Microbiologically proven bacterial infections in AIDS

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Summary

We have reviewed the incidence, type and site of microbiologically proven bacterial infection occurring in 52 patients with the acquired immunodeficiency syndrome (AIDS) who presented to Southmead Hospital, Bristol between 1990 and 1994. A total of 30 (58%) patients had significant bacterial isolates. The majority of infections were community acquired. Overall, more infections were caused by Gram-negative organisms but Gram-positive organisms predominated in bacteraemia. *Mycobacterium avium intracellulare* (MAI) caused infection in the largest number of patients, followed by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas* sp, and *Campylobacter* sp. When individual episodes of infection were considered, after MAI, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Pseudomonas* sp were the organisms most frequently isolated; often these same organisms caused recurrent chest infection. Bacterial infections in AIDS patients are common and although they generally respond well to antimicrobial chemotherapy there is a high recurrence rate, particularly in the respiratory tract, which is the commonest site of infection.

Keywords: acquired immunodeficiency syndrome, bacterial infection

The acquired immune deficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV) infection, the main abnormality of which is immunosuppression. Although T lymphocyte dysfunction gives rise to infection with opportunist organisms, B lymphocyte dysfunction and neutrophil abnormalities (both of number and function) lead to infection with conventional bacterial pathogens. In children, bacterial infections are the commonest manifestation of immunodeficiency due to HIV.¹ Adults with HIV disease have a higher frequency of bacterial infection than the general population¹ and serious nonopportunistic bacterial infections are recognised more frequently than in the past.²

It is important to be aware of the pattern and incidence of infections associated with AIDS and so we have reviewed the bacterial infections which have occurred in 52 AIDS patients admitted to a district general hospital in order

to identify the rate, type and site of infection occurring in these patients.

Methods

Patients who presented to the Infectious Diseases Service at Southmead Hospital, Bristol and were notified as having AIDS during the period 1990–94 were included in the review. Data were collected from Communicable Disease Surveillance Centre notifications of AIDS in order to discover patient age, sex, length of AIDS illness and mortality. Information on the source of HIV infection as well as the AIDS-defining diagnosis was also obtained. Data were collected on the patients' bacterial isolates and in those patients with potentially significant bacterial isolates the hospital notes were reviewed to assess the isolate's clinical importance. Only those patients who had clinically significant isolates after the diagnosis of AIDS was made were included in the review. Data were collected on the type of organism and site of infection, the source of infection (whether community acquired or not), therapy and outcome. Peripheral blood white cell counts and CD4 counts for each individual episode of infection were also recorded.

Results

Thirty patients (57.7% of patients studied) had bacterial isolates which were judged as having clinical significance (table 1). *Mycobacterium avium intracellulare* (MAI) was the organism which caused infection in the largest number of patients. If the number of episodes of infection caused by each individual organism per 'at risk' patient per year are considered, the highest rate is caused by MAI (0.16), followed by *H influenzae* (0.14), *S pneumoniae* (0.13) and *Pseudomonas* sp (0.1). A large number of episodes of infection caused by *H influenzae* and *S pneumoniae* were related to four patients who had recurrent chest infections caused by these organisms.

AGE, SEX, MORTALITY AND PERIPHERAL BLOOD CD4 COUNT

Most of the 30 patients with significant bacterial isolates reviewed were male (27). The age range was 23–51 years, with a mean of 36.6 at the time when AIDS was diagnosed. Of the 30 with bacterial infection, three were still alive at the time of the review (and one was

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Table 1 Bacterial isolates from AIDS patients

Isolate	Number of patients infected (n=30)*	Number of episodes of bacterial infection	Number of episodes per patient year
<i>Staphylococcus aureus</i>	4	4**	0.06
Coagulase-negative staphylococci	3	3	0.04
<i>Streptococcus pneumoniae</i>	4	9	0.13
<i>Enterococcus faecalis</i>	3	6	0.09
<i>Enterococcus faecium</i>	1	1	0.01
<i>Diphtheroid</i> sp	1	1	0.01
<i>Bacillus carotarium</i>	1	1	0.01
<i>Pseudomonas</i> sp	4	7†	0.1
<i>Escherichia coli</i>	1	2	0.03
Coliforms	2	3††	0.04
<i>Salmonella</i> sp	2	2	0.03
<i>Shigella sonnei</i>	1	1	0.01
<i>Campylobacter</i> sp	4	4	0.06
<i>Haemophilus influenzae</i>	2	10	0.14
<i>Moraxella catarrhalis</i>	3	3	0.04
Mixed bacteria from urine	1	2	0.03
Mixed anaerobes	1	1	0.01
Acid-fast bacilli	1	1	0.01
<i>Mycobacterium kansasii</i>	2	2	0.03
<i>Mycobacterium avium intracellulare</i>	11	11	0.16

*Some patients were infected on more than one occasion; **four episodes but five sites culture positive, as blood cultures and MSU positive at the same time; †seven episodes but nine isolates as blood cultures and Hickman line site culture positive at the same time on two occasions; ††three coliform urinary tract infections of which one resulted in *E coli* bacteraemia

lost to follow-up). The time from the diagnosis of AIDS to death ranged from 1–51 months (mean of 18.1 months; data available for 24 patients). Where CD4 counts were documented at the time of each infection, these were $\leq 0.1 \times 10^9/l$, in all but one patient.

SOURCE OF HIV INFECTION AND AIDS-DEFINING ILLNESS

Twenty-one patients were homosexual, of whom one was also an intravenous drug user and one also had had sexual intercourse abroad. Four were heterosexual patients who had had sexual intercourse abroad, all in Africa. A further two heterosexual patients were intravenous drug users, one woman had a partner who abused intravenous drugs while another woman had a bisexual partner. In one patient the risk factor for contracting HIV was not known. The AIDS-defining illnesses are given in table 2.

SITE OF INFECTION

If mycobacterial infections are excluded, most patients had respiratory tract infection (11) followed by gastrointestinal tract infection (7), urinary tract infection (5) and bacteraemia (5) (table 3). Where actual episodes of infection are considered and the rate of infectious episode per 'at risk' patient year calculated, the highest rates were still recorded for respiratory tract infections (0.37), followed by urinary tract infection (0.17), bacteraemia (0.13) and gastrointestinal tract infection (0.1) (table 3). Patients with recurrent infection account for this alteration in order when episodes per patient year are compared with individual patient rates.

Table 2 AIDS-defining illnesses in those who developed bacterial infection

AIDS-defining illness	No of patients (n=30)
<i>Pneumocystis carinii</i> pneumonia (PCP)	10
PCP and <i>Mycobacterium avium intracellulare</i> (MAI)	1
PCP and Kaposi's sarcoma	1
Kaposi's sarcoma	3
Kaposi's and chronic cryptosporidia	1
MAI	3
MAI and wasting syndrome due to HIV	1
MAI and cytomegalovirus (CMV) retinitis	1
CMV chest infection	1
Recurrent chest infection	1
Oesophageal candidiasis	4
Chronic diarrhoea due to cryptosporidia	1
HIV encephalopathy	2

BACTERAEMIA

Five patients had positive blood cultures on nine separate occasions, and on eight occasions patients were actively treated with appropriate antimicrobial therapy (table 4). One patient who was terminally ill had treatment withheld. Two patients had multiple episodes of bacteraemia, the first due to *E coli* and then *S aureus*, and the second patient due to *S pneumoniae*, *S aureus* and then two episodes of *Ps aeruginosa* bacteraemia. The source of infection for these bacteraemias was presumed to be lung in one patient (*S pneumoniae*), urine in one patient (*E coli*), Hickman line in five (*Ps aeruginosa*—two episodes in one patient, *Diphtheroid* sp, coagulase-negative staphylococci and *E faecium*).

Positive blood cultures occurred on average 23 months after the patients' diagnosis of AIDS was made (range 9–29 months, seven observations). Eight episodes of bacteraemia were acquired in the community and only one (*E faecalis*) appeared to be hospital acquired.

BACTERIAL GASTROENTERITIS

Seven patients had enteric pathogens isolated on stool culture, of which six were of definite clinical significance. One patient had a *Campylobacter upsaliensis* isolated from two specimens and although a history of loose stool was recorded, its clinical significance was difficult to assess. Three other patients had *Campylobacter* sp isolated from faeces. One patient also had a co-existent infection with Cryptosporidia. Another patient with *Campylobacter* sp improved after five days therapy with ciprofloxacin but a third died one week following isolation of *Campylobacter* sp, despite appropriate antimicrobial therapy. However, it is likely that this patient had other ongoing infection which contributed to his death (see below). The time taken from the AIDS diagnosis to *Campylobacter* infection ranged between two and 16 months (mean eight months). Two patients developed salmonella infections (*S chester* and *S enteritidis*) and both responded to therapy with ciprofloxacin. These patients both developed these infections at the

same time as their diagnosis of AIDS was made. The last patient with gastrointestinal infection was a woman who developed *Shigella sonnei* infection which again responded to ciprofloxacin. Shigella infection developed five months after her diagnosis of AIDS was made.

Table 3 Sites of bacterial infections and incidence of infection

	Number of patients notified as having AIDS who had bacterial infection (n=52) (%) *	Episodes per patient year
All bacterial infections	30 (57.7%)	1.06
Bacteraemia	5 (9.6%)	0.13
multiple episodes of bacteraemia	2 (3.8%)	
Bacterial gastroenteritis	7 (13.5%)	0.1
Skin and soft tissue infection	2 (3.8%)	0.03
Line-related infection	2 (3.8%)	0.06
recurrent line-related infection	1 (1.9%)	
Respiratory tract infection	11 (21.1%)	0.37
recurrent respiratory tract infection	5 (9.6%)	
Urinary tract infection	5 (9.6%)	0.17
recurrent urinary tract infection	3 (5.8%)	
Mycobacterial infection (all sites)	13 (25%)	0.19
Other infection	1 (1.9%)	0.01

*Some patients had more than infection

Table 4 Sites of infection and bacterial isolates

Site of infection	Isolates	Number of episodes
Bacteraemia	<i>Staphylococcus aureus</i>	2
	<i>Enterococcus faecalis</i>	1
	<i>Enterococcus faecium</i>	1
	Diphtheroid sp	1
	<i>Streptococcus pneumoniae</i> + coagulase-negative staphylococci	1
	<i>Escherichia coli</i>	1
Gastrointestinal tract infection	<i>Ps aeruginosa</i> *	2
	<i>Campylobacter</i> sp	4
	<i>Salmonella</i> sp	2
	<i>Shigella sonnei</i>	1
Skin and soft tissue infection	Mixed anaerobes and coagulase-negative staphylococci	1
	<i>Ps aeruginosa</i>	1
Line-related infection	<i>Ps aeruginosa</i> *	3
	Coagulase-negative staphylococci	1
Respiratory tract infection	<i>H influenzae</i> *	10
	<i>S pneumoniae</i> *	8
	<i>Moraxella catarrhalis</i>	3
	<i>S aureus</i>	2
	<i>Ps aeruginosa</i> *	3
Urinary tract infection	<i>Enterococcus faecalis</i> *	5
	coliforms	3
	<i>E coli</i>	1
	<i>S aureus</i>	1
	Mixed growth *	2
Mycobacterial infection	MAI	10
	MAI and <i>Mycobacterium kansasii</i>	1
	<i>M kansasii</i>	1
	Acid-fast bacilli only	1
Other infection	<i>Bacillus carotarium</i>	1

*Recurrent infection accounted for some of these episodes

SKIN AND SOFT TISSUE INFECTION

Two patients had significant infection from which a bacterial diagnosis was made. The first developed infected facial sores which were treated empirically with anti-staphylococcal therapy but then these progressed and he became systemically unwell. A diagnosis of ecthyma gangrenosum was made and *Ps aeruginosa* was grown from several sites on face and chest. This patient had other significant infections which included *S chester* enteritis and *E faecium* bacteraemia.

The second patient who had anaerobes and coagulase-negative staphylococci isolated from scrotal pus at *post mortem*, was admitted two months before death when he was found to have a rectovesical fistula, scrotal abscess, cellulitis and chronic sacral osteomyelitis. He also had two urine cultures with mixed organisms including anaerobic cocci which supported the diagnosis of rectovesical fistula and at the same time had a *Campylobacter* sp isolated from a faecal specimen (see above).

HICKMAN LINE INFECTIONS

One patient had *Pseudomonas* sp isolated from his Hickman line exit site on two occasions five weeks apart and simultaneously had *Pseudomonas* sp isolated from blood cultures at both these times. His line was removed following the second episode. *Pseudomonas* sp was again isolated from his Hickman line site five months later.

The significance of coagulase-negative staphylococci grown from a Hickman entry site in an intravenous drug abuser with a fever and treated with vancomycin has not been established as this patient also suffered from disseminated MAI infection which was being treated simultaneously.

RESPIRATORY TRACT INFECTIONS

Eleven patients had significant respiratory tract isolates and of these five had recurrent infections, (two episodes of *Pseudomonas* sp infection, three episodes of *H influenzae* and one episode of *S pneumoniae*, two episodes of *S pneumoniae* infection, five episodes of *S pneumoniae* and seven episodes of *H influenzae* infection, respectively). The two patients with recurrent *H influenzae* infection both survived all their *H influenzae* infections. One had three episodes of *H influenzae* infection which responded firstly to co-amoxiclav; four months later he developed a clinically and bronchoscopically confirmed chest infection with *H influenzae* and was treated with clarithromycin but he required re-admission 12 days later for a course of intravenous ciprofloxacin as *H influenzae* was still being isolated. Three weeks later he developed a right basal bronchopneumonia due to *S pneumoniae* and despite appropriate therapy he died. The second patient had nine isolates of *H influenzae* from sputum over a period of 16 months, seven of which were thought to have been clinically significant and were actively treated. His therapy included three courses of oral cephalosporins, four courses of parenteral cephalosporins, three courses of ciprofloxacin, two

courses of erythromycin, clarithromycin, oxy-tetracycline, and rifampicin as well as long-term cefixime and ceftriaxone.

Three patients had documented *S pneumoniae* infections, two of whom had recurrent infections. All were male and two were intravenous drug abusers. One patient had five episodes which occurred over a 21-month period and all episodes were appropriately treated. Following this it was planned that he should have long-term therapy rotating co-amoxiclav with clarithromycin. A further patient who had two episodes of *S pneumoniae* infection recovered from the first after a course of co-amoxiclav only to be re-admitted the following month with another episode which eventually responded to a third generation cephalosporin. *M kansasii* was also found in his sputum and blood at this time and he died shortly afterwards. The third patient was one who had recurrent *H influenzae* infection and then had an episode of *S pneumoniae* infection from which he died.

M catarrhalis was isolated from sputum or bronchoalveolar lavages of three patients, all of whom had Kaposi's sarcoma. *S aureus* was isolated from two patients each in mixed growth with *Candida* sp. Two patients acquired clinically significant *Ps aeruginosa* infections, the first of whom had HIV encephalopathy diagnosed three months earlier. The second patient had two episodes of *Pseudomonas* infection two years apart.

Two out of the total 26 episodes of pulmonary infection were nosocomially acquired (*Pseudomonas* sp and *M catarrhalis*).

SIGNIFICANT BACTERIURIA

Urinary tract infections were difficult to review as it was not always clear from the notes whether the patient was symptomatic, the isolate was interpreted as being clinically significant or whether therapy was prescribed. In all, 12 urine samples (the majority of which were MSU samples) from five patients had significant bacteriuria. Five isolates were appropriately treated and two patients were on antimicrobial therapy for other infections which would also have been active against the urinary isolates. The 12 isolates included *E faecalis* (5), coliforms (3), *S aureus* (1), *E coli* (1), mixed growth (two samples from a single patient with a rectovesical fistula). Two of these isolates were assumed to be hospital acquired.

MYCOBACTERIAL INFECTIONS

Thirteen patients had microbiologically documented mycobacterial infections, 10 of which were due to MAI alone, one had both MAI plus *M kansasii* infection and one *M kansasii* alone. The thirteenth patient had a liver biopsy in which acid-fast bacilli were seen and although these were not subsequently grown, this was treated as a definite infection.

For the 10 patients who had MAI alone, all isolates were grown from blood samples, five also grew from bone marrow and two from faeces. The patient with *M kansasii* alone had it in both sputum and blood, and the patient with

a mixed infection of *M kansasii* and MAI had the former in blood, abdominal ulcer and rectal specimens and the latter in sputum. Twelve patients died at a mean time of 8.6 months (range 1–32 months) after the infection was diagnosed and in one patient the diagnosis was only made after death. Nine of these patients had no other bacterial infections. The other four patients' bacterial infections included pneumococcal chest infections (1), *S enteritidis* from faeces (1), recurrent bacteraemia (1) and *S aureus* chest infection (1). For six, the mycobacterial infection was the AIDS-defining illness and in seven it occurred from 1 to 51 months (mean 18.6 months) after the diagnosis of AIDS was made.

OTHER INFECTION

Bacillus carotarium was isolated from liver biopsy in a patient who was diagnosed as having AIDS 23 months earlier. It was regarded as clinically significant and he received appropriate antimicrobial chemotherapy.

NEUTROPENIA

Only four patients were neutropenic (neutrophils $< 1.0 \times 10^9$ g/l) at the time a significant bacterial isolation was made. This may be an underestimate as neutrophil counts were not available for all. The isolates which were documented at the time of the neutropenia included *C upsaliensis* enteric infection, *Pseudomonas* sp from blood cultures, *Pseudomonas* sp from skin and tissue samples from the patient with ecthyma gangrenosum and an *E faecalis* urinary tract infection. Only two of the patients were on zidovudine at this time and in addition one had completed chemotherapy and radiotherapy for Kaposi's sarcoma.

Discussion

By 1994 over 9000 cases of AIDS had been notified in the UK.³ We have reviewed microbiologically proven bacterial infections in a group of 52 AIDS patients who presented to a district general hospital. The majority of patients in this review were homosexual males who were at an advanced stage in their disease with CD4 counts less than 0.1×10^9 /l.

In this group of patients the commonest AIDS-defining illness was that of PCP followed by MAI, Kaposi's sarcoma, and oesophageal candidiasis. With severe T-cell defects and dysfunction in patients such as these, infection due to atypical mycobacteria (predominantly MAI) is the commonest type of bacterial infection. Disseminated infection with MAI tends to occur late in the course of HIV infection.⁴ As these patients all had AIDS and were therefore reviewed at a late stage in their disease when CD4 counts in the majority were $< 0.1 \times 10^9$ /l, it is not surprising that this was the commonest infection recorded. In Hickey's review of septicaemia in 131 AIDS patients, MAI was the organism most frequently isolated.⁵

Excluding infection due to MAI, patients with respiratory tract infection, followed by gastrointestinal tract infection, urinary tract

infection and bacteraemia were most numerous. If episodes of infection per patient at risk per year are considered, the highest rates (due to recurrent infection) were recorded in the respiratory or urinary tracts. In a review of 444 AIDS patients by Rolston *et al.*,² 136 episodes of bacterial infection were recorded (a rate of 31 episodes per 100 admissions) with bacteraemia the commonest infection. In Rolston's review Gram-negative aerobic bacilli caused 51% of bacterial infections and Gram-positives 46%, four infections being polymicrobial. We also found an excess of Gram-negative infections over Gram-positive ones but less than 10% of infections in Rolston's review were community-acquired in contrast to our findings, where the majority were community-acquired. Rolston² also found that overall the organisms most frequently isolated were *S aureus*, *S epidermidis*, *Pseudomonas* sp and *E coli*. In our study, after MAI infection, more patients had *S aureus*, *S pneumoniae*, *Pseudomonas* sp and *Campylobacter* sp than other organisms, but if episodes of infection are considered, the highest rates were caused by *H influenzae*, *S pneumoniae* and *Pseudomonas* sp.

In this review (excluding MAI) *S aureus* and *Ps aeruginosa* were more frequently isolated as causes of bacteraemia than the other organisms (although numbers are small) but overall in bacteraemia, Gram-positive organisms predominated. The commonest source of bacteraemia appeared to be related to a Hickman line. Common causes of bacteraemia in AIDS patients include *S aureus*, *S pneumoniae*, *E coli*, *Salmonella* sp, *H influenzae* and *S epidermidis*.¹ In Hickey's review of AIDS patients with non-mycobacterial septicaemias,⁵ 61% were associated with an intravenous access device and of these 28% were due to Gram-negative organisms. A large proportion of cases of septicaemia caused by Gram-negative organisms in AIDS patients with no intravenous access device were due to *Salmonella* sp or *Shigella* sp and this was at a higher rate than in the normal population. They found a rate of 44 septicaemic episodes per 1000 HIV or AIDS admissions, the majority of which were community-acquired.

More of the patients in this review had *Campylobacter* infection than *Salmonella* or *Shigella*. Bacterial diarrhoeal pathogens are more common in patients with HIV than in the rest of the population.¹ Nontyphoidal salmonellas can present with enteric fever-like illness and disseminated salmonella is 20 times more frequent in HIV patients than in the normal population.¹ Many HIV-positive patients can have severe complications and prolonged disease with recurrences and relapses despite appropriate therapy.⁶ Although *Campylobacter* can cause bacteraemia, become chronic or relapse,⁶ this did not occur in our patients.

Skin and soft tissue infections, as in other immunocompromised patients, may require long-term therapy, as did the patient with ecthyma gangrenosum. Three Hickman-related infections were due to *Ps aeruginosa* and on two occasions there was an associated bacteraemia. Central venous catheters are

useful for nutrition, therapy and administration of blood products in these patients but infection with the risk of bacteraemia is a major hazard. The risk increases with previous catheter infection and advanced AIDS.⁷ Skoutelis⁷ found Gram-positive cocci to predominate in these infections but where there were Gram-negatives, *Pseudomonas* sp was the most common.

Eleven of our patients had respiratory tract infections, of whom five had recurrent infection with *H influenzae*, *S pneumoniae* and *Ps aeruginosa*, only two episodes of infection were nosocomial.

Between two and 10% of pneumonia in AIDS patients is caused by encapsulated bacteria.⁸ The predominant organisms include *S pneumoniae*, *H influenzae*, other streptococci and *M cattarhalis*.⁸ Nosocomial bacterial pneumonia accounts for 10–15% of all bacterial pneumonia in AIDS-related complex or AIDS and is more likely to be Gram-negative.¹ In AIDS patients with pneumococcal pneumonia 50–80% develop bacteraemia and with *H influenzae* pneumonia, 5–25% develop bacteraemia.⁸ Recurrences occur, presumably due to lack of production of antibody. The response to pneumococcal vaccine varies and is worth considering if the CD4 is greater than 450 but for those with advanced disease protective antibody levels may not develop.¹ The use of prophylactic antibiotics^{1,8} for selected patients can be considered after one or two episodes of pneumococcal pneumonia but no trials of this have been performed. In HIV patients Hib vaccine has been tried but studies are needed to evaluate its use.⁶

Although probably an underestimate, only four of our patients were neutropenic but presumably many more had impaired neutrophil function. While neutropenia is an important factor leading to Gram-negative bacterial infection, Krumholtz⁹ found more Gram-positive infections in neutropenic AIDS patients who developed community-acquired bacteraemia.

We have reviewed the rates of bacterial infection in these severely immunocompromised patients and compared the rates between the different sites of infection and organisms causing infection. Although there are many other causes of infection the diversity and frequency of bacterial causes need to be considered in the patient with AIDS who presents with a febrile illness.

Summary points

- bacterial infections in AIDS patients are common
- the majority of these infections are community acquired
- bacterial infections in AIDS patients generally respond well to antimicrobial therapy but there is a high recurrence rate, particularly in the respiratory tract, which is the commonest site of infection
- after MAI, *H influenzae*, *S pneumoniae* and *Pseudomonas* sp were more frequently isolated than other organisms, often these same organisms caused recurrent chest infection

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