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Management of Pneumonia in Immunosuppressed States : Malignancies & HIV Infection

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Abstract

The lungs are a common site of infection in patients with cancer and HIV infection. The presentation and management of pneumonia is influenced by factors related to the disease as well as those related to the host. The type of malignancy (solid organ vs. haematological), its status (controlled vs. uncontrolled) and its treatment (administration of chemotherapy and/or radiotherapy) are some of the important malignancy related factors. Host factors include age of the patient, performance status, functional status of body organs and past history of infection. Considering all the above factors, a net risk assessment (NRA) is made in a given patient for determining the overall state of immunosuppression and hence choosing the best form and duration of treatment. In human immunodeficiency virus (HIV) infected individuals, CAP has a 6-25 fold higher incidence. HIV infected patients have higher rates of bacteremia, infection with opportunistic bacterial and non-bacterial pathogens, unusual radiographic abnormalities, complicated parapneumonic pleural effusions/empyema and recurrence. Optimization of anti retroviral therapy, administration of polyvalent pneumococcal vaccine and co-

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trimoxazole prophylaxis are other adjunctive measures that may be considered for reducing the morbidity and mortality associated with CAP in the setting of HIV infection.

Key Words: Pneumonia, malignancy, net risk assessment, human immunodeficiency virus, *Streptococcus pneumoniae*

Management of Pneumonia In Malignancies

Introduction

The lungs are common site of infections in patients with cancer and HIV infection. Hence, understanding the principles of management of pneumonia in these patients would lead to decrease in morbidity and mortality. However, the management issues are complex. The management issues may be related to malignancy per se or pertain to the factors related to patient (Table 1).

Factors Related To Malignancy

Type of Malignancy

Out of most malignancies, haematological malignancies and sarcomas are usually considered aggressive cancers that need aggressive treatment (1). The immune defects are also more common in these types of cancers.

Table 1: Risk-factors for pneumonia in patients with underlying malignancies

1. Quantitative defects in neutrophils (Neutropenia)
2. Qualitative defect in neutrophils (Functional abnormalities)
3. Defects in cellular immunity (disease or drugs)
4. Defects in humoral immunity (disease or drugs)
5. Disruption of physical barriers e.g. central venous lines, urinary catheters
6. Use and misuse of antibiotics, antifungals and antivirals drugs
7. Environmental factors
8. Overcrowded wards, inpatient and outpatient management
9. Co-morbidities e.g. Diabetes, Coronary heart disease, past tuberculosis etc.

Cancer is controlled or uncontrolled

Generally, the outcome of bronchopneumonia in a patient whose cancer is under control is better than in a patient whose cancer is uncontrolled.

Patient on Chemotherapy and or Radiotherapy

Pneumonia has a worse outcome if it develops during the time when patient is receiving chemotherapy. This is because the body is immune-suppressed during the time of chemotherapy (2). Most chemotherapies lead to decrease in white cell count as their side effect. Neutrophils are the primary defence against microorganisms in the body. The risk of infection becomes greater when absolute neutrophil count is below 500/ mm^3 and greatest if the ANC is less than 100/mm^3. The risk of infection also depends on the duration of neutropenia. In the initial period, the risk of bacterial infections is high, however, as the duration of neutropenia become prolonged, the risk of fungal infections also increases. A rapid decline in neutrophil again is an additional risk. Chemotherapy can also lead to functional defect in the neutrophils (Table 1).

Repeated courses of chemotherapy lead to decrease in the immunoglobulin levels (especially the IgG and IgA) that remain depressed for a considerable period of time depending upon the type of chemotherapy used.

Radiotherapy also leads to predisposition of body to infection. The factors related to radiotherapy are dose and duration of radiation.

Factors Related To Patient

Type of pneumonia and its management also depends upon the factors that are related to patient. These factors are age of the patient, performance status of patient, functional status of body organs and past history of infection. Older patients are more prone for complications following pneumonia if they have any underlying malignancy. Similarly if the performance status of the patient is low, there are lower chances of successful outcome of treatment. Co-morbidities in patients with cancer are considered additional risk factors that add complexities to the management. These co-morbidities may be presence of diabetes, coronary heart disease, hypertension, parkinsonism, neuropathy etc. Past history of recurrent infections also predisposes the patient for future risk of infections. Recurrent chest infections lead to structural lung damage and bronchiectasis.

Net Risk Assessment

Considering all the above factors, a net risk assessment (NRA) is made in a given patient for choosing the best form of treatment and duration of treatment. Net risk assessment takes into account all the variables in a given patient (related to cancer or related to patient himself) and helps in making treatment decision (tables 1 and 2).

Investigations

The investigations are directed towards making a diagnosis of pneumonia and its management (Table 2) (3). Besides taking into account the usual parameters for admission of patient with pneumonia, the other factors that help in immediate decision making consists of whether the malignancy is controlled or uncontrolled, whether patient is on chemotherapy and if yes when did he receive his last dose of chemotherapy. In uncontrolled cancer, the chances of success of treatment are low (vide supra). The importance of knowing the first day of chemotherapy is to assess for neutropenia which is perhaps the most important parameter in deciding about the choice of antibiotics and admission of patient into the hospital. Absolute neutrophil count of below 500/ mm^3 poses the greatest risk to the patient and one has to consider possibility of fungal pneumonia early in the course of treatment if patient is not responding to broad spectrum antibiotics. The other tests for diagnosis of pneumonia have already been highlighted in different presentations.

Treatment

The general guidelines for treatment of bronchopneumonia apply here. However, as has already been

Table 2: Pulmonary infiltrates on radiological investigations in cancer patients

Parenchymal
Acute Bacterial Pneumonias
Subacute/Chronic (Tuberculosis, Fungal, Neoplasm)
Interstitial
Acute Pulmonary Oedema, Diffuse alveolar haemorrhage, Viral Pneumonias, Mycoplasma Pneumonia, Pneumocystis jirovecii
Subacute/Chronic (Tuberculosis, Nocardia)

highlighted, unusual organisms do occur in patients with underlying malignancies and one has to be aware of that while deciding treatment. In neutropenic patients, gram positive organisms are the main culprit especially if patient has central lines *in situ*. The spectrum of gram positive to gram negative organisms infections is ever changing and one has to consider the local flora and type of infections occurring in their hospital environment before deciding empiric antibiotics (4). If neutropenia is prolonged and severe, fungal infections especially the Aspergillus species are common cause for fungal pneumonia. Zygomycosis is another emerging cause of pneumonia especially in patients who are on prophylactic antifungal therapy with voriconazole. In these patients, amphotericin B is the treatment of choice.

Patients with impaired cell immunity due to lymphoproliferative disorders or due to high-dose corticosteroid therapy have different spectrum of infections as compared to patients who have only neutropenia. Patients with impaired cellular immunity are more prone for infections with Nocardia, Pneumocystis jirovecii, Legionella and tuberculosis and viral infections with cytomegalovirus, influenza, respiratory syncytial virus etc. Co-trimoxazole is given for the treatment of Nocardia and Pneumocystis pneumonia. Gancyclovir is the treatment of choice for CMV pneumonia.

Patients with impaired humoral immunity (post splenectomy, multiple myeloma, chronic lymphocytic leukaemia etc.) are susceptible to infections caused by encapsulated organisms such as *S. pneumoniae* and *H. Influenza*. Penicillins are the drug of choice in this group of patients.

More often than not several immune defects exist together in a given patient and treatment decision covering all these aspects has to be taken in an emergency situation. However, a detailed assessment after stabilisation of patient and de-escalation of therapy can be done based on above-mentioned parameters.

Finally non-infectious causes of pneumonia have to be considered in patients with malignancies. Pulmonary haemorrhage can occur because of coagulopathy or thrombocytopenia. Many of the chemotherapeutic drugs such as busulphan, melphalan etc. can cause pulmonary infiltrates mimicking pneumonia. Radiation injury after several weeks may produce radiation induced pneumonitis. Lastly infiltration by neoplasm into the lung parenchyma itself can mimic pneumonia.

Some of the special treatment consideration in patients with malignancies consists of post obstructive pneumonia because of lung neoplasm or metastasis. Patients with brain tumours can have loss of gag reflex leading to aspiration pneumonia. Radiation can lead to loss of ciliary function further predisposing the patient to aspiration pneumonia.

Prevention

Patients with malignancies are in a state of immunosuppression as already stated. Taking good care of personal hygiene, drinking boiled water in our country, eating cooked food and avoiding contacts with persons having infections are some of the measure that can be taken at patient level. The role of prophylactic antibiotics, antifungals and antivirals in these patients generates considerable discussion and controversies (5). Primary prophylaxis with antibiotics, antifungals and antivirals is considered when patient is at a high-risk of getting these infections. Secondary prophylaxis consists of when patient already had an episode of infection and prophylaxis is given for prevention of future risk of infections. Briefly both primary and secondary prophylaxis can be considered in high- risk situations such as patients undergoing high-dose chemotherapy and stem cell transplant. In all other situations, physicians have to follow a balanced approach in deciding about the prophylaxis in the best interest of the patient.

Community Acquired Pneumonia In Patients With HIV Infection

Epidemiology

Community acquired pneumonia (CAP) is a common cause of morbidity in individuals infected with the human immunodeficiency virus (HIV). Incidence of CAP in HIV infected individuals is 6-25 fold higher than those not infected (6). CAP is frequently the first clinical manifestation of HIV infection. Despite the use of extensive testing, no organism may be identified in as many as one third-two third of cases of HIV-related CAP (7).

Among patients in whom lower respiratory tract symptoms predominate, the common etiological agents include: *S. pneumoniae* (28%), *Mycobacterium tuberculosis* (26%), *Klebsiella pneumoniae* (27%), *Pneumocystis jirovecii* (15%). On the other hand, those in whom upper respiratory tract symptoms predominate, *S. aureus* (15%), coagulase negative staphylococci (11%), streptococci (11%) and *Moraxella catarrhalis* (12%) are commonly responsible (8).

The incidence and the severity of bacterial lower respiratory tract infections (LRTIs), including the CAP increase in HIV infected patients as the CD4 lymphocyte count declines (Table 3).

Diagnosis

There are certain differences in the clinical presentation of bacterial CAP in HIV positive and negative individuals (9). HIV infected patients tend to have:

- Higher frequency of bacteremia
- Higher rate of unusual radiographic abnormalities
- Higher rate of parapneumonic pleural effusions (PPE) including a significantly higher rate of complicated PPEs and empyema. *S. aureus* is the most common microorganism isolated from pleural fluid and blood cultures (10).
- Higher incidence of opportunistic bacteria

Table 3: Common etiological agents for LRTIs at different levels of CD4 count

CD4 Count	Level of immune suppression	Common infectious agents
>500 cells/μL	Very mild impairment	Encapsulated bacteria
		M. tuberculosis
200-499 cells/μL	Mild impairment	Encapsulated bacteria
		M. tuberculosis
<200 cells/μL	Moderate impairment	Bacteria
		M. tuberculosis
		Pneumocystis jirovecii
<100 cells/μL	Severe impairment	Bacteria
		M. tuberculosis
		Pneumocystis jirovecii
		Non tubercular mycobacteria
		Fungi
		Cytomegalovirus (CMV)

Risk factors for hospitalization due to CAP (11) include:

- Prophylaxis with fluconazole in the recent past – reduced risk
- Prophylaxis with co-trimoxazole (protective) in the recent past – reduced risk
- Breathing chemical irritants in the recent past – increased risk
- Hospitalized for pneumonia in the preceding six months – increased risk
- Tobacco smoking: HIV-infected smokers are twice as likely to be hospitalized with CAP as non-smokers. The increased risk exists in a dose-dependent manner and is independent of the administration of HAART and antimicrobial prophylaxis (12).

Investigations include total and differential white cell count, sputum Gram stain and culture and blood culture. Further evaluation is generally warranted in case of clinical and/or radiological deterioration or absence of clinical improvement and this holds true even if = 1 bacteria as etiological pathogen(s) have been identified. The additional investigations that may be helpful under such circumstances include detection of *Legionella pneumophila* antigen in urine, IgM and IgG serology for *M pneumoniae* and *C pneumoniae*, high resolution computed tomography (HRCT) scan, bronchoscopy and bronchoalveolar lavage (BAL) with/without bronchoscopic lung biopsy (BLB). Depending upon the level of CD_4 count and clinical scenario, one may need to carry out a work up aimed at diagnosing Pneumocystis pneumonia (PCP), pulmonary tuberculosis (PTB) or non tubercular mycobacterial (NTM) disease as well as other oppoprtunistic infections since the latter may coexist with bacterial CAP (13).

Induced sputum, when compared with BAL/BLB as gold standards, has a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of approximately 60%, 40%, 80%, 20% and 56% respectively for the diagnosis of bacterial CAP in the HIV infected at a cut-off value of 10^6 colony forming units (CFU) per mL in quantitative cultures (14).

In comparison to plain chest radiographs (CXR), HRCT scans of the thorax can demonstrate parenchymal lesions that are not visualized on CXR and the discrepancy can be as high as 82%. Among patients in whom a microbiological diagnosis was established later, a correct diagnosis of bacterial CAP could be made in 84% of cases after a HRCT scan (15). A CT scan

can also identify mediastinal and pleural abnormalities that may not be apparent on CXR. Imaging findings of bacterial CAP in HIV infected individuals are similar to those in immunocompetent patients. The most common pattern is again that of single/ multifocal consolidation (16). Classically lobar consolidation has been related to infection by *Streptococcus pneumoniae*. A lobular pattern characterized by the presence of centrilobular nodules, tree-in-bud abnormalities and patchy consolidation has been described as "bronchopneumonia" and the common bacteria that have been related to such a presentation include *Staphylococcus* spp., *Streptococcus* spp., *Pseudomonas* spp., *Klebsiella* spp. and *Haemophilus* spp. (Table 4).

In a prospective study on the profile of pulmonary infections in 300 newly diagnosed HAART- naive HIV patients at this institute, pulmonary symptoms and abnormal chest radiographs were observed in 33 (11%) and 44 (14.6%) patients respectively (Table 5) (17). PTB and tubercular

Table 4: Important radiological findings of common pulmonary infections in HIV infected individuals

Infection	CD4 Count	Symptom duration	Parenchymal abnormalities	Lymph-adenopathy	Pleural Effusion
Bacterial	None	≤ 7 days	Focal consolidation	Rare	Common
PCP	<200 cells/μL	≅ 30 days	Bilateral, symmetrical interstitial; GGO on CT	Absent	Absent
MTB	None	> 7 days	CD4 >200: cavitation CD4 <200: consolidation	CD4 >200: common	Rare
NTM	<100 cells/μL	Variable (> 7 days)	Patchy consolidation; Bronchiectasis + nodules	Common	Rare
Fungal	<100 cells/μL	Variable (> 7 days)	Reticular and nodular opacities	Common	Common
CMV	<100 cells/μL	Variable (> 7 days)	GGO, consolidation, nodules	Rare	Rare

PCP = Pneumocystis pneumonia, MTB = Mycobacterium tuberculosis, NTM = Non tubercular mycobacteria, CMV = Cytomegalovirus, GGO = Ground glass opacification

Table 5: Profile of pulmonary infections in HIV infected patients observed at the PGIMER, Chandigarh

	Number (%)
Pulmonary Symptoms	**33**
• Cough	27 (81.8)
• Dyspnea	14 (42.4)
• Sputum	11 (33.3)
Abnormal CXR findings	**44**
• Consolidation	12 (27.3)
• Pleural effusion	8 (18.2)
• Hilar adenopathy	7 (15.9)
• Miliary nodules	5 (11.4)
Patient Groups	**Mean (SD) CD4 Count**
• Asymptomatic	245.1 ± 125.9 cells/μL
• Tuberculosis	117.1 ± 104.5 cells/μL
• Bacterial pneumonia	51.0 ± 40.3 cells/μL
• PCP	66.9 ± 33.9 cells/μL
• Cryptococcal infection	36.5 ± 25.6 cells/μL

CXR = Chest X Ray (chest radiograph), SD = Standard Deviation,
PCP = *Pneumocystis jirovecii* pneumonia

pleural effusion were diagnosed in 19 and 6 patients respectively. Sputum and BAL/BLB staining yielded the presence of acid fast bacilli (AFB) in 10 (52.6%) and 5 (26.3%) patients with PTB. The diagnosis of PCP was made in 87.5% patients on the basis of BAL/BLB. The mean CD4 count differed significantly ($p<0.001$) between asymptomatic patients and those with different pulmonary infections (Table 5).

Treatment

The principles of treatment remain the same as for HIV-uninfected patients. Generally the most common pathogens especially pneumococcus should be targeted. The preferred choice of antibacterial agents consists

of a combination of a β-lactam [extended-spectrum cephalosporin (ceftriaxone or cefotaxime)] with a macrolide [azithromycin, clarithromycin]. As an alternative to macrolides, a fluoroquinolone with anti-pneumococcal activity like levofloxacin, moxifloxacin or gemifloxacin may be used. However, this should be done only if pulmonary tuberculosis is not a diagnostic consideration. Wherever possible, the agents used should be selected on the basis of available sensitivity results. For individuals with a CD4 count <100 cells/μL, prior history of *P. aeruginosa* infection or neutropenia, consider broader coverage for Gram negative bacilli including *Pseudomonas* spp. Clinical improvement is expected in 48-72 hours after initiation of appropriate therapy. As mentioned earlier, in case of worsening symptoms/signs/radiology or no clinical improvement, further evaluation is required and pending additional diagnostic testing, one should consider addition of broader spectrum antimicrobials.

One of the most important aspects of treatment of CAP in the setting of HIV infection is prevention of recurrence and this can be achieved in the following ways:

- **Optimization of ART**: This remains the key to reducing secondary infections and the morbidity as well as mortality related to them in HIV infected individuals. Improvement in immune function can resolve or lessen the severity of certain infections.
- **23-valent pneumococcal vaccine**: It is indicated for adults and adolescents with a CD4 count of more than 200 cells/μL, if not given in the preceding five years.
- **Prophylactic antibiotics**: Frequent and serious bacterial LRTIs and CAP are considered by some to be an indication for the use of prophylactic antibiotics. Use of co-trimoxazole is associated with a reduction in the incidence of bacterial infections also. However, concerns regarding promotion of drug resistance remain unanswered, as of now.

Outcome

HIV-infected patients with CAP are more likely to present with severe symptoms but they tend to respond similarly to non infected patients and have similar short term mortality rates as the latter (18). In a case-control study, HIV patients admitted for CAP had longer hospital length of stay (LOS) and higher in-hospital and one year

mortality rates in comparison to matched controls (19). However, in another case-control study involving patients with a mean CD4 count of less than 200/μL, no differences were observed in the time to clinical stability, hospital LOS or mortality (20). Furthermore, in a prospective study of patients with a mean CD4 count of 153/μL, the in-hospital mortality was lower in those with HIV infection (15.7% vs. 26.7%) (21).

A staging system for predicting mortality in HIV-associated CAP has been developed. It is based on presence/absence of neurologic symptoms, respiratory rate and serum creatinine. This staging system has five categories and the mortality rates increase from 2.3% for patients falling in the first category (least sick) to 40.5% for those in the last category (sickest). The overall accuracy of this system is approximately 85% (22). Additional predictors for mortality include presence of CD4 cell count <100/μL and presence of pleural effusion or cavitation on CXR (23).

Despite similar short-term mortality rates, CAP in HIV infected patients may be associated with high rates of recurrence. The latter is true for both common and uncommon/opportunistic bacterial pathogens (9). Moreover, long term mortality is higher in HIV infected patients with CAP in comparison to non HIV infected. This has been attributed to the fact that occurrence of CAP leads to enhanced local and systemic replication of HIV and thus an acceleration in the progression of HIV disease. Infact, bacterial CAP especially if it is recurrent or severe, is itself a marker of severe degree of immune suppression.

Conclusions

Lungs are the commonest site of infections in patients with cancer and HIV infection. While managing pneumonia in these patients, one has to have the high index of suspicion, consider the overall state of immunosuppression and make net risk assessment. Lastly one should not forget the non-infectious cause of pneumonia in these patients. In HIV infected individuals, bacterial LRTIs including CAP are the most frequent respiratory diseases. The presentation, management and short-term outcome is similar to non infected patients if appropriate and prompt treatment is initiated. Higher recurrence rates and lower long term survival may be altered with optimal HAART.

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