

# HIV-associated Bacterial Pneumonia

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## SYNOPSIS

Community-acquired bacterial pneumonia (CAP) remains one of the most common opportunistic in patients who are HIV-infected, this despite the use of co-trimoxazole prophylaxis and even the introduction of HAART. HIV itself is a risk factor for CAP, but additional risk factors exist and include increased age, previous pneumonia, other co-morbid conditions and also cigarette smoking. The risk of CAP increases as the CD4 cell count decreases. The pathological changes that occur in the immune system as a consequence of

HIV infection explain the mechanisms associated with the increased risk of CAP. The common bacterial pathogens that cause CAP in HIV-infected persons are similar to those in HIV-non-infected individuals, with the pneumococcus being the most common pathogen. The clinical features of CAP in HIV-infected persons are similar to those in HIV-non-infected persons. However, contrary to the findings of early investigations, many recent studies indicate that the mortality of pneumococcal CAP is higher in HIV-infected patients and the mortality tends to stratify according to the CD4 cell count, being greater at lower CD4 cell counts. While the diagnostic workup of HIV-infected patients with CAP is similar to those cases that are HIV-uninfected, use of the newer rapid laboratory techniques has expedited the diagnosis of these infections. Not only does the mortality remain high in HIV-infected persons with CAP, but the occurrence of CAP is associated with a permanent decline in lung function in these patients. Prevention of CAP remains critical and necessitates a comprehensive approach addressing, among many other factors, cigarette smoking cessation strategies, HAART adherence and immunization against those infections for which effective vaccinations are available.

**Keywords:** CD4 cell count, community-acquired bacterial pneumonia, HAART, HIV infection, mortality, smoking, treatment, vaccination

## **INTRODUCTION**

The respiratory tract is recognized to be the site most critically affected as a consequence of human deficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS) [1]. While in the initial phase of the epidemic the lung was involved in almost 100% of the cases, currently, in the era of highly active retroviral therapy (HAART), it is involved in some 70% of the patients [1]. Pulmonary infections are the major component

of these complications, with lower respiratory tract infections being 25-fold more common than in the general population. Respiratory infections in general, rather than only AIDS-related opportunistic infections, remain a major cause of morbidity and mortality and reason for hospital admission [1]. The spectrum of pathogens causing pulmonary infections in HIV infected persons is vast, differs in the various geographical areas, and has changed over the evolution of the epidemic due to the introduction of co-trimoxazole prophylaxis and HAART [1]. Most importantly, the three most common infections, namely tuberculosis (TB), bacterial pneumonia and *Pneumocystis pneumonia* (PCP), have been documented to result in a worse course of HIV disease, as well as permanent impairment in lung function in most studies [1].

## **EPIDEMIOLOGY, PATHOGENESIS AND RISK FACTORS FOR BACTERIAL PNEUMONIA**

### ***Epidemiology***

While community-acquired pneumonia (CAP) is usually described as the most frequent pulmonary infection in HIV infected individuals followed by PCP and TB, the relative prevalences of these three infections does vary in the different geographical regions [1]. In the early phases of the epidemic, PCP was the most common infection overall, but this has decreased considerably in prevalence as a consequence of the use of co-trimoxazole prophylaxis initially, and subsequently to the introduction of HAART [1]. Presently in Africa, for example, TB is the most common pulmonary infection, whereas in the US and Western Europe, CAP is the most common [1]. Bacterial pneumonia is also the most common admission diagnosis in patients with HIV infection and occurs with a more than 10-fold increased risk of frequency [1]. Undoubtedly, the risk for the development of each of these infections is also influenced by degree of immunosuppression of the patients, their

demographic characteristics, their place(s) of residence, their use of prophylaxis and possibly genetic influences [1].

### ***Pathogenesis***

The human lung, with its highly organized network of mediastinal lymph nodes, is a major target of HIV infection [2,3]. Relative to the gastrointestinal tract, however, the rate of immune attrition in the lungs is considerably slower [4-6]. There are several reasons for this, including: i) the mediastinal lymph nodes are the primary sites of T cell antigen priming in the lung, with secondary bronchus-associated lymphoid tissue being much less prominent than that of the gut-associated secondary lymphoid tissue [4,7,8]; ii) the diversity and efficacy of the innate immune mechanisms of the airways [9]; iii) the relative resistance of lung CD4<sup>+</sup> T cells of the Th1 [5] and Th17 [6] subtypes, as well as alveolar macrophages [10], to productive infection with, and depletion by HIV; and iv) initiation of a vigorous anti-HIV response mediated by antigen-specific CD8<sup>+</sup> cytotoxic T cells, as well as natural killer (NK) cells and NKT cells [3].

Spread of HIV to the lungs is achieved by several mechanisms including: i) infection of hematopoietic progenitor cells, especially those which differentiate into monocytes; these, in turn, mature into alveolar macrophages and myeloid dendritic cells following trafficking to the lungs [11]; ii) capture of HIV by DC-specific intercellular adhesion molecule grabbing integrin (DC-SIGN) by monocytes and immature DCs, predominantly myeloid DCs, in blood [12,13]; iii) infection of these cells, as well as plasmacytoid DCs, with HIV via CD4/CCR5 interactions, albeit at low level [14,15]; and iv) acquisition of the integrins LFA-1 and VLA-4 by HIV during budding from infected cells, promoting attachment to, and productive infection of vascular endothelial cells [16,17].

In spite of the relative resistance of the lungs to HIV-mediated immune attrition, progressive infection inevitably impacts negatively on the numbers and functions of

pulmonary CD4<sup>+</sup> T cells and it is noteworthy, as mentioned earlier, that respiratory infections are the leading cause of mortality in HIV/AIDS. As is the case in other tissues, it is the CD4/CXCR6 co-expressing T cells of the effector/memory phenotype which are most vulnerable [2, 3]. HIV-mediated depletion of CD4<sup>+</sup> T cells is a direct consequence of both productive virus infection [18] and induction of Fas-mediated apoptosis in both HIV-infected and –uninfected cells [19]. In addition to these direct mechanisms of HIV-induced T cell depletion, increasing evidence has implicated chronic activation of plasmacytoid DCs as being an indirect mechanism of T cell dysfunction and cytotoxicity [20,21]. In this setting, pulmonary plasmacytoid DCs interact with HIV via CD4, resulting in internalization of the virus. In the cell cytoplasm, viral RNA is recognized by intracellular pathogen recognition receptors known as Toll-like receptors (TLRs)-7 and -9 [20-23], and possibly by the more recently described cytoplasmic pathogen nucleic acid sensors [24]. This leads, in turn, to excessive and sustained production of: i) type I interferon (IFN); ii) the tryptophan catabolizing enzyme, indoleamine 2,3-dioxygenase; and iii) the cytokine, transforming growth factor  $\beta$  (TGF- $\beta$ ), all of which contribute to immune dysfunction [20,25-33]. These immunosuppressive mechanisms are summarized in Table 1. With respect to TGF- $\beta$ -mediated pro-fibrotic activity, it is noteworthy, that extensive fibrosis of the T cell zone of lymphoid tissue has been proposed to be a significant factor in the failure of T cell reconstitution following initiation of antiretroviral therapy (ART), despite viral suppression [33].

### *Pneumococcal pneumonia*

The striking association of HIV infection with increased susceptibility for development of bacterial CAP, due in particular to *Streptococcus pneumoniae* (the pneumococcus), is well recognized and has been the subject of several recent reviews [3,34-36]. The risk index increases significantly with advanced disease and associated

immunosuppression, and is further increased when HIV infection is associated with other risk factors.

Clearly, the adaptive immune responses operative against the pneumococcus are extremely vulnerable to HIV-mediated suppression. Foremost among these are: i) the production of IgG and secretory IgA antibodies with opsonophagocytic and adherence-neutralizing properties respectively, directed against capsular polysaccharides; and ii) the generation of CD4<sup>+</sup> T cells of the Th1 and Th17 subtypes which target various protein antigens, resulting in production of the cytokines IFN- $\gamma$  and IL-17A respectively. IFN- $\gamma$  promotes activation of alveolar macrophages and neutrophil influx, while IL-17A promotes recruitment and activation of monocytes and neutrophils [reviewed in 37,38]. In the case of the former, the production and reactivity of capsular antibodies are compromised as a consequence of: i) depletion of CD154-expressing memory helper T cells of the Th1 and Th2 subtypes, which provide help to antibody producing B cells [39]; and ii) loss of antigen-specific memory B cells with advancing disease [3]. Progressive loss of Th1 and Th17 cells results from the mechanisms described in the preceding section.

In addition, HIV-associated neutropenia and monocytopenia, as well as dysfunction of several of the protective activities of these cells, including chemotaxis to bacterial proteins, as well as antimicrobial activity, are potential contributors to predisposition to pneumococcal disease [40,41].

Cigarette smoking may cause further impairment of innate and adaptive immune host defences by compromising the protective activities of the mucociliary escalator, as well as those of alveolar macrophages and pulmonary T cells, underscoring the interactions between HIV infection and smoking in promoting colonization of the airways by the pneumococcus, a prerequisite for future development of invasive pneumococcal disease [reviewed in 42].

These various mechanisms which predispose the HIV-infected to severe pneumococcal disease are shown in Table 2.

### *Haemophilus influenzae*

Although less common than the pneumococcus, *H. influenzae*, usually non-typeable, is a major etiologic agent of pneumonia in the HIV-infected, being most evident in very advanced disease when the total circulating CD4<sup>+</sup> T cell count declines to <100 $\mu$ l/blood [43]. The risk for development of invasive disease is around 100 times higher than that of HIV-uninfected subjects of comparable age [44].

### **Risk factors**

HIV infection is, itself, a risk factor for pneumonia, and the incidence in infected persons is greater than that in non-infected individuals, although the exact mechanism(s) are uncertain [35,45]. While bacterial pneumonia can occur throughout the course of HIV infection the stage of the HIV infection is most consistent [46]. The frequency of CAP has an inverse relationship with the CD4 cell count, occurring most commonly occurs when the CD4 cell count decreases and the median CD4 cell count when pneumonia occurs is said to be 200 cells/mm<sup>3</sup> [1]. It becomes particularly more common in cases with a CD4 cell count below 200 cells/mm<sup>3</sup> [47].

Among the specific risk factors for CAP in HIV infected individuals are cigarette and illicit drug smoking and IVI drug use, cigarette smoking being associated with an increased risk of up to 5-fold [1, 46-48]. Studies have suggested that cigarette smoking is associated with poorer virological and immunological responses to HAART and this may explain, at least partly, why patients on HAART have an ongoing increased risk of pneumonia [34,49,50]. Furthermore, smoking may also accelerate the progression to AIDS [49,51]. Numerous studies attest to the negative impact of cigarette smoking and the positive benefit of smoking cessation [34,35,47,52,53].

Additional risk factors include increased age, increased viral load and previous pneumonia, underlying co-morbid conditions, including alcoholism, cirrhosis, asthma, cardiovascular disease, renal conditions and sickle cell disease, malnutrition and lower socioeconomic circumstances (BOX 1) [46].

Effective control of the viral load has a significant positive impact on the risk of the development of pneumonia [1]. Relatively few reports have documented the impact of HAART on the occurrence of pneumonia [1]. There have been some reports suggesting that HAART does decrease the prevalence, being particularly beneficial in patients with a CD4 cell count below 200 cells/mm<sup>3</sup>, and more effective with continuous rather than intermittent therapy [1,52], but rates of pneumonia in patients on HAART may still be higher than in the general population [35,54,55]. One study documented a persistent high burden of invasive pneumococcal disease in HIV-infected adults, despite a stable prevalence of HIV and an increased roll-out of antiretroviral therapy [56].

## **ETIOLOGY OF COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA**

An etiological diagnosis is obtained in some 35-75% of HIV-infected patients with bacterial CAP [35,46]. In general, the bacterial etiology of CAP is very similar in HIV-infected and HIV-non-infected individuals (BOX 2). Polymicrobial infections do occur and co-infections with the common bacterial pathogens with any of the other opportunistic pathogens, such as *Pneumocystis jirovecii* and even *Mycobacterium tuberculosis*, have been described [57]. Bacteremia is more commonly noted with the bacterial pneumonias and relapses or recurrent infections have also been documented in HIV infected patients [1]. *Streptococcus pneumoniae*.

As is commonly noted, *Streptococcus pneumoniae* is by far the commonest cause of bacterial pneumonia, being implicated in some 20% of cases overall, 40% of cases in which a



microbiological diagnosis is made, and 70% of bacteremic pneumonias [1,46,48]. In several studies, such infections have been associated with an increased risk of bacteremia, and rates of invasive pneumococcal disease have been reported to be up to 100-fold higher than that of non-HIV-infected subjects [3,34-36, 46,48].

While recurrent infections are also commonly noted, there has been some data, although conflicting, suggesting that HAART has not had a major impact on the incidence of CAP, and particularly invasive pneumococcal infections, as indicated elsewhere [1,34]. Thus even in the post-ART era, the risk for development of invasive disease remains extremely high, being about 35-fold higher than that of the HIV-uninfected [3]. There have also been conflicting data on the impact of prior pneumococcal vaccination on subsequent risk for pneumococcal infections [1].

#### *Haemophilus influenzae*

This pathogen is said to account for approximately 10-15% of cases of bacterial pneumonia of known microbiological etiology [1,46]. It is more common among patients with advanced HIV disease and usually presents as a subacute infection [1,58]. Quite commonly, both clinically and on chest radiograph, it presents as a diffuse pulmonary infiltrate [1,58]. The mortality rate is not higher with this form of pneumonia than that occurring in the general population [58].

#### *Staphylococcus aureus*

This pathogen is said to be the third most common cause of bacterial CAP [1], accounting for some 5% of cases [54]. For reasons that are quite obvious, this infection is most common among IVI drug abusers and such infections can be associated with endocarditis, with or without septic pulmonary emboli, even in patients without prior evidence of cardiac valvular disease [1]. Recent viral or influenza infection is also a risk factor for this infection [45]. HIV-infected persons are also at increased risk for community-

acquired methicillin resistant *Staphylococcus aureus* [59]. When infections with *S. aureus* are suspected or proven, specific therapy needs to be initiated, but despite appropriate treatment this infection is associated with a high mortality rate [60].

#### *Gram-negative pathogens*

Gram-negative organisms currently account for approximately 5% of pneumonias in HIV infected persons, and in particular this is due to *Pseudomonas aeruginosa* [46,61]. Both community-acquired and nosocomial pneumonia infections occur in HIV-infected patients, although infections other than pneumonia are also found [61]. In the pre-HAART era, *Pseudomonas aeruginosa* was a not unusual cause of community-acquired bacterial pneumonia, while currently, some studies have suggested that much fewer infections are caused by this microorganism [1,61]. Since pseudomonal infections occur especially among patients with advanced immunosuppression (CD4 cell counts < 50 cells/mm<sup>3</sup>), it follows that after the introduction of HAART, these infections have become much less common [1,51]. The mortality rate for pneumonia caused by this microorganism is higher than that for the other, more common, bacterial pathogens [61,62].

#### *Atypical pathogens*

While *Legionella* infections are said to be relatively uncommon, they appear to occur much more frequently in patients with AIDS, compared to the general population, and may possibly be associated with a more severe clinical course and a worse prognosis [1,63,64]. Infections with *Mycoplasma pneumonia* and *Chlamydomphila pneumoniae* appear to be relatively uncommon causes of pneumonia in HIV-infected individuals, but there are no studies systematically evaluating their exact role [1,45,51].

#### *Other infections*

A number of other, less common, bacterial infections also occur. For example, *Rhodococcus equi* can cause pneumonia in HIV-infected persons, especially in cases with

advanced immunosuppression, and this pathogen typically causes an infection with an indolent course, with clinical and even radiological features (e.g. cavitation) mimicking those of pulmonary (TB) [1,51,65]. For the treatment of both these infections, early initiation of antiretroviral therapy and the use of combination antimicrobial agents is recommended, which needs tapering according to the antimicrobial sensitivity patterns of the cultured isolates [1,65].

*Moraxella catarrhalis* may also cause pneumonia in HIV-infected patients, especially in those cases with a low CD4 cell count and/or coexisting respiratory diseases, and may be associated with considerable morbidity [66]. *Nocardia* is an aerobic actinomycete that can cause infections, including pneumonia, usually in association with immunosuppression, including HIV infection [67,68]. The clinical course is often chronic, although dissemination can occur and be associated with a high mortality [68]. The diagnosis is frequently delayed and a high index of suspicion is required [68]. Treatment with antimicrobial agents with proven synergy is recommended for initial therapy [68].

## **CLINICAL PRESENTATION**

In general, it is said that the clinical presentation of bacterial CAP in HIV-infected patients is similar to that occurring in cases that are not HIV-infected [1,35,45]. Patients usually present with the typical features of a cough productive of sputum, fever, rigors, and chest pain together with focal consolidation(s) in the lung [45]. Clinical differences noted include the fact that more of the cases are female, that the patients are younger, more likely to be drug users, and that they have a higher frequency of respiratory symptoms [69]. Presentation with pneumonia may be the first manifestation of underlying HIV infection occurring particularly in younger patients with pneumonia and no apparent risk factors, HIV infection should be considered [45]. There is a spectrum of disease severities, as in HIV-

uninfected patients, and the commonly used severity of illness scoring indices, such as the PSI and the CURB-65 score, are of equivalent value in predicting severity and/or outcome [48]. The pneumonia most commonly presents as a lobar or segmental consolidation, although patchy consolidation may sometimes occur and occasionally the presentation is as a diffuse reticulonodular infiltrate, particularly in the case of *H. influenzae* infection, that may mimic that of PCP [1,51]. Cavitation may be seen in the presence of *P. aeruginosa*, *S. aureus*, and *R. equi* infections [1,45]. Some studies have indicated a higher prevalence of complicated parapneumonic effusions with either *S. pneumoniae* or *S. aureus* [45].

## **LABORATORY DIAGNOSIS OF PULMONARY INFECTION IN HIV/AIDS**

Although the principles of laboratory diagnosis of pulmonary infection in the setting of HIV/AIDS are based on conventional microbiological, immunological, radiological and histological strategies, interpretation is often complicated in advanced disease with atypical presentation. For example, in the case of HIV/*M.tuberculosis* co-infection, acid-fast bacilli sputum positivity, as well as cavitation and upper lobe infiltrates are less common in patients with severe immunosuppression [70], necessitating the acquisition of more sensitive procedures for the rapid detection of MTB in smear-negative sputum or other body fluids. One of the most promising of these is the GeneXpert MTB/RIF, an automated molecular diagnostic procedure which has a reported sensitivity and specificity for the detection of mycobacterial DNA in sputum of 86% and >97% respectively [71]. IFN- $\gamma$ -release assays (IGRAs) have limited utility in the diagnosis of active TB in HIV-infected patients with advanced disease in a high prevalence setting such as sub-Saharan Africa [72].

In the case of the pneumococcus, second only to *M.tuberculosis* as the major cause of opportunistic pneumonia in the HIV-infected in the developing world [70], confirmation of invasive disease has been improved by the acquisition of improved laboratory diagnostic

procedures. Foremost amongst these are: i) quantitative real-time PCR procedures for the detection of pneumococcal DNA in biological fluids; and ii) the BINAX NOW *Streptococcus pneumoniae* immunochromatographic procedure which detects the C-polysaccharide antigen in urine with good sensitivity and specificity in adult patients with invasive disease [73].

Laboratory diagnosis of opportunistic pneumonia caused by *Pneumocystis jirovecii*, the third most frequently encountered respiratory pathogen in the HIV-infected in the developing world, is based on detection of the organism and/or its DNA using microscopy with specialized stains or molecular procedures respectively [70].

Recently, multiplex, molecular analytical procedures for the detection of bacterial and fungal DNA in biological fluids have become available. However, these are largely untested in the setting of advanced HIV infection in which interpretation may be complicated by the complexity of the lung microbiome, as well as by leakage of microbial nucleic acid from the GIT [3,74].

## **TREATMENT OF BACTERIAL CAP IN HIV INFECTED PERSONS**

There has not been any consensus on an appropriate diagnostic and treatment algorithm for patients with pulmonary infections in HIV infected patients overall [1]. While some have suggested that an aggressive invasive initial diagnostic approach should be followed, it is more commonly recommended that the patients should initially be treated empirically. This should be based on epidemiological evidence, and current clinical, and radiological features together with an aggressive non-invasive diagnostic approach. Thereafter, invasive techniques should be undertaken in patients not responding to initial therapy, in whom the diagnostic workup has not helped [1]. One such approach is illustrated in Figure 1 [75]. While it is commonly recommended that a CD4 cell count should be performed as part of the diagnostic workup and may be helpful in indicating likely microbial

etiology, this is potentially of limited value in that in a number of infections, including pneumococcal pneumonia, a transient and often substantial decrease in the CD4 cell count occurs [1,34,76]. This is reinforced by at least one additional study indicating that the outcome of HIV-infected patients with CAP is not predicted by the CD4 cell count (or even HIV-RNA levels) after adjusting for confounders [77]. However, others have suggested that the CD4 cell count should be considered as a crucial factor in the decision as to whether to admit HIV infected patients with bacterial CAP to hospital (Figure 2) [35].

The treatment of bacterial CAP is said to be similar to that of patients not infected with HIV infection, although no specific guidelines have been developed [1,35,45]. Antibiotic treatment should be directed at the most common bacterial pathogens and be modified according to subsequent microbiological findings [1]. Commonly the treatment recommended is the use of either a beta-lactam-macrolide combination or fluoroquinolone monotherapy [35,45,48]. A large prospective multicenter international observational study of antibiotic treatment in patients with invasive pneumococcal disease (predominantly due to pneumonia), showed a positive impact of combination antibiotic therapy on outcome, even in the subset of patients that were HIV-infected [34]. One consideration with the use of fluoroquinolones in areas where tuberculosis is common is that empiric use of these agents in cases suspected as having CAP, but who actually have tuberculosis, may potentially be associated with masking of the tuberculosis diagnosis and/or development of drug resistance among the tuberculous microorganisms [45].

## **MORTALITY**

While studies have indicated that the mortality of HIV infected patients with bacterial pneumonia may reach 30%, most have indicated that the mortality is in the range of 10-15% [1]. In the post-HAART era, there appears to have been a decrease in the mortality, most

probably due to the fact that infections with certain microbial pathogens (e.g. gram negative microorganisms), have become less common [1]. One area that has been particularly controversial, both in all cause CAP and specifically in pneumococcal pneumonia is whether the outcome is worse in HIV-infected versus HIV-uninfected persons [1]. While some studies have suggested that the outcome is no different [1,78,79], more recent studies in both all-cause CAP and pneumococcal pneumonia have suggested that the mortality of CAP is higher in HIV-infected patients [1,35,69,82]. In one of these studies, which was in patients with bacteraemic pneumococcal pneumonia, when cases were stratified according to age and severity of illness, HIV infected patients had a higher mortality with a significant trend for increasing mortality in those with lower CD4 cell counts [35,69]. For this reason some investigators have suggested that the CD4 cell count should be used as an indicator of the need for hospital admission of cases, as indicated previously [35].

Importantly, both bacterial pneumonia and PCP have been found to be associated with a decline in lung function (as measured by FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC ratio and diffusing capacity of carbon monoxide) that persists following infection [81]. This highlights the importance of the prevention of opportunistic infections in HIV-infected persons.

## **PREVENTION OF BACTERIAL CAP**

### **General measures**

Given the considerable impact of bacterial CAP on HIV infected patients, aggressive strategies should be implemented for the prevention of such infections. This should be a comprehensive approach and include efforts to reduce drug and alcohol abuse, to initiate and assist with smoking cessation strategies, and to either initiate HAART in those fulfilling the criteria for such treatment or HAART adherence support programs for those already on such treatment [48]. These efforts should be combined with appropriate vaccination where this is available.

## **Immunoprophylaxis**

### ***Pneumococcal vaccine***

As mentioned above, those infected with HIV are at extremely high risk for development of invasive pneumococcal disease, which persists, albeit at lesser magnitude, following implementation of HAART. Pneumococcal vaccination strategies are clearly a priority in the setting of HIV infection and the current status of these has been covered in several recent reviews [34-36,38]. In summary, early studies undertaken in various geographical regions in the pre-/early HAART period using the 23-valent pneumococcal polysaccharide vaccine were largely inconclusive with respect to efficacy. More recent studies undertaken in the post-HAART era have, however, established that the timing of immunization, particularly in relation to concomitant HAART, degree of immunosuppression, viral load, and presence of other risk factors, particularly cigarette smoking, is a major determinant of vaccine efficacy [34-36]. According to Hibberd, as reported in “UpToDate,” the current recommendation of the CDC, NIH, and the HIV Medicine Association of the Infectious Diseases Society of America with respect to pneumococcal immunization, is “to administer pneumococcal vaccine to adults and children with CD4 counts of >200  $\mu$ l/blood as soon as HIV infection is diagnosed, providing that they have not had the vaccine during the previous five years” [82,83]. In those with CD4 counts of < 200  $\mu$ l/blood who had been previously immunized, re-vaccination could be considered when the CD4 count increased to 200  $\mu$ l/blood or higher following implementation of ART [82,83]. To sustain efficacy, a single re-vaccination is recommended after 5 years for the HIV-infected [82,84].

Future prospects with respect to improved efficacy of immunization include the development of novel conjugate vaccines which utilize highly-conserved, broadly serotype-unrestricted, recombinant surface and sub-surface pneumococcal protein antigens as carriers



of capsular polysaccharides [37]. Ideally, these should confer much broader coverage than current vaccines in the setting of induction of both cell-mediated (Th1/Th17-based) and humoral protective immune responses [37,38].

### ***Haemophilus influenzae***

Most cases of severe *H.influenzae* infection in HIV-infected persons occurring with advanced immunosuppression involve non-typeable strains of this pathogen [42].

Accordingly, immunization of adults, unlike children, with *H.influenzae* type B (Hib) conjugate vaccine is not recommended [82,83], although this situation may change with the development of novel vaccines based on conserved surface proteins [85]. In the case of children, both HIV-infected and -uninfected, high rates of Hib conjugate vaccine failure have raised concerns about current immunization schedules [86].

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### **Box 1 Risk factors for bacterial CAP in HIV infected patients**

- Cigarette and illicit drug smoking
- IVI drug abuse
- Older age
- Detectable HIV viral load
- Lower CD4 cell count
- Previous pneumonia
- Underlying co-morbid conditions (including cardiovascular, renal disease, respiratory diseases, hepatic cirrhosis, alcoholism)
- Lower socioeconomic status
- Genetic factors?

## **BOX 2 Bacterial etiology of community-acquired pneumonia in HIV infected persons**

- **Most common**
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
- **Not infrequent**
  - *Staphylococcus aureus*
  - *Klebsiella pneumoniae*
- **Less common**
  - Atypical pathogens
- **Uncommon/Unusual infections**
  - *Rhodococcus equi*
  - *Pseudomonas aeruginosa*

**Table 1:** Mechanisms by which HIV-mediated chronic activation of plasmacytoid dendritic cells contributes to dysfunction and depletion of T cells

<u>Mechanism</u>	<u>Consequence</u>	<u>References</u>
Excessive production of IFN- $\alpha$	Apoptosis of CD4 <sup>+</sup> and CD8 <sup>+</sup> T cells	25-28
Increased activity of indoleamine 2,3-dioxygenase	Acquisition of a tolerogenic phenotype with resultant suppression of T cell responses	20
Acquisition of expression of CCR7	Enables migration of HIV-infected, activated plasmacytoid dendritic cells to lymphoid tissue	25
Increased synthesis of the cytokine, transforming growth factor- $\beta$ (TGF- $\beta$ )	Promotes: i) the generation of immunosuppressive CD4 <sup>+</sup> , CD25 <sup>+</sup> , FoxP3 <sup>+</sup> regulatory T cells; and ii) collagen deposition in lymphatic tissues, resulting in disruption of architecture and failure to maintain T cell populations	29-33

**Table 2:** HIV-mediated alterations in innate and adaptive immune mechanisms which predispose to severe pneumococcal disease

<u>Abnormality</u>	<u>Mechanism</u>	<u>References</u>
↓ Production and reactivity of anti-capsular antibodies of the IgA and IgG classes, as well as antibodies to pneumococcal protein surface adhesins	↓ Numbers of Th1 and Th2 effector / memory cells, as well as antigen-specific T cells	37,38
↓ Mobilization and activation of neutrophils / monocytes / alveolar macrophages	↓ Production of IL-17 and IFN- $\gamma$ due to loss of Th1 and Th17 cells, as well as to intrinsic defects in these cells	10,37-40
↓ Production of neutrophils and monocytes in the bone marrow	Dysfunction of progenitor cells	40,41

## **Legend to the Figures**

**Figure 1. An algorithmic approach to the evaluation of hospitalized HIV-seropositive patients with community-acquired pneumonia, based on the chest radiographic features. This needs to be considered in conjunction with the clinical features. (Figure from Feldman C. Bacterial pneumonia in the HIV-seropositive patient. CME 2001; 19: 390-394, reproduced with permission).**

**Figure 2. Proposed flowchart for the management of HIV-infected patients with bacterial community-acquired pneumonia. (Figure reproduced from Maddedu G, Fiori ML, Mura MS. Bacterial community-acquired pneumonia in HIV-infected patients. Curr Opin Pulm Med 2010; 16: 201-207, with permission).**

Figure 1

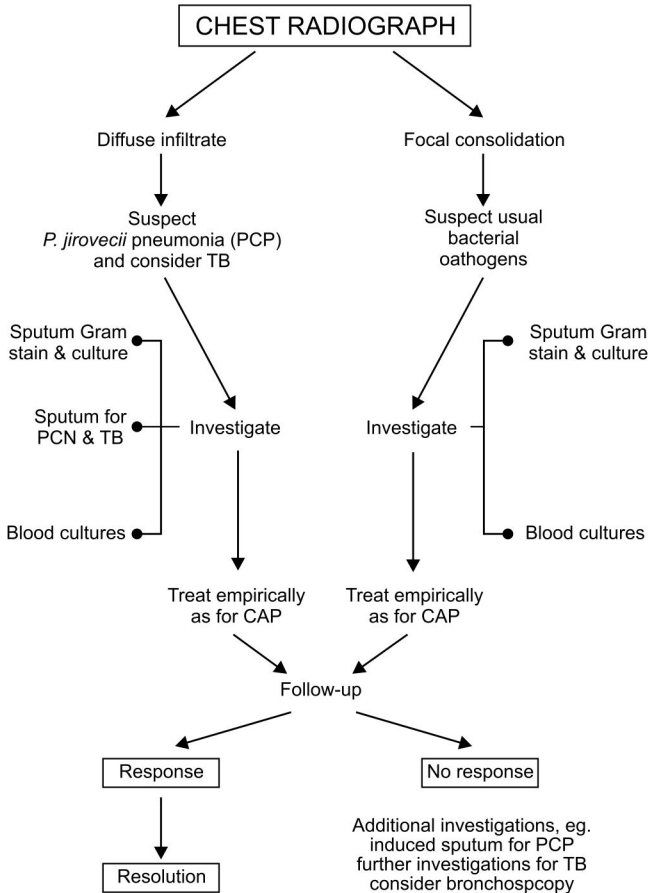
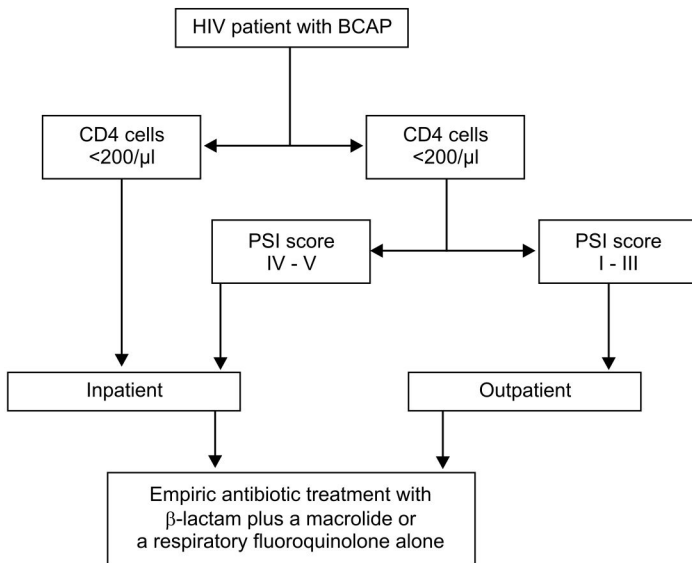


Figure 2



In HIV-infected patients with BCAP, CD4 cell count should be evaluated. Patients with a CD4 cell count of < 200 cells/μl should be always hospitalized, whereas those with a CD4 count of at least 200 cells/μl could be managed according to PSI. Both inpatients and outpatients should start empiric antibiotic therapy with a β-lactam and a macrolide or a respiratory fluoroquinolone alone. BCAP, community-acquired pneumonia; PSI pneumonia severity index.