Acute bacterial infections and HIV disease

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Some acute bacterial infections, notably those caused by the pneumococcus and the non-typhi salmonellae, have not traditionally been considered as leading diseases in tropical medicine, despite their ubiquitous distribution and impact on health. The HIV/AIDS epidemic is forcing a re-evaluation of this position because of their importance in immunosuppressed adults, particularly where exposure is high and treatment relatively inadequate. The problem of acute bacterial disease in HIV/AIDS is outlined in industrialised countries and contrasted with the problem in tropical countries. Specific insights into HIV-related pneumococcal disease and non-typhi salmonellosis that have come from work in the tropics are then discussed. These infections need now to be recognised as an important element of tropical medicine.

Acute bacterial infections have always been important causes of morbidity and mortality in the tropics, in much the same way as they were in temperate regions a century ago. In industrialised countries nowadays, as a result of improvements in socio-economic status, widely accessible good-quality medical services and highly effective antimicrobial therapy, pneumococcal pneumonia is clearly not the problem it was; typhoid and cholera are no longer endemic diseases; and rheumatic fever is very rarely diagnosed. The epidemiological transition has been slow in many regions of the tropics, and acute bacterial infections remain leading killers today.

Despite their undoubted importance, several of the most common acute bacterial infections have remained on the fringes of classical tropical medicine, at least as diseases of adults. In particular, Gram-positive cocci hardly attract any attention in standard UK or US textbooks; and salmonellosis essentially means typhoid fever. While the founders of tropical medicine would have been surprised to have to consider the pneumococcus or the non-typhi Salmonellae as particular tropical problems – infection by these pathogens was ubiquitous and 100 years ago pneumonia or food poisoning was very similar in London or Lagos – today such an approach seems less valid. There are clearly special features of these pathogens in the tropical regions, and it is predictable that bacterial infections will receive more prominence in the next 100 years of tropical medicine. One of the most important features
is the rapid spread of HIV across resource-poor countries\textsuperscript{7}, and the great importance of acute bacterial infections in those immunosuppressed by this virus.

**The problem in industrialised countries**

Early in the HIV epidemic in the US, it was recognised that there was an increased susceptibility to some, but not all, bacterial and mycobacterial infections, as well as to a restricted range of opportunistic parasitic and fungal infections. In the first surveillance definition, recurrent non-typhi *Salmonella* (NTS) bacteraemia was included as an AIDS-defining event because it was such an unusual clinical problem and was highly associated with, and predictive of, underlying HIV infection\textsuperscript{8}. There was also a much higher rate of bacterial pneumonia in drug users in excess of their already higher susceptibility to pneumonia, and in homosexual men. Most often the pneumococcus was implicated, but *Haemophilus influenzae* and *Staphylococcus aureus* were also recovered\textsuperscript{9,10}.

It was soon shown that HTV-infected patients had defective B-cell, monocyte/macrophage and neutrophil function\textsuperscript{11-13} although it remains largely unclear why HIV infection predisposes to a relatively restricted range of pathogenic bacteria. It is debatable whether these virulent bacteria and *Mycobactium tuberculosis*, all pathogens capable of causing severe disease and death in immunocompetent individuals, should be considered as opportunistic pathogens merely because they cause infection in a patient with HIV/AIDS. It is perhaps more useful, and logical, nowadays to consider most acute HTV-related bacterial pathogens as high-grade infections, particularly because they may occur early on in the natural history of HTV infection; and reserve the term opportunistic infection for those highly unusual problems characteristic of marked immunosuppression and AIDS itself.

Pneumococcal pneumonia is now recognised as a leading early HIV-related problem\textsuperscript{14}; susceptibility increases with progressive immunosuppression\textsuperscript{15}; a wider spectrum of disease with some unusual manifestations is recognised\textsuperscript{16}; and rates of pneumococcal bacteraemia are estimated to be 100-fold higher in patients with AIDS\textsuperscript{17}. There can be a good response to therapy and survival from bacteraemic disease is better than in some groups of more elderly patients with other risk factors for pneumococcal disease\textsuperscript{14}. As with many HIV-related pathogens, there is a greatly elevated risk of subsequent infection following the initial event, although the risks have not been well defined. Recently, recurrent bacterial pneumonia, within 12 months of the initial event, has been included as an AIDS defining event\textsuperscript{18}. Since 1988, it has
been recommended that any person with HIV infection, irrespective of the stage of disease, be offered pneumococcal polysaccharide vaccine. These guidelines are based on the premise that the vaccine may be immunogenic and is relatively safe and cheap; no efficacy trials have been carried out\textsuperscript{19}.

NTS bacteraemia is relatively rare, probably because of limited environmental exposure in communities that have good public health and hygiene. In one multi-centre study in the US, NTS bacteraemia was ranked 20th out of 21 problems, and accounted for just 0.4\% of major clinical events\textsuperscript{20}. Other \textit{Enterobacteriaceae}, especially \textit{Escherichia coli}, but also \textit{Klebsiella} spp, are well recognised in AIDS patients with acute community-acquired bacteraemia\textsuperscript{21}. \textit{H. influenzae} infection, both with b and other capsular types, is described particularly in patients with marked immunosuppression\textsuperscript{22}. The conjugate vaccine is immunogenic but probably not of particular use because overall invasive disease is a relatively infrequent event\textsuperscript{23}. \textit{Pseudomonas} septicaemia is also seen with increased frequency with advanced immunosuppression and is associated with central venous catheters; it may be either nosocomial or community-acquired\textsuperscript{24}. Staphylococcal infections are common especially in patients with long lines and indwelling catheters and are seen with higher frequency in intravenous drug users\textsuperscript{25}.

There have been numerous case reports of unusual bacterial, or other, pathogens causing acute or chronic septicaemic illnesses\textsuperscript{26}, but few strong associations have emerged. \textit{Rhodococcus equi} is a cause of unusual cavitary pulmonary lesions but tends to present chronically\textsuperscript{27}. There are no convincing data to suggest that organisms like \textit{Brucella} or \textit{Listeria} are significantly associated with HIV, despite their intracellular location.

**The problem in tropical countries**

Acute high-grade bacterial infections are, in general, far more common than opportunistic infections in patients infected with HIV who live in Africa. This is most clearly seen in cross-sectional studies of HIV-infected patients admitted to hospital. In two separate studies in Nairobi, done 3 years apart with the same methodology, one-quarter of patients were bacteraemic on initial assessment which included a single 5–10 ml blood culture\textsuperscript{28,29}. In this population prior, self-administered antimicrobial therapy was common and relatively indiscriminate. \textit{Streptococcus pneumoniae} and \textit{Salmonella typhimurium} predominated. Similar results were obtained in cross-sectional blood culture studies of patients at or around the time of admission from central and western
Table 1  Bacteraemia and fungaemia in HIV-positive adults admitted to hospital in Africa: a summary of cross-sectional studies from East, Central and West Africa

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<tr>
<td><strong>Total with bacteraemia (%)</strong></td>
<td>26.3</td>
<td>23.3</td>
<td>15.3</td>
<td>24.4</td>
<td>19.6</td>
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<td><strong>Non-typhi Salmonellae (%)</strong></td>
<td>10.5</td>
<td>6.1</td>
<td>7.9</td>
<td>10.4</td>
<td>11.6</td>
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<tr>
<td><strong>Strep. pneumoniae (%)</strong></td>
<td>7.4</td>
<td>7.4</td>
<td>1.5*</td>
<td>10.4</td>
<td>2.0*</td>
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<td><strong>Mortality in patients bacteraemia (%)</strong></td>
<td>58</td>
<td>NA</td>
<td>63</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td><strong>C. neoformans (%)</strong></td>
<td>1.1</td>
<td>8.0**</td>
<td>2.5</td>
<td>0.7</td>
<td>0.0</td>
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NA, data not available; *significantly lower than other studies (P < 0.001); **significantly higher than other studies (P < 0.001).

The low rate of pneumococcal isolation in both studies in Abidjan is explained by the patient population selected for study. They were patients screened and referred to an Infectious Diseases and AIDS Unit, whereas in the other studies, unscreened general medical patients were studied.

In hospital, most pneumococci in blood are recovered from patients with relatively typical lobar pneumonia. Patients with NTS bacteraemia tend to present with a typhoid or enteric fever-like illness. There is some geographical variability in the types of NTS recovered. *Salmonella enteritidis* made up about 20% of NTS isolated from blood in West Africa but was less than 5% in East and Central Africa. Such regional differences have not yet been explained. It is interesting that there is much more variation in cryptococcal fungaemia rates than in bacteraemia rates. Rates are far higher in Central than East or West Africa. Limited cohort data from East Africa confirm the high rates of invasive pneumococcal disease and NTS bacteraemia, that rise with worsening immunosuppression. So far, there are very few data from other regions in the tropics, although it is probable that many of the features seen in Africa will be common in other resource-poor communities in Asia and the Americas.

The WHO has proposed a clinical staging system for HIV infection and disease, to be used particularly in resource-poor countries where laboratory indicators of stage or status, such as CD4 counts and viral loads, are not widely available. Because of their importance, acute bacterial problems figure prominently in this clinical staging, especially in the earlier stages: stage 2, indicative of mild disease, includes recurrent upper respiratory infections (*i.e.* bacterial sinusitis); stage 3, indicative of intermediate or moderate disease includes severe bacterial infections (*i.e.* pneumonia, pyomyositis) as well as pulmonary tuberculosis; and stage 4, equivalent to AIDS, includes NTS septicaemia.

In Nairobi rates of acute bacterial infection were high and more than 50% of patients on admission to hospital were in stage 2 or 3, or pre-AIDS;
they were generally not recognisable as patients with underlying HIV infection. Similar figures have been reported from comprehensive admission surveys in both Uganda\textsuperscript{36} and Zaire\textsuperscript{37}. In contrast, the low CD4 counts noted in one of the Abidjan studies reflected the fact that the patients had been referred to a specialist AIDS and infectious diseases service\textsuperscript{32}. One problem in interpreting CD4 counts in cross-sectional studies is that they are reversibly suppressed in acute bacterial infection\textsuperscript{33}. An important consequence of this is that disease surveillance with any clinical AIDS definition consistently misses at least half the morbidity, and much of the mortality directly attributable to HIV; thus the true impact of HIV/AIDS can be seriously underestimated\textsuperscript{38}. Another problem is that major shifts in hospital performance and care may not be appreciated, in particular the crowding out and displacement of HIV-uninfected patients by those with HIV-related disease\textsuperscript{39}.

Although there are few data about the natural history of HIV/AIDS in tropical as opposed to industrialised countries, it seems that the time for progression to AIDS or stage 4 disease is similar, but that once AIDS occurs, survival time is far shorter. Thus in Uganda, while progression rates to AIDS are similar to those in developed countries, the subsequent median survival time with AIDS was only 9.3 months\textsuperscript{40}. In contrast, Africans living in London have very similar disease progression and survival to UK patients attending the same clinics\textsuperscript{41}. Limited clinical and post-mortem data about causes of death in HIV-infected patients in Africa suggest that a different spectrum of pathogens is responsible; and that acute high-grade bacterial (and mycobacterial) pathogens predominate\textsuperscript{42}.

There are a variety of interlinked environmental and socio-economic reasons that explain the different features of HIV disease and AIDS in the tropics, especially the clinical spectrum and early death. In particular, this relates to the high background prevalence of acute bacterial and mycobacterial disease. Pathogen exposure in poor, overcrowded urban and rural settlements with inadequate sanitation and limited clean water is far higher than in the more affluent and better housed communities more typical of industrialised countries. In children, this is reflected in very high rates of acute respiratory infections and diarrhoeal disease that are several fold higher than in the US or Europe, and tuberculosis is endemic; these syndromes are, therefore, an important cause of severe paediatric morbidity and mortality. The consequences for HIV-infected adults are hardly surprising: a far higher rate of acute bacterial and mycobacterial infection presenting relatively early in the course of progressive immunosuppression. A poor nutritional status may further compromise an HIV-infected individual's resistance to acute bacterial and mycobacterial disease, although so far there are no firm data supporting this.
Once sick, HIV-positive individuals tend to fare badly. Appropriate health seeking behaviour may be adversely affected by poverty. Far more patients are forced to present relatively late in the course of their acute intercurrent illness. The standard of health-care available may be sub-optimal: health workers may not be always available, well motivated or adequately supervised; facilities are often overcrowded and under-funded; and even essential drugs may be scarce or unavailable. Under these circumstances, survival with any severe and life-threatening disease is likely to be greatly compromised by the inadequate level of health care to which the individual with HIV infection has access. Many poor, sick individuals die with their first or second episode of intercurrent disease. Neither antiretroviral therapy nor specific disease prophylaxis are widely used or generally recommended.

Insights into pneumococcal disease

Several features of the interaction of HIV with *Strep. pneumoniae* have been highlighted by studies done in the tropics, but it is still not clear exactly why individuals with a specific loss of CD4 lymphocytes are so susceptible to one of the classic B-cell pathogens. One factor may be related to nasopharyngeal carriage and disrupted mucosal immunity. In the US, it appears that nasopharyngeal carriage in adults is not affected by HIV infection, although it is in children. Where exposure is relatively intense, it seems that pneumococcal carriage rates are approximately double in those with HIV infection. In Nairobi, rates in adults ranged from 21-25%, about double those in HIV-uninfected people (unpublished data).

In Uganda, the efficacy of pneumococcal vaccine in HIV/AIDS is currently under study. This includes a detailed investigation of carriage, in relation to different levels of immunosuppression, serotype distribution, extent of antimicrobial resistance, and seasonal patterns. Preliminary data indicate a higher rate of carriage with HIV infection (N French and C Gilks, unpublished data). At higher rates, intensities and levels of carriage, more nasopharyngeal secretions may be infected with the pneumococcus, thus predisposing to higher rates of disease by inhalation and aspiration into the alveolar spaces or by direct extension into the blood.

Very few cohort data have emerged from the US or Europe about HIV and the risks of pneumococcal infection. In part this is because, in such countries, bacterial pneumonia is rarely life-threatening and therapy is usually started rapidly, often in the community and early on in the disease episode. Prophylactic antibiotics, for whatever indication, will
reduce the rate of bacterial pneumonia\textsuperscript{45}. In one cohort of female sex workers in Kenya, an annual rate of invasive disease of 4.25\% was described, and the relative risk for invasive disease with HIV infection was 17.8\textsuperscript{33}. This relative risk is comparable to that seen in TB disease with HIV infection. In Uganda, rates of pneumococcal bacteraemia, unadjusted for whether placebo or vaccine has been administered, show a sharp rise with falling CD4 count at enrollment: rates of 10/1000 per person year have been found\textsuperscript{34} in all study recruits with CD4 count at entry of over 500/mm\textsuperscript{3} rising to 29/1000 per person years in people with CD4 counts ranging between 200 and 500/mm\textsuperscript{3} and 52/1000 per person years in those with CD4 counts below 200/mm\textsuperscript{3}.

Mortality in patients with HIV-related pneumococcal disease can be very low, even when there is associated bacteraemia\textsuperscript{14,33}, especially if disease is diagnosed early and appropriate therapy is started rapidly. People with HIV tend to be younger and with less serious underlying problems than many HIV-seronegative patients with pneumococcal bacteraemia. When presentation is delayed and pulmonary disease is well established, mortality may be more than twice that seen in patients with pneumonia who are HIV-uninfected. Mortality rates in excess of 15\% have been seen in HIV-infected young adults presenting for hospital care, compared to about 8\% for HIV-uninfected. Both rates are far higher than in a population of similar age in the US or Europe, where a 2–3\% mortality rate would be expected. Inadequate resources for appropriate health-seeking behaviour is clearly a major obstacle to effective HIV/AIDS disease management in Africa.

Those who survive the acute episode are predisposed to recurrent problems or problems with other HIV-related pathogens. This is well-recognised in temperate countries, and indeed justified the inclusion of recurrent bacterial pneumonia within 1 year as an AIDS-defining clinical event. However, several issues are unresolved. Are relapses attributable to the same organism failing to be cleared fully or persisting in the nasopharynx, or are they re-infections? In Nairobi, more than 90\% of cases were clearly re-infected with serotypes quite different from the initial infecting strain\textsuperscript{33}. What is the average time to relapse? In Nairobi, this was just under 6 months; most occurred within 1 year. What is the rate of re-infection? In Nairobi, it was 264/1000 person years; very similar rates are being described in Uganda.

Penicillin resistant pneumococci have recently been ‘discovered’ by the various initiatives for emerging diseases now heavily involved in surveillance, both regionally and globally. In Nairobi, the background level of penicillin resistance was of the order of 25\%. One very alarming observation was association of penicillin resistance (and other drug-resistant phenotypes) with underlying HIV infection\textsuperscript{46}. This can probably be explained by higher antimicrobial use in HIV-positive patients,
particularly with sub-therapeutic dosages or incomplete treatment courses. With high rates of nasopharyngeal carriage, there exists the clear and alarming potential for further, and perhaps more rapid, spread and evolution of penicillin resistance. If this were to be the case, the consequences for the tropics could be truly disastrous.

Options for disease prophylaxis include either vaccination or long-term cotrimoxazole, presumably for life. Both are being evaluated in Africa and results should be available in late 1998. If vaccination works, the issue will be cost; the manufacturer’s price for the single dose vial is currently about US$ 12. The vaccine itself is simple to use and needs only a single injection; there are no adverse public health consequences of failure. If cotrimoxazole prophylaxis works, the operational issue is compliance, as well as the accrued costs for drugs and for clinical follow-up. As with isoniazid prophylaxis for TB therapy, the biggest constraint will be long-term adherence. The public health consequences of a failing prophylaxis intervention are likely to be complex, but will almost certainly include higher rates of cotrimoxazole resistance.

**Insights into Gram-negative infections**

With high exposure, several *Enterobacteriaceae* are common causes of bacteraemia and septicaemia in adults with HIV infection in the tropics. The most important are the *Salmonellae*, as they are in temperate zones. In Africa, the non-typhi salmonellae (NTS), particularly *S. typhimurium* and to a lesser extent *S. enteritidis*, predominate. There is no association of *S. typhi* or *S. paratyphi* with underlying infection. Typhoid is a virulent infection, whether the patient has adequate T-cell immunity or not, whereas NTS are only capable of regularly causing an enteric fever-like illness with bacteraemia in immunosuppressed adults. Consistently, about 1 in 10 adults admitted to hospital with underlying HIV infection has NTS bacteraemia (Table 1), and mortality is high.

NTS may not predominate in other tropical regions. In South America, one study has shown an association of HIV infection with *S. paratyphi* infection. Preliminary data from Vietnam (C. Parry, personal communication) suggest that while the NTSs are uncommon in HIV infection, classical *S. typhi* is associated with immunosuppression. If these intriguing regional differences are confirmed, they suggest great differences in salmonella epidemiology, important variations in virulence or susceptibility, or perhaps differences in first-line community therapy with more powerful broad-spectrum antibiotics such as the quinolones.

Although NTS infections are highly associated with HIV infection across Africa, little descriptive epidemiology and few clinical case series
have been published. Limited data from Nairobi showed an overall bacteraemia rate in a cohort of female sex workers of 16/1000 person years of observation\textsuperscript{33}. In Uganda, NTS bacteraemia is rare in adults with CD4 counts above 500, is seen at a rate of 5/1000 in adults with CD4 counts between 2–500, and occurs at a rate of about 75/1000 in adults with CD4 counts below 200\textsuperscript{43}. The commonest presentation is with an enteric fever-like illness (which before the era of HIV would have been called clinical typhoid). Blind therapy can be difficult because antibiotic resistance rates in NTS across Africa are high but variable. First line empirical therapy also depends on what is available and affordable. Ideally a quinolone or third generation cephalosporin should be used; however, chloramphenicol or ampicillin with gentamicin were effective therapy in Kenya, when the more expensive drugs were not generally available.

Mortality can be very high particularly when there is little awareness of the problem. When the problem was first described in Nairobi, mortality was 80\% but with better recognition and more appropriate therapy mortality declined to 29\%\textsuperscript{28,29}. Under trial conditions, mortality was reduced to 12\%\textsuperscript{33}. As with most other HIV-related infections, survivors suffer high recurrence rates. In a limited study in Nairobi, the recurrence rate was 26\%. Both re-infection and true relapse (which responded well to a resumption of the same treatment regimen) were seen in about equal numbers (C.F. Gilks, unpublished data)\textsuperscript{33}.

Other important Gram-negative infections include \textit{E. coli}, \textit{Klebsiella} and \textit{Shigella} spp. All appear to occur at much higher rates in HIV immunosuppressed individuals, but no large case series have yet been published. In some patients, there is an obvious association with bowel or urinary tract infection. In Nairobi, no special phenotypes of \textit{E. coli} were responsible for bacteraemia or chronic diarrhoea. In particular, there was no obvious excess of EAEC, EIEC or other recognised virulent phenotypes (C.F. Gilks \textit{et al}, unpublished data)\textsuperscript{48}.

The only option for prevention is cotrimoxazole prophylaxis. Given the generally high, but heterogeneous, rate of drug resistance, antimicrobial prophylaxis may not be particularly effective. Long-term compliance may be difficult. Another unresolved issue in therapy is whether long-term secondary prophylaxis is needed after the initial episode of bacteraemia. Other simpler strategies, such as identifying risky behaviour, or the likely sources of NTS exposure, have not yet been explored. Vaccination against typhoid may be an option in those areas where \textit{S. typhi} infection is genuinely associated with underlying HIV infection. In Africa, this will have little benefit and, at present, there are no NTS vaccines for human use.

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