

Bacterial pneumonia

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Bacteria are tiny single-celled micro-organisms which are found everywhere in nature. They can cause infection even when a person's immune system is unaffected by HIV.

In an uninfected person, various parts of the immune system play different roles in protecting against bacteria. People with HIV may have abnormalities in their immune system which make them more vulnerable to bacterial infections: immunoglobulins (antibodies) are not secreted properly; monocytes do not work properly; the bone marrow may be damaged by drugs such as AZT (zidovudine, Retrovir), ganciclovir (Cymevene) or anti-cancer chemo-therapy; and HIV itself may prevent the release of neutrophils.

Bacteria can cause a range of different problems in different parts of the body; the commonest among people with advanced HIV infection are sinusitis, pneumonia, diarrhoea, bronchitis and skin and soft tissue infections. Co-trimoxazole (Septrin) as Pneumocystis pneumonia (PCP) prophylaxis offers a good level of protection against bacterial infections.

Bacterial infections of the lungs

Bacteria can infect the lungs in people with HIV, especially after the CD4 count falls below 200 cells/mm³. They can cause either a mild cough or a severe pneumonia. This pneumonia can be extremely difficult to distinguish from PCP. A bronchoscopy may be necessary to diagnose bacterial pneumonia.

People taking T-20 (enfuvirtide, Fuzeon) seem to be at slightly increased risk of bacterial pneumonia. Studies suggest that if 100 people take T-20 for a year, four or five will develop bacterial pneumonia. Experts believe this increased

risk of bacterial pneumonia is occurring because T-20 is injected.

As with other opportunistic infections, the incidence of bacterial pneumonia has fallen since combination antiretroviral therapy was introduced. However, when bacterial pneumonia does occur now, it is associated with a relatively poor prognosis. A study of bacterial pneumonia in Barcelona, Spain, found that the yearly rate of bacterial pneumonia between 1997 and 2002 was eight per 1000 HIV patients. In the era of combination therapy, people who develop bacterial pneumonia tend to have advanced HIV disease and other conditions such as cirrhosis. Prognosis was poorer than before HAART (Grau 2003).

Between 1995 and 1998, 9% of HIV admissions to one clinic were due to bacterial lung infections and this group often had more severe illness and longer hospital stays than individuals with other HIV-related illnesses (Bekele 2000). Injecting drug users tend to be at increased risk of bacterial pneumonia (Greenberg 1992; Chaisson 1997). Such infection is more common in smokers than non-smokers. Other risk factors for bacterial pneumonia include breathing chemical irritants and hospitalisation for pneumonia (Navin 2000). However, more recent findings have suggested that being HIV-positive does not lead to a worse outcome following hospitalisation for bacterial pneumonia. The length of hospitalisation and mortality rates were similar in 58 HIV-positive and 178 HIV-negative patients, although the HIV-positive patients' CD4 cell counts were mostly below 200 cells/mm³ (Christensen 2005).

Streptococcus pneumoniae and *Haemophilus influenzae* are common bacterial causes of lung infection (pneumococcal pneumonia), as well as other bacteria in the streptococci family. In a Spanish study, a type of pneumococcal pneumonia was the first HIV-related illness in 48% of people

with HIV (Garcia-Leoni 1992). However, recent studies have shown that despite the fall in incidence since the introduction of HAART, the rate of pneumococcal disease remains elevated in HIV-positive patients, and at equal levels in patients with CD4 cell counts above and below 200 cells/mm³ (Jordano 2004). Even in the HAART era, patients with AIDS are 35 times more likely to become ill with invasive pneumonia than HIV-negative people. Invasive pneumonia occurs when the bacteria invade normally sterile sites, like the blood or cerebrospinal fluid (Heffernan 2005). The elevated susceptibility may be due to impaired secretion of the cytokine interleukin-8 (Gordon 2005).

The bacterium *Pseudomonas aeruginosa* has also been reported as an increasingly common cause of cases of bacterial pneumonia in people with HIV.

Pneumococcal infections usually respond to antibiotics such as penicillin, ciprofloxacin (Ciproxin), amoxicillin (Amoxin / Amix / Amox-ident / Amoram / Galenamox / Rimoxallin) or antibiotics belonging to the macrolide or second-generation cephalosporin families. If the condition does not respond, this may indicate the presence of a concurrent infection such as PCP. Co-trimoxazole, which is effective against PCP as well as pneumococcal pneumonia, may be recommended if the symptoms are particularly severe.

Bacterial pneumonia caused by rarer organisms, such as *Rhodococcus equi*, *Nocardia* or *Bordetella* may require intensive, prolonged therapy with antibiotics.

A significant minority of people experience recurrent bacterial pneumonia. If tests show levels of immunoglobulin to be low, intravenous immunoglobulin may be given, although this has only been proven effective among children with CD4 counts greater than 200 cells/mm³. Co-trimoxazole effectively prevents many bacterial infections.

Doctors may recommend an immunisation against *S. pneumoniae* and *H. influenzae*, as well as the standard influenza immunisation. The pneumococcal vaccine was approved without efficacy trials, based on evidence that the vaccine stimulated immune response. However, a recent study has raised serious doubts about the vaccine, since it did not affect the number of cases of pneumococcal disease and was associated with an increased rate

of overall cases of pneumonia when it was tested in Uganda (French 2000). The researchers suggested that while the vaccine might be effective in adults in Europe or North America, it was probably ineffective among Ugandan adults because the strains of pneumococcus used to develop the vaccine were different from those which are found in Uganda.

Streptococcal pneumonia may also be prevented by co-trimoxazole prophylaxis, providing that co-trimoxazole resistance is not widespread in the local population. If resistance is present, this means that the streptococcal bacteria circulating in the area will have some degree of resistance to co-trimoxazole, and the widespread use of co-trimoxazole prophylaxis may actually encourage the development of further resistance and the loss of protection from this useful antibiotic.

Key research into bacterial pneumonia

Grau studied 142 cases of invasive pneumococcal disease caused by *Streptococcus pneumoniae* in HIV-infected people between 1986 and 2002, comparing the pre and post-HAART eras (1986-1996 and 1997-2002). Overall incidence fell from 24 to 8 cases per 1000 patients. In the later period, bacterial pneumonia was associated with advanced disease and severe co-morbidities such as cirrhosis, and was associated with poorer outcomes. In the HAART era, a quarter of patients died within 30 days compared to 8% in the pre-HAART era.

Sullivan assessed the incidence of and risk factors for bacterial pneumonia in 1,898 HIV-infected patients with CD4 cell counts below 200 who attended the Johns Hopkins HIV Clinic between 1993 and 1998. 352 cases of bacterial pneumonia were reported during 2,310 patient-years of follow-up. Incidence of bacterial pneumonia was 22.7 episodes/100 person-years in early 1993, 12.3 episodes/100 patient-years in early 1996, and 9.1 episodes/100 patient-years in late 1997 ($p < 0.05$). The use of protease inhibitor-containing regimens was associated with a decreased risk of bacterial pneumonia. Lower CD4 cell count, injecting drug use and prior PCP were associated with a greater risk of bacterial pneumonia.

Greenberg reported that in a review of 2983 patient records in New York, bacterial pneumonia was more common among injecting drug users than gay men. Non-Haitian black people were more likely to develop Salmonella sepsis than white people. There are no differences in bacterial infections between men and women.

French conducted a randomised, placebo-controlled trial of the 23-valent pneumococcal polysaccharide vaccine. 1323 HIV-infected adults were randomised, with final analysis of 1158 individuals. There was no significant difference in the number of first events of invasive pneumococcal disease and all pneumonia between the two groups. Cases of pneumonia were significantly more common in the vaccine group. Forty new cases (56.9 per 1000 person years) of all-cause pneumonia occurred in the vaccine group compared to 21 cases (30 per 1000 person years) in the placebo group (0.02). Adjusted first event analysis found this difference highly statistically significant ($p < 0.008$) while the all event, non-adjusted figure was also significant ($p < 0.03$).

Bekele found that 9% of nearly 600 HIV admissions between 1995-1998 were due to bacterial pneumonia. Median CD4 count was 38 versus 66 cells/mm³ for all other admission groups. Length of hospital stay was longer, and intensive care admission and case-fatality rates were higher. The most common bacteria was *Pseudomonas aeruginosa* (32 admissions), followed by *Streptococcus pneumoniae* (22 admissions), *Staphylococcus aureus* (16 admissions), and *Haemophilus influenzae* (11 admissions). Thirty-three of the pneumonias were bacteraemic, which was more common in pneumococcal than in pseudomonal pneumonia groups.

Navin reviewed 211 HIV-infected cases of pneumonia between 1994-1996, comparing them with age and CD4-matched individuals hospitalised for other reasons. Bacterial pneumonia was associated with breathing chemical irritants such as insect spray, petrol or paint fumes in the previous month or hospitalisation for pneumonia within the last 6 months on multivariate analysis.

Chaisson (1997) reported that in a group of 2,888 patients prospectively followed between 1989 and 1996, 14% of drug users developed bacterial pneu-

monia versus 11% of non-drug users. 14% of blacks developed bacterial pneumonia versus 9% of whites. People with lower CD4 counts were at greater risk. People receiving co-trimoxazole did not appear to be at reduced risk, and a history of PCP increased the relative risk of developing bacterial pneumonia, suggesting that the bacteria might have acquired resistant to co-trimoxazole. There was no decrease in bacterial pneumonia during 1996, even though other opportunistic infections were becoming less common due to the use of protease inhibitors.

Garcia-Leoni conducted a retrospective (13-month) and prospective (14-month) study of 106 adult hospitalized patients with pneumococcal pneumonia, 22% of whom were HIV-positive. The estimated attack rate was 5.9 per 1000 for HIV-infected patients and 0.31 per 1000 for HIV-seronegative patients. Pneumococcal pneumonia was the first manifestation of HIV infection in 48% of cases. Seventy-two percent of patients younger than 40 years of age with pneumococcal pneumonia were HIV-infected.

Steinhoff compared H. influenzae type b polysaccharide (PRP) vaccine to the polysaccharide-mutant diphtheria toxoid conjugate vaccine (PRP-CRM). In asymptomatic and early symptomatic HIV-positive men (and in HIV-negative men), the PRP-CRM vaccine caused a threefold greater antibody response than the PRP vaccine. However, in men with AIDS, the PRP vaccine caused a greater response.

Glaser reported that AZT improves response to pneumococcal vaccine among people with AIDS or ARC.

Schuster reported on 16 people with *Pseudomonas Aeruginosa* pneumonia. Most had AIDS with a mean CD4 count of 27. Traditional risk factors were often missing. Cavitory infiltrates were present on admission chest radiograph in 50% of cases. In-hospital mortality was 19%, and an additional 25% developed chronic or recurrent disease.

Hirschtick reported that the risk of bacterial pneumonia in HIV-positive people increases sharply when CD4 counts fall below 200, particularly among smokers. Injecting drug users were twice as likely to develop bacterial pneumonia than gay men with the same CD4 count. Taking co-trimoxazole for PCP prophylaxis appears to reduce the risk of bacterial pneumonia by about a third.



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