HIV and pneumococcal disease

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Purpose of review

To describe the impact of highly active antiretroviral therapy on the burden of pneumococcal disease and advances in our understanding of the impact of HIV on this disease.

Recent findings

Although highly active antiretroviral therapy has reduced the burden of pneumococcal disease among HIV-infected adults, these infections remain far more common than in HIV uninfected adults. HIV-infected adults who smoke or have comorbidities are at particular risk. In the absence of highly active antiretroviral therapy, pneumococcal meningitis has emerged in Africa as a major disease burden with a high mortality among HIV-infected children and adults. Conjugate pneumococcal vaccine protects HIV-infected infants from pneumococcal pneumonia. In the United States, where conjugate vaccine is given to children, herd immunity has reduced the burden of invasive pneumococcal disease among HIV-infected adults.

Summary

The pneumococcus remains a significant cause of morbidity and mortality among HIV-infected children and adults, both in developed and in developing countries.

Keywords

HIV, meningitis, pneumococcus, pneumonia

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Abbreviations

CPV	conjugate pneumococcal vaccine
IL	interleukin
IPD	invasive pneumococcal disease
HAART	highly active antiretroviral therapy

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Introduction

Acute respiratory infections are the leading infectious causes of death in both children and adults. Among HIV-infected people, the burden of these infections is greatly increased, and particularly in developing countries with little access to highly active antiretroviral therapy (HAART), the burden of pneumococcal disease falls disproportionately on the HIV-infected population. This review describes the significant remaining burden of pneumococcal disease in the HAART era, new insights into pathogenesis of pneumococcal disease in HIV-infected persons, and the impact of HIV on pneumococcal disease, antimicrobial resistance and vaccination.

Burden of disease and impact of highly active antiretroviral therapy

The burden of invasive pneumococcal disease in African HIV-infected children less than 2 years of age (3036 per 100 000) was 42-fold (95% confidence interval (CI) 27–66) greater than that in HIV-uninfected children in the pre-HAART era [1]. In the USA, the burden of invasive pneumococcal disease was 9–13-fold greater in HIV-infected children (incidence 11 300–12 240 per 100 000 person years) prior to the introduction of HAART [2,3]. The apparently greater absolute disease incidence in the US is likely to be a measure of the greater likelihood of febrile children in the US getting a blood culture.

Similarly high rates of pneumococcal bacteremia existed in adults living with AIDS in the US prior to the introduction of HAART (1094/100 000 in 1995/6) [4••]. Availability of HAART has more than halved this disease burden in the US (to 467/100 000 in 1999/2000), but the residual disease burden remains 35-fold higher than that in age-matched HIV-uninfected people in the US [4••]. In an analysis of the impact of HAART on pneumococcal disease in Spain [5••], disease burden reduced from 2410 episodes per 100 000 patient-years pre-HAART (1986–1996) to 820 episodes per 100 000 patient-years in the HAART era ($P = 0.01$). Compared with patients in the pre-HAART era, patients in the HAART era had more associated comorbidity (42% versus 26%; $P = 0.04$), fewer recurrences of bacteremia (4% versus 15%; $P = 0.04$), and a higher 30-day mortality rate (26% versus 8%; $P = 0.004$). High antibiotic resistance rates were observed in both periods. By multivariate analysis, the major risk factors for pneumococcal bacteremia in the HAART era were associated comorbidity [adjusted odds ratio (OR) 3.36], alcohol abuse

(adjusted OR 5.28), prior hospitalization (adjusted OR 3.38), current smoking (adjusted OR 5.19), and CD4 cell count lower than 100 cells/μl (adjusted OR 2.38). Use of HAART (adjusted OR 0.37) and pneumococcal vaccine (adjusted OR 0.39) were protective factors [5••]. Risk factors and prognosis of pneumococcal bacteremia in the HAART era are thus more similar than previously to those reported in non-HIV-infected individuals.

Pathogenesis of pneumococcal infections in HIV-infected patients

To better understand why HIV-infected adults have an increased susceptibility to pneumococcal disease, an in-vitro study was undertaken to demonstrate whether impaired cytokine release from alveolar macrophages of HIV-infected patients occurred in response to *Streptococcus pneumoniae* challenge [6•]. The investigators documented that interleukin (IL)-1, 6 and 8 increased in both the HIV-infected and uninfected groups following challenge, but whereas IL-1 and IL-6 were higher in the HIV-infected group, the IL-8 levels were significantly lower. The authors suggest that the reduced IL-8 may result in impaired neutrophil recruitment, thereby increasing the susceptibility of HIV-infected patients to pneumococcal infections.

Pneumococcal pneumonia

Community-acquired bacterial pneumonia occurs less frequently in HIV-infected patients initiated on a protease inhibitor-containing antiretroviral regimen [7•]. In a follow-up period of 43 months, 29 cases of pneumonia were documented in the antiprotease cohort (APROCO) in France, giving an incidence of 800/100 000 patient-years. Of the 11 definitive cases, nine were due to *Streptococcus pneumoniae*, one to *Legionella pneumophila* and one to *Haemophilus influenzae*. The occurrence of bacterial pneumonia was associated with various host factors including older age, smoking, presumed HIV infection through injecting drug use, and factors associated with lower virological efficacy of antiretroviral therapy.

Nosocomial bacterial pneumonia has been considered to be an important cause of morbidity and mortality among patients with advanced AIDS, but has declined in incidence since the introduction of HAART [8•]. A retrospective study of all HIV-infected patients admitted to the Infectious Disease Clinic in Milan between 1988 and 2002 was undertaken [8•] in which investigators identified 120 episodes of nosocomial bacterial pneumonia, of which 21% were due to *Streptococcus pneumoniae*. The overall mortality rate for the nosocomial bacterial pneumonias was 25.8% and the only independent predictor of mortality was the presence of methicillin-resistant *Staphylococcus* as the cause.

Pneumococcal meningitis

In sub-Saharan Africa the burden of HIV among patients with meningitis is considerable, and is associated with an extreme level of mortality. Among adults in Malawi with meningitis, 158 out of 167 patients consenting to testing (95%) were HIV positive [9]. Inpatient mortality was 65% for pneumococcal meningitis. The remaining 35% of hospital survivors were followed for a median of 414 days, and 39% of these patients died in the community during the study period. Among children, 62 (42.2%) of 147 with meningitis in Soweto tested for HIV-1 infection were infected [10]. *S. pneumoniae* exceeded *H. influenzae* type b (Hib) as the most important cause of meningitis in HIV-1-infected (74.2% versus 12.9%, respectively) compared with uninfected children (29.4% versus 42.3%, respectively; $P < 0.00005$) even prior to the introduction of Hib conjugate vaccines. The estimated relative risk of pneumococcal meningitis was much greater in HIV-1-infected [relative risk (RR) 40.4; 95% CI 17.7–92.2] than in uninfected children under 2 years of age. HIV-1-infected children had a higher rate of morbidity or mortality (60.8% versus 36.0%, respectively; $P = 0.04$).

Antibiotic resistance

The unusual occurrence of an altered penicillin binding protein PBP 2A associated with β-lactam resistance was reported in an HIV-seropositive child with recurrent pneumonia in whom three identical *S. pneumoniae* serotype 14 isolates were cultured sequentially [11•]. The third isolate showed a decrease in penicillin, cefotaxime and ceftriaxone resistance compared with isolates 1 and 2, associated with replacement of an altered PBP 2A with a wild type PBP 2A. Interestingly, faster growth rates and larger capsules were seen in isolates 2 and 3 compared with isolate 1, suggesting that these events produce a strain which evolved into a fitter and more virulent type, albeit less antibiotic resistant, which ultimately led to the child's death.

For some years it has been known that pneumococci causing invasive disease among HIV-infected adults [12] and children [1] are more resistant to antibiotics. The preponderance of pediatric serotypes among HIV-infected adults (see below) may be a factor that increases the resistance of strains isolated from HIV-infected adults, as may exposure to antibiotics as therapy or prophylaxis. Of particular concern is the impact of trimethoprim–sulfamethoxazole prophylaxis on susceptibility of the pneumococcus to that drug, and the role of trimethoprim–sulfamethoxazole in selecting multiply resistant pneumococci. Children on prophylaxis have been shown to be more frequently colonized with drug-resistant strains of pneumococci [13] and more likely to develop invasive disease associated with more highly resistant strains [1]. The rates of resistance to

trimethoprim–sulfamethoxazole are high in many African countries. No impact of prophylaxis could be found on pneumococcal disease in Uganda in a setting of 70% resistance to the drug [14], so reductions in pneumonia incidence may not be primarily due to reductions in pneumococcal disease. Cotrimoxazole prophylaxis was, however, associated with a 63% reduction in hospitalization for pneumonia, of unknown etiology, among African children from an area with a high prevalence of *S. pneumoniae* resistance to cotrimoxazole [15]. There is indirect evidence that cotrimoxazole prophylaxis may reduce bacterial infections (26.8% versus 11.3%), especially due to *S. pneumoniae* [16], although the susceptibility of the pathogens was not reported in that paper.

An investigation was undertaken in Kenya of 162 upper respiratory tract isolates from 104 HIV-infected adults and 46 children enrolled in a cotrimoxazole prophylaxis study [17•]. Levels of antibiotic resistance were very high [152 isolates were cotrimoxazole nonsusceptible (134 fully resistant) and 124 intermediately resistant to penicillin]. Resistance was noted among a number of different serotypes, 15 of which have never or rarely had documented resistance to penicillin, including serotypes 3, 4, 7C, 10A, 11A, 13, 15A, 16F, 17F, 19B, 21, 35A, and 35B. Limited *pbp2b* and *dhfr* sequence analysis documented that the majority of clones contained alleles that were very different from other known resistance containing *pbp2b* and *dhfr* genes, although they did contain the same key codon substitutions required for resistance.

Pneumococcal vaccines

Case control studies among HIV-infected people in developed countries who have access to antiretrovirals have generally shown protection from invasive disease among those who have received the 23-valent pneumococcal vaccine (PPV) as mentioned above. The only randomized trial of this vaccine among HIV-infected people without access to antiretrovirals showed an increase in pneumonia among vaccinees (40 episodes versus 21; hazard ratio 1.89; 95% CI 1.1–3.2), and a 6-year follow-up of that study showed no further increase in pneumonia but a paradoxical significant 16% reduction in mortality in the vaccinated group [14]. The issue of the usefulness versus the risk of polysaccharide vaccine in Africa thus remains unresolved.

The immunogenicity of a 7-valent conjugate pneumococcal vaccine (CPV) was studied in the original study cohort of HIV-infected Ugandan patients described above with the administration of two doses of CPV to 54 past PPV recipients and 55 past placebo recipients [18•]. Postvaccination anticapsular immunoglobulin G (IgG) concentrations were directly correlated with CD4 cell counts and there were significant increases in anticapsular IgG for all serotypes after the first dose and for all serotypes except 14 and 9V after the second dose, with no effect of past PPV on the vaccine response.

Conjugate pneumococcal vaccine given to HIV-infected children in infancy not only prevents 65% of vaccine type invasive infections by intent to treat analysis [19], but also reduces the burden of clinical pneumonia by an estimated 2573 episodes/100 000 children immunized per year [20••]. The vaccine also reduces the burden of antibiotic-resistant invasive infections in HIV-infected children [19].

Although the antibodies to pneumococcal capsules induced by CPV in HIV-infected infants are similar quantitatively to those induced in HIV-uninfected infants, recent data suggest that there are qualitative differences – these antibodies are less able to facilitate opsonophagocytosis of pneumococci than are those induced in HIV-uninfected children [21•]. In symptomatic HIV-infected children there are both qualitative and quantitative reductions in antibody response to the pneumococcal conjugate [21•].

In populations where children receive CPV, there are data to suggest that the burden of pneumococcal disease due to the conjugate vaccine types may fall in HIV-infected adults through herd immunity. It has been known for some time that close exposure to children is a risk for pneumococcal bacteremia in HIV-infected adults [22] and that the pediatric serogroups of pneumococci are more commonly found in HIV-infected adults than in uninfected adults [12,23]. Young HIV-infected women are at particular risk for infection with pediatric serotypes [24]. Direct evidence for the impact of conjugate vaccine use in children on the burden of disease in adults is now available from a CDC study in which all invasive disease in HIV-infected adults post vaccine introduction decreased by 19% ($P = 0.002$) [25••] and pediatric conjugate vaccine serotypes were reduced by 62% ($P < 0.001$). Of concern, however, is the degree of replacement disease by nonvaccine serotypes that increased by 44% ($P < 0.001$) [25••].

Invasive pneumococcal disease

In a retrospective record review from the US, the demographic, clinical, laboratory, radiographic and microbiologic data were compared in 52 HIV-infected and 51 noninfected patients with invasive pneumococcal disease (IPD) [26•]. For that study the definition of IPD used was the isolation of *S. pneumoniae* from the blood, normal sterile fluids (e.g. cerebrospinal fluid or synovial fluid), abscess fluid from soft tissues or the respiratory tract of patients with signs, symptoms, and radiographic findings suggestive of a pulmonary infection. At the time of initial

presentation, the duration and severity of symptoms, signs, radiographic manifestations and laboratory abnormalities were generally similar in the two groups. There was a higher incidence of bacteremia among the HIV-infected group (77% versus 55%; $P < 0.01$). There was a trend for the length of hospital stay to be shorter in these patients and less of the HIV-infected patients required admission to the intensive care unit or mechanical ventilation. Interestingly, the mortality of the HIV-infected patients was one-fifth of that of the patients that were not HIV infected. The authors suggested that the reasons for the lower mortality may be due to less advanced age and fewer comorbidities in the HIV-infected cases or possibly that the inflammatory response to IPD may be blunted in HIV-infected patients.

Conclusion

The pneumococcus continues to cause significant morbidity and mortality among HIV-infected individuals. Prevention efforts have reduced this burden by the introduction of HAART and by herd immunity of adults in communities where children receive conjugate pneumococcal vaccine. The impact of trimethoprim–sulfamethoxazole on pneumococcal disease may be frustrated by resistance emergence but more data are needed on the impact of resistance on the prophylactic, as opposed to the therapeutic, efficacy of this drug against resistant strains. The impact of polysaccharide pneumococcal vaccine on HIV-infected people not on HAART remains controversial, and research is needed on the impact of conjugate vaccine on adult disease, both by direct vaccination and by vaccinating children to induce herd immunity in developing countries.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 91).

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