates. 93% of isolates were resistant to co-trimoxazole, 50% were resistant to tetracycline and 26% of isolates were resistant to chloramphenicol. Only 2% of pneumococcal isolates were resistant to erythromycin (ie 98% sensitive).

Meningitis Study design

This study ran for 1 year (April 1, 1998 to March 31, 1999) during which time all patients admitted with a clinical diagnosis of meningitis, defined as at least 2 of fever, headache, neck stiffness or altered mental status, underwent lumbar puncture.8 The clinical outcome of all patients with a confirmed diagnosis of meningitis was recorded. Patients with bacterial meningitis were treated with benzyl-penicillin 2 MU 4 hourly and chloramphenicol 1g 6 hourly with the addition of gentamicin 240mg IV daily in those patients who failed to respond, or who had Gram-negative rods in the CSF. All patients with a diagnosis of bacterial meningitis received 7 days of antibiotics, except those with pneumococcal disease who received a total of 3 weeks of antibiotics. Patients with confirmed cryptococcal meningitis were sent home with analgesia, as no anti-fungal chemotherapy was routinely available. Patients with a provisional diagnosis of tuberculous meningitis were treated with short course chemotherapy according to local guidelines.

CSF analysis: All samples were routinely analysed for total cell count and differential white cell count. Protein and glucose were estimated qualitatively, using urine dipsticks (Multistix 8SG, Bayer Diagnostics). An India Ink stain was performed on all samples, except those with cell counts that fulfilled the criteria for bacterial meningitis. Gram stains were done if the white cell count was greater than or equal to 10/mm3. All samples were cultured; these were incubated for a minimum of 48 hours. Mycobacterial and viral cultures were not performed. Antibiotic susceptibilities were tested by disc diffusion. In samples in which no organism was seen, probable diagnoses were made according to the following criteria. Probable bacterial meningitis was diagnosed if the CSF white cell count (WCC) was greater than 100 cells/mm^3, differential cell count greater than 65% polymorphs, protein 3 or 4+ and glucose trace or absent. In addition, probable tuberculous meningitis was diagnosed if the CSF WCC was greater than 100 cells/mm3 differential more than 65% lymphocytes, protein 3 or 4+ and glucose trace or absent and probable viral meningitis if the CSF WCC less than 50 cells/mm3, with differential more than 60% lymphocytes and CSF protein 1 or 2+. Abnormal CSF samples falling outside these criteria were described as meningitis of uncertain etiology.

Results

Patients: During the period 1st April 1998 - 31st March 1999 there were 9553 adult medical admissions, 996 patients had a clinical diagnosis of meningitis resulting in lumbar puncture. 502 patients (5.25% of medical admissions; 222 female and 280 male) had abnormal CSF. The inpatient mortality of patients with meningitis was 41% (204 deaths; male 43.2%, female 38.1%, X^2=2.08, p=0.35).

Microbiological isolates obtained: The microbial yield from CSF analysis is summarised in Table 2. *Cryptococcus neoformans* (n=138) was the most common isolate obtained. *S. pneumoniae* (n=88) was the most common bacterial diagnosis; it was cultured from CSF and/or blood in 81 patients; in 7 patients S. pneumoniae was identified solely on Gram stain of CSF. Meningococcal meningitis was diagnosed in 64 patients. The group of Gram-negative rod isolates comprised *Escherichia coli* (n=7),

Klebsiella spp., (n=5), Pseudomonas spp. (n=3), *Salmonella typhimurium* (n=3), Salmonella spp. (n=1), Acinetobacter spp, (n=1), Enterobacter spp. (n=1), and Proteus spp. (n=1). Gram-positive cocci other than *S. pneumoniae* were *Staphylococcus aureus* (n= 1), *Staphylococcus epidermidis* (n= 1) and untyped alpha-haemolytic streptococci (n=4). The case fatality according to microbiological diagnosis is also shown in Table 1. Pneumococcal meningitis was responsible for most of the

inpatient deaths, although the highest mortality rate was seen among those patients with Gram-negative bacillary meningitis. Patients with cryptococcal meningitis were not included in this analysis because our policy is to discharge patients with cryptococcal meningitis to be cared for at home as soon as possible after diagnosis.

Laboratory indices: There was no significant difference in mean total CSF WBC or % polymorphs in CSF obtained from patients with confirmed or probable bacterial meningitis who survived compared with those who died.

Antibiotic resistance: Oxacillin disk susceptibility testing suggested the presence of penicillin resistance in 8 (10%) of 81 pneumococcal isolates from blood or CSF; 14% were resistant to chloramphenicol. None of the N. meningitidis isolates were resistant to penicillin or chloramphenicol. Among the pneumococcal meningitis patients, there was no significant difference in the associated mortality rate in the small numbers of patients with organisms showing reduced susceptibility compared to those with susceptible organisms for either penicillin or chloramphenicol. The one patient, whose pneumococcal isolate was resistant to both penicillin and chloramphenicol, died.

Clinical features: Detailed clinical information was recorded on 103 consecutive patients 33 of whom were subsequently found to have cryptococcal meningitis and discharged home.
Glasgow Coma Scale Scores were available for 77 patients with non-cryptococcal meningitis. Admission GCS was significantly lower in those who subsequently died; GCS was below normal in 22 out of 30 patients (73%) who died versus 17 out of 47(36%) who survived ((2=10.1, p=0.001).

Seasonality: The relation of rainfall and temperature to numbers of diagnosed cases of bacterial meningitis per month is shown in Figure 2. Forty-two of the 64 cases of meningitis due to N. meningitidis group A occurred during the cool dry months of June to August, when the incidence of pneumococcal meningitis also dramatically increased. The incidence of both infections fell before the rains began but after mean temperatures had risen.

Pneumonia

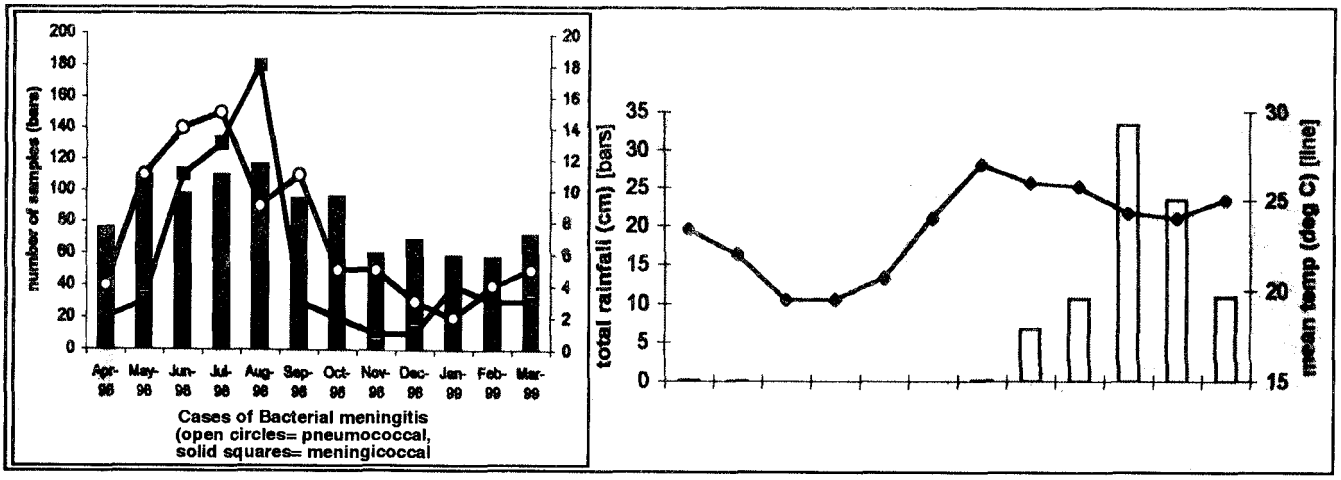
Study populations in Blantyre and Kenya

During 1999, 100 sequential adult cases of lobar pneumonia admitted to QECH were studied following radiological confirmation of diagnosis. The results of this study are not yet available, but fortunately a larger study from Kenya with similar design has recently been published.[9] This study reports the causes, risk factors and prognostic indicators in a population from the Kenya coast with similar characteristics to that in southern Malawi and allows us to predict the likely significance of pneumococcal disease in pneumonia patients in Blantyre. 85% of patients in the Kenyan study were less than 44 years old, and the median age of patients dying of pneumonia was 33 years (as compared to European studies with a median age of 65yrs). 52% of the study population were HIV positive - preliminary (unpublished) data from Blantyre indicate that this figure is 75% for consecutive cases of lobar pneumonia admitted to QECH. Finally, the Kenyan study reports both rural and urban hospital admissions, which is a further reason why the population studied closely resembles that of the Blantyre area. Important differences in the populations studied are climate and the availability of antibiotics. The Kenyan study was carried out in a hot coastal area where people may have greater access to penicillin, as judged from the number of patients reported as visiting a pharmacy and the level of penicillin resistance in the pneumococcal isolates obtained.

Methods of study in Kenya

In this study,[9] Scott et al. studied 281 Kenyan adults who presented to two public hospitals (one urban and one rural) with acute pneumonia during 1994-96. A case of pneumonia was defined as having an illness of 14 days or less duration with at least two respiratory symptoms (cough, sputum, breathlessness, chest pain, haemoptysis or fever) and radiological confirmation of consolidation. Aetiological diagnoses were sought using blood and

Figure 2: Seasonal pattern of bacterial meningitis



lung-aspirate cultures, mycobacterial cultures, serotype-specific pneumococcal antigen detection, and serology for viral and atypical agents. Clinical and demographic details were recorded in detail.

Table I: Bacterial isolates and patient mortality from 449 positive blood cultures

Organism	n	% of total	died (%)
Non-typhi salmonellae	164	36.5	54 (33)
Streptococcus pneumoniae	136	30.3	49 (36)
Escherichia coli	43	9.6	23 (53)
Klebsiella spp	19	4.2	11 (58)
Neisseria meningitidis group A	16	3.6	7 (44)
Other streptococci	16	3.6	
Salmonella typhi	12	2.7	2 (17)
Cryptococcus neoformans	8	1.8	
Staphylococcus aureus	6	1.3	
Miscellaneous	29	6.4	
All isolates	449	100	170 (38)

Results of study in Kenya

An infective cause of pneumonia was defined in 182 (65%) patients. Streptococcus pneumoniae was the most common causative agent, being found in 129 (46%) of cases; Mycobacterium tuberculosis was found in 26 (9%). Of 255 patients followed up for at least 3 weeks, 25 (10%) died. In multivariate analyses, factors in the history associated with increased mortality were age (odds ratio 1.5 per decade [95% CI 1.04-2.19]), unemployment (4.42 [1.21-16.1]) and visiting a traditional healer (5.26 [1.67-16.5]). Patients presenting to a rural hospital also had a greater mortality. On examination, increasing pulse carried a poor prognosis (OR=1.64 per 10 beats [1.24-2.16]), as did the presence of herpes labialis (OR=15.4 [2.22-107]). HIV-1 seropositivity was found in 52% and was not associated with mortality. Data regarding the clinical features of AIDS, or CD4 count were not reported.

Factors associated with good outcome were visiting a pharmacy (OR=0.30 [0.10-0.91]) and presenting to an urban hospital. Death or failure to recover after 3 weeks was more common in patients with pneumococci of intermediate resistance to benzylpenicillin, which comprised 28% of pneumococcal isolates, than in those infected with susceptible pneumococci (OR=5.60 [1.33-23.6]). A large number of cases of TB were found in this study (26, of whom 19 were HIV positive) and so the authors suggested that tuberculosis was a sufficiently common cause of acute pneumonia in Kenyan adults to justify routine sputum culture.

Discussion

The descriptions of community acquired bacteraemia, meningitis and pneumonia reviewed here are each the largest to be reported from Africa in the post-HIV era.

Bacteraemia

The bactaeremia study shows that blood stream infections occur among at least 4.8% of all medical admissions, and 16.1% of febrile admissions in Blantyre. These figures are likely to be an underestimate, as only a single bottle was taken for bacterial culture, and samples were only taken from selected admissions. Our rate of isolation from

Table 2 Laboratory diagnosed meningitis and mortality by group

Diagnosis	Number of patients	% of patients	No. of deaths (% of cases)	% of all deaths
Cryptococcus neoformans	133	26.5	NA[Ü]	NA[Ü]
Streptococcus pneumoniae	88	17.5	54 (61)	32.0
Neisseria meningitidis	64	12.7	14 (22)	8.3
Gram negative rods*	22	4.4	17 (77)	10.1
Gram positive cocci*	6	1.2	2 (33)	1.2
Probable bacterial - meningitis	68	13.5	36(53)	21.3
Probable tuberculous - meningitis	44	8.8	17 (39)	10.1
Probable viral meningitis	18	3.6	3 (17)	1.8
Uncertain aetiology	59	11.8	26 (44)	15.4

* Details of the composition of these groups are found in the text

[Ü] NA: Not applicable, as discharged before outcome known.

culture is slightly higher than other contemporary African studies of blood cultures from consecutive febrile medical admissions, which reported culture positivity rates of 1410 and 11%.[11] HIV-infected patients are known to have a higher rate of bacteraemia than non-HIV infected patients in Africa,[10,12,13] and we attribute our high rate of isolation to the high HIV seroprevalence in our patients. The mortality of bacteraemic patients in our series is 37.9% which is comparable to other series. In a Kenyan series from 1990,[12] mortality among bacteraemic HIV positive patients was 58% whilst that among HIV negative bacteraemic patients was 32%.

The observation that pneumococci were a common cause of bacteraemic illness in HIV positive patients was reported in Kenya,[12] and is now an established pattern in HIV endemic areas of Africa.[14] Reports of blood culture series from Africa in the pre-HIV era do not show either NTS or S. pneumoniae to have been common isolates in adults.[15,16]

Meningitis

The large series of cases of meningitis reviewed here[8] documents the predominance of disease due to *C. neoformans* and *S. pneumoniae*. A similar series from our unit in 1975 described a lower incidence of meningitis amongst acute medical admissions (2 % then compared to over 5% now) and disease that was mostly due to *N. meningitidis* and *S. pneumoniae*.[17] The changing overall pattern in this series is likely due to the influence of HIV infection. These findings differ from those described recently amongst patients with meningitis presenting to Baragwanath Hospital, South Africa.[18] There, pneumococcal meningitis was rare; this difference could result either from local deployment of vaccines, or the availability of antibiotics within the Soweto community. Penicillin resistance is common in South Africa,[19] but was relatively rare in the pneumococcal isolates we describe here; we speculate that relatively low antibiotic consumption in Malawi may be the cause of these differences. Our findings in these adult patients are also different from those observed in local children presenting to Queen Elizabeth Central Hospital between 1996 and 1997[20] in whom bacterial meningitis was caused by *S. pneumoniae* (27%), *Haemophilus influenzae* (21%) and *Salmonella typhimurium* (6%).

Pneumonia

Detailed information regarding the aetiology of pneumonia in adults is not yet available from Blantyre. Fortunately, the excellent study of Scott et al.[9] is set in an area of high HIV endemicity and reports details of patients from both urban and rural districts with similar age profiles to that of the population in southern Malawi. As such, this study is of value to Malawian physicians. In keeping with previous studies, aetiological diagnoses in cases of community acquired pneumonia were hard to obtain.[21,22] 65% of patients obtained a precise diagnosis in this study and that is a high success rate. From the number of cases of pneumococcal pneumonia proven, it is possible to estimate that two-thirds of cases of community acquired pneumonia were due to *S.pneumoniae*. The study differs from studies in the intensive care units of South Africa, where a high incidence of Klebsiella was noted, leading to an antibiotic policy that includes gentamicin for treatment of severe pneumonia.[23]

Seasonal patterns

Seasonal patterns are properly assessed over more than a single year of data. It is interesting to note, however, the predilection of the pneumococcus for the cold season in both the bacteraemia and meningitis series in Blantyre. The incidence of invasive pneumococcal disease in the USA is known to correlate with cold weather and the isolation of respiratory viruses.[24] Thus, these limited data suggest a preserved pattern of seasonality, despite the overwhelming association of pneumococcal infection with HIV infection in Malawi. The different climate experienced on the Kenya coast does not allow analysis of the effect of season on pneumonia. This, along with the possibility that atypical infections are more common in Malawi, provides an incentive to complete studies of local pneumonia cases in Blantyre.

Mortality

Mortality from *S.pneumoniae* bacteraemia in our series was 36%, but is generally reported to be lower than this in other series. Cases with meningitis and bacteraemia contributed to the high mortality reported in this series and poor outcome may also have been due to late treatment or untreated secondary infection.[4] In the meningitis series, the inpatient mortality among all cases (i.e. including cryptococcal meningitis) was 41% which is much higher than that seen in the developed world,[25] and also higher than that seen in our unit in 1975 (29%).

The mortality among patients with pneumococcal meningitis (61.4%) was strikingly high, even compared to a large West African series in 1976, which reported a mortality of 48%.[26] In the pneumonia series from Kenya reviewed here,[9] the follow-up mortality of 10% was similar to that seen in preliminary Blantyre results (15%, unpublished). It is possible that concurrent HIV infection explains the high mortality in our bacteraemia and meningitis series. This hypothesis is not supported by a recent pneumococcal bacteraemia series from South Africa,[27] however, which showed mortality of 12.1% and 21.1% in HIV positive and negative adults respectively, In addition, recent data from Europe showed that AIDS patients with meningitis did not have an increased mortality compared to those without HIV infection.[28] It may not be possible to usefully compare our population with those series, however, in view of the fact that patients we studied did not have access to either antimicrobial prophylaxis or HIV therapy. Interestingly, Scott et al.

did not show an association of HIV status with mortality in acute pneumonia either, despite careful statistical analysis to exclude confounding variables. Moreover, Scott demonstrated that behaviour and lifestyle variables (rural residence, unemployment, use of traditional healer) had marked prognostic signficance. Our observation was that among adult meningitis cases, those presenting to hospital with a low coma score had a poor prognosis. Increased public awareness of the risk in delayed healthcare seeking behaviour could reduce the number of patients presenting to hospital with advanced disease.

Antibiotic resistance and implications for local policy

The relatively low levels of antibiotic resistance to penicillin and chloramphenicol among *S. pneumoniae* isolates were surprising and reassuring. In addition, the low resistance (2%) of pneumococci to erythromycin gives Malawian physicians a good alternative to penicillin in penicillin-allergic cases. Should penicillin resistance increase, physicians will have to be guided by experience in other countries where the use of cephalosporins to treat pneumococcal infections has become widespread.

Tuberculosis

The large number of TB cases found among patients with a clinical presentation of acute pneumonia in Kenya is consistent with recent bacteraemia series from Africa in which mycobacterial cultures have been carried out.[10,13] These studies have shown that up to 48% of blood stream infections in HIV infected adults may be due to mycobacteria. Tuberculosis can therefore cause an acute lobar pneumonia, meningitis or bacteraemia in a population with high HIV endemicity. Tuberculosis is the diagnosis to consider in cases of failed treatment of pneumonia in Africa - not aytpical pneumonias of the types seen in Europe.

Prevention of pneumococcal disease

A recent randomised, double-blind, placebo-controlled trial of 23-valent pneumococcal polysaccharide vaccine in HIV infected adults has failed to show a protective benefit.[6] Newer conjugate vaccines have been shown to be immunogenic,[29,30] but are expensive and do not cover all disease-causing serotypes. There is concern that vaccination against predominant serotypes may simply alter the balance of pneumococcal serotypes in circulation, without changing the incidence of carriage or disease.[31]

Prophylactic cotrimoxazole has been shown to reduce mortality and morbidity among HIV infected patients with sputum positive tuberculosis in Abidjan.[32,33] Protection from non-typhi salmonella (NTS) bacteraemia and enteritis accounted for much of this beneficial effect, susceptibility of NTS to cotrimoxazole in Abidjan being 91%. Both NTS and pneumococci are highly resistant to cotrimoxazole in Blantyre (86% and 93% respectively) and so less benefit can be anticipated. The widespread use of sulfadoxine-containing antimalarials may be a factor in this resistance pattern as antibiotic use has not been sufficient to generate significant penicillin resistance in local pneumococcal isolates.

We believe that increasing public awareness of the potential danger of meningitis could lower mortality from bacterial meningitis in our local community. The Kenya study suggest that the same is also true for pneumonia. The known association of invasive pneumococcal disease with HIV infection makes it important to advise all HIV infected patients to seek medical help early in the course of acute febrile illness.

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Cholera epidemic control

Some practical steps in a district level approach.

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INTRODUCTION

Cholera is characterised by a profuse watery and painless diarrhoea (rice water stools) often associated with vomiting. In the absence of early treatment, cholera may lead to severe dehydration, rapid cardio-vascular collapse and death. In Malawi cholera epidemics have been occurring every year in several districts and cholera control poses an important public health challenge at the district health level. The main objectives of a response to a cholera epidemic are:

To reduce cholera related mortality by appropriate and accessible rehydration treatment, and to limit the total number of cholera cases by implementing effective preventive measures.

In this article I outline some practical steps and approaches towards achieving these main objectives. The paper is targeted at district health officers and health personnel suddenly faced with a cholera epidemic .

Practical steps in response to a cholera epidemic:

1) ***Is this a cholera epidemic?***

An outbreak of cholera should be suspected when

* There is a sudden increase in the daily number of patients with acute watery diarrhoea especially those who pass the typical rice water stools or
* A patient aged 5 years or more develops severe dehydration or dies from acute watery diarrhoea.

2) ***Confirmation of an epidemic***

A case of cholera is confirmed when Vibrio cholera 01 is isolated from the stool of a patient with diarrhoea. Specimens can be collected and stored for laboratory confirmation at the beginning of a possible outbreak by immersing a cotton-tipped swab or a piece of filter paper in liquid stool, and then inserting it into a plastic bag containing 3-4 drops of normal saline (NaCl, 0.9%) and sealing hermetically. Specimens should be collected before any antibiotics are given to the patient. Laboratory confirmation is essential at the beginning of an epidemic, to confirm the biotype, serotype and if possible antibiotic sensitivity patterns. Transport medium (Cary-Blair) is often available later for specimen collection and transport.

3) ***Cholera co-ordination committee (Task force) at the district level.***

Establish a **district cholera co-ordinating committee** (*task*