Prevention of Community-Acquired Pneumonia in Special Situations: Chronic Lung Diseases

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Common chronic lung diseases include chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, interstitial lung diseases, sarcoidosis, pulmonary hypertension, and cor pulmonale. Patients with chronic lung diseases are at two- to four-fold risk of community-acquired pneumonia (CAP) as compared to controls.¹

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is characterized by persistent and usually progressive airflow limitation, associated with enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.² Estimated global prevalence of COPD is 7.6%; prevalence in India is reported to be 6.5 to 7.7%.³,⁴ Chronic obstructive pulmonary disease is expected to become the third leading cause of mortality worldwide by 2030. It is important to note that almost 90% of deaths due to COPD occur in low- and middle-income countries.⁵

Patients with COPD are at an increased risk of CAP. At least one-third of patients hospitalized with CAP have COPD as comorbidity. Also, CAP has been associated with increased 30-day and 90-day mortality in patients with COPD.⁶ The risk factors for CAP in COPD include age ≥ 55 years, forced expiratory volume in 1 s (FEV₁) < 50% predicted, history of exacerbations in the prior year, worse Medical Research Council dyspnea scores, and body mass index < 25 kg/m²;⁷ activeness smoking and male gender are other reported risk factors.⁸ The use of inhaled corticosteroids (ICS) has emerged as another important modifiable risk factor for CAP in COPD, however, with paradoxically decreased mortality.⁹

Preventive Strategies

Vaccination remains an important mode of prevention of infective exacerbations. Influenza vaccination has been associated with significant reduction in influenza-related acute respiratory illness with overall vaccine effectiveness of 76%, without any significant differences with respect to age, gender, severity of obstruction, smoking status, or comorbidities. Numerically lower (not approaching statistical significance) rates of hospitalization and mechanical ventilation have also been observed.¹⁰

Pneumococcal vaccination has shown clinical efficacy in preventing CAP in COPD in subgroup with age less than 65 years, and those with severe obstruction in a randomized controlled trial. No differences, however, have been found among the other groups of patients with COPD.¹¹ In another study, however, there was a borderline significant reduction of 30% in the risk of all-cause hospitalization for CAP with pneumococcal vaccination [hazard ratio (HR): 0.70; 95% confidence interval (CI): 0.48–1.00; p = 0.052].¹² In a recent systematic review, pneumococcal vaccine did not increase the time to first episode of CAP and did not show significant reduction in hospital admission, length of hospital stay, or mortality. However, it was found to be effective in subgroup of COPD patients with age less than 65 years (p = 0.009), and severe obstruction (p = 0.04). For patients who were less than 65 years of age (FEV₁ < 40% predicted), vaccine effectiveness was 91% (95% CI: 35–99; P = 0.002). Also, there was significant decrease in the incidence of pneumococcal pneumonia.¹⁰

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest vaccination with both pneumococcal and annual influenza vaccination in all patients with COPD subjected to local guidelines, availability, and affordability.³ The Indian guidelines on COPD recommend pneumococcal and annual influenza vaccination in severe COPD with frequent exacerbations.¹³

Inhaled corticosteroids should be offered to patients with severe and very severe COPD and frequent exacerbations (i.e., GOLD class C and D) that are not adequately controlled by long-acting bronchodilators.² It is important not to prescribe ICS outside their indications to minimize the risk. Available evidence suggests intraclass differences of ICS regarding the risk of CAP.¹⁴ Thus, if required, budesonide or fluticasone furoate may be preferred to fluticasone propionate, till further evidence becomes available. As per the GOLD guidelines, ICS should be stopped if patients develop repeated pneumonias on ICS “to see whether this medication could be the cause of repeated infections”.² Insights into phenotypic management of COPD¹⁵ may be used to rationalize ICS usage in COPD to minimize the risk of CAP.

Using prophylactic macrolide therapy has been demonstrated to decrease the risk of COPD exacerbation, without specific reference to pneumonia prevention.¹⁶ In a recent randomized controlled trial, chronic azithromycin usage had numerically fewer incidence of pneumonia as compared to controls (26 vs. 41; p = 0.11).¹⁷

As smoking itself predisposes to CAP,¹⁸ patients should be advised for smoking cessation at every visit. Other non-pharmacologic measures include good nutrition, clearance of secretions (if associated bronchiectasis), respiratory hygiene measures, and optimal treatment of comorbidities (such as diabetes mellitus).

Asthma

Asthma is defined as a chronic inflammatory disorder of the airways, which manifests itself as recurrent episodes of wheezing, breathlessness, chest tightness, and cough. It is characterized by bronchial hyper-responsiveness and variable airflow obstruction, that is often
Individuals with asthma have been observed to be at a greater risk of CAP and invasive pneumococcal disease. Also, rhinovirus and influenza infections have been associated with exacerbations of bronchial asthma. In contrast to COPD, there is no clear evidence of increase in the incidence of pneumonia with ICS use.

When asthma patients acquire viral infections, an asthmatic response is induced, which may ultimately lead to bacterial infections. Most of these infections are caused by *Streptococcus pneumoniae* or *Pneumococcus*. *Streptococcus pneumoniae* is a T cell-independent antigen, and T cells are reported to play a role in the immune response to *S. pneumoniae*.

A study of the response to *S. pneumoniae* in cells from atopic asthmatic children found a significantly lower production of tumor necrosis factor (TNF)-α and a significantly higher production of interleukin (IL)-5 in asthma patients compared to healthy individuals. However, IL-4, IL-13, or IL-10 showed no difference. Cells of asthmatic patients demonstrated a greater early activation response against *Mycobacterium tuberculosis* than *S. pneumoniae*, and this may explain the frequent development of *S. pneumoniae* infections in asthmatic patients.

Preventive strategies

Optimal use of ICS, and utilization of the least effective dose for asthma control and limiting long-term use of systemic steroids are other potential measures to decrease the risk of CAP in these patients.

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends that adults aged 19–64 years with chronic lung disease (including asthma) should be administered PPSV23. Those aged 65 years and above should be given PCV13 at least 1 year after PPSV23, followed by another dose of PPSV23 at least 1 year after PCV13 and at least 5 years after the last dose of PPSV23.

A joint consensus document by various Spanish societies also recommends the use of PCV13 in chronic respiratory diseases, such as COPD, asthma, and interstitial lung disease.

**Bronchiectasis**

Bronchiectasis, characterized by permanent and abnormal widening of the airways, is associated with increased frequency of ambulatory visits, antibiotic usage, chest computed tomography, and hospitalization. Viruses, such as respiratory syncytial virus (RSV) and influenza have implicated as frequent causes of exacerbations in cystic fibrosis (CF). Pneumococci are infrequent causes of exacerbations in CF, yet it is important to note that most data are from countries with universal provision of pneumococcal vaccination. In one study, 17% to 39% of non-immunized CF patients did not have protective titers against pneumococci.

Patients with non-cystic fibrosis bronchiectasis (NCFB) are predisposed to infective exacerbations and pneumonia due to structural lung disease and ongoing inflammation. However, limited literature is available on the topic. Predisposing factors for CAP in NCFB include older age, ICS use. *Streptococcus pneumoniae* followed by viral and mixed infections has been reported as the most common cause of CAP in these patients, along with increased frequency of *Pseudomonas* and enterobacteriaceae. Respiratory viruses, including coronaviruses, rhinovirus, and influenza have been shown to play a crucial role in bronchiectasis exacerbations.

Post infective or post tubercular pleuroparenchymal fibrosis, another important subgroup in tuberculosis endemic countries, also predisposes to CAP. The responsible organisms are somewhat similar to NCFB.

Preventive strategies

Though there are no randomized trials or prospective studies demonstrating benefit in CF, pneumococcal vaccination is recommended in view of favorable risk benefit profile.

Annual influenza vaccination is also recommended using injectable inactivated vaccine based on efficacy in other populations. Palivizumab, a humanized monoclonal antibody against RSV, has conflicting efficacy in preventing serious RSV infection in high-risk patients; more evidence is required before recommending its use.

Regular pneumococcal and influenza vaccination has been shown to have mortality benefit in patients with NCFB.

Other interventions in bronchiectasis which decrease infective exacerbations include clearance of secretions, optimal bronchodilation, eradication of bacterial colonization, chronic inhaled antibiotics, and anti-inflammatory therapies.

**Interstitial Lung Diseases**

Though there is sparse data regarding the risk of CAP in interstitial lung diseases (ILDs), patients of ILDs, including idiopathic pulmonary fibrosis, non-specific interstitial fibrosis, connective tissue disorder-related ILDs, sarcoidosis, hypersensitivity pneumonitis are at an increased risk of invasive pneumococcal infections, including pneumonia. Prolonged immunosuppression is another risk factor predisposing these patients to infections. These patients have more than two-fold hospital mortality with CAP as compared to controls, underlining the importance of optimal preventive strategies. Pulmonary arterial hypertension, though not per se associated with increased mortality in CAP, does predispose to complications of pneumonia such as congestive cardiac failure and myocardial infarction.

**Preventive strategies**

As most of the patients with ILDs remain on long-term immunosuppressant, they should be considered at high risk for infective complications, including pneumonia and should be vaccinated accordingly.

Prophylactic use of cotrimoxazole has been associated with decrease in respiratory tract infections and all-cause mortality in fibrotic ILD patients, albeit with significant drug-related adverse side-effects. Other strategies to decrease the risk of pneumonia include judicious use of systemic steroids or other immunosuppressants.

Treatment with immunosuppressants puts ILD patients at an increased risk of infections. Hence, these patients should be given a pneumococcal vaccine and a yearly influenza virus vaccine. In addition, patients should be encouraged to practice good hand hygiene (e.g., frequent hand washing);
use of masks or special antibacterial products is not required.  

Pneumocystis prophylaxis is recommended for patients treated with certain specific immunosuppressive agents. 

As stated above, the use of PCV13 has been recommended in chronic respiratory diseases, including interstitial lung disease, by various Spanish societies. 

Sleep-related Breathing Disorders

Though there is obesity survival paradox in CAP, obstructive sleep apnea has been shown to increase the risk of incident pneumonia, and poses a higher risk in patients receiving continuous positive airway pressure (CPAP) therapy. Possible mechanisms include immune dysfunction related to insufficient sleep, hypercapnia-induced impaired neutrophil function, decreased expectoration due to drying of secretions with CPAP, and impaired immunity. Optimal management of primary disease, selection of appropriate vaccines (13 or 23 valent PSV) depending upon age and comorbidities, timely booster dosing (5 years or later, or 13 followed by 23 valent PSV for *Pneumococcus*), annual influenza vaccination, judicious use of inhaled or systemic steroids and immunosuppressive drugs, and other non-pharmacologic measures like cough hygiene and clearing of secretions are important factors in the prevention of pneumonia and infective exacerbations.

General recommendations of ACIP about schedule of pneumococcal vaccines in adults: 

- PCV13 should be given as the first dose. 
- If PPV23 has already been given, give PCV13 after at least 1 year. 
- Give PPSV23 at least 1 year after PCV13, except among adults with immunocompromising conditions, anatomical or functional asplenia, cerebrospinal fluid leak, or cochlear implant, for whom the interval should be at least 8 weeks; the PPSV23 doses should be spaced at least 5 years apart. 
- No need to give additional dose of PPSV23 to adults who have received PPSV23 at or after the age of 65 years. 
- When both PCV13 and PPSV23 are indicated, give PCV13 first; do not give PCV13 and PPSV23 on the same visit. 
- If pneumococcal vaccination history is incomplete or unknown, give PCV13 and PPSV23 when indicated.

**References**

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**Preventive strategies**

Interventions to prevent CAP in this subgroup should include lifestyle modifications, CPAP therapy with optimal humidification, proper cleaning and disinfection of CPAP and humidifier circuits, and being vigilant about schedule of pneumococcal vaccination. In patients with COPD, PCV13 should be given only once, and PPSV23 is not required. If PPV23 has already been given, give PCV13 at least 1 year after PPV23, while in patients who have received PPSV23 at or after the age of 65 years, only PPV23 is recommended. The interval between PCV13 and PPSV23 should be at least 5 years, and the same visit should be avoided in order to prevent complications of pneumococcal infection.

**Conclusion**

Patients with chronic lung diseases are at an increased risk of pneumonia and probably greater mortality. Infections lead to worsening of primary disease, which again predisposes to infections, thus initiating a vicious cycle. Greatest risk factors for community-acquired pneumonia in adults in Europe: A literature review. *Thorax* 2013; 68:1057–65.

7.  Crim C, Calverley PM, Anderson JA, et al. Infections lead to worsening of primary disease, which again predisposes to infections, thus initiating a vicious cycle. Greater body of literature regarding the risk of pneumonia and preventive strategies is available for COPD and asthma. There is limited literature on risk and preventive measures in subgroups of chronic lung diseases, like bronchiectasis, pulmonary arterial hypertension, and sleep-related breathing disorders. Patients with chronic lung diseases on prolonged immunosuppression are at a higher risk due to both structural defects and impaired immunity. Optimal management of primary disease, selection of appropriate vaccines (13 or 23 valent PSV) depending upon age and comorbidities, timely booster dosing (5 years or later, or 13 followed by 23 valent PSV for *Pneumococcus*), annual influenza vaccination, judicious use of inhaled or systemic steroids and immunosuppressive drugs, and other non-pharmacologic measures like cough hygiene and clearing of secretions are important factors in the prevention of pneumonia and infective exacerbations.

**Preventive strategies**

Interventions to prevent CAP in this subgroup should include lifestyle modifications, CPAP therapy with optimal humidification, proper cleaning and disinfection of CPAP and humidifier circuits, and being vigilant in cases of recurrent pneumonia.

Vaccination has not been studied in sleep-related breathing disorders per se, yet should be considered if these patients have comorbidities or other indications for the same. Pneumococcal vaccination is recommended for patients with chronic lung diseases by various respiratory societies, such as the GOLD, Joint Indian Chest Society (ICS) and National College of Chest Physicians (NCCP), Swiss Respiratory Society, National Institute for Health and Clinical Excellence (NICE) guidelines, British Columbia Medical Association (BCMA), etc.

**Conclusion**

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