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Community-Acquired Pneumonia in Patients with Chronic Obstructive Pulmonary Disease

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Abstract Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Patients with COPD are at increased risk for community-acquired pneumonia (CAP). COPD has been reported as a comorbidity in at least one third of the hospitalized patients with CAP. There is a controversy that the presence of concomitant COPD and CAP is associated with a greater risk of death when compared to either condition alone. Risk factors, clinical and immunological characteristics, microbiological etiology, as well as prognosis and treatment of COPD patients with CAP are reviewed in this article.

Keywords Chronic obstructive pulmonary disease · Community-acquired pneumonia

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways. The prevalence and burden of COPD are projected to increase in the coming decades due to continued risk factors and the changing age structure of the world's population [1]. Community-acquired pneumonia (CAP) is an acute infection of the lung parenchyma in a patient who has acquired the infection in the community. CAP occurs commonly in patients with COPD. In a multivariate analysis, COPD was an independent risk factor for developing severe CAP, with an odds ratio (OR) of 1.91 [2]. A cohort of COPD patients aged ≥45 years consisted of 40,414 adults who showed an incidence rate of 22.4 (95 % confidence interval (CI) 21.7–23.2) of CAP per 1000 person-years [3••]. In another cohort of COPD patients monitored over 3 years, the incidence of pneumonia was 55.1 per 1000 person-years [4]. Seventy-six episodes (86.3 %) were CAP, and 12 (13.6 %) were acquired in the hospital. Elderly with COPD had nearly six times the incidence of pneumonia compared with elders without COPD (167.6/1000 vs 29.5/1000 person-years; relative risk (RR)=5.7, $p<0.01$) [5]. The RR increased to 8.1 for elderly with COPD and congestive heart failure compared with elderly without COPD. COPD is also frequent among CAP patients. COPD as a comorbidity is reported in 35 to 50 % of hospitalized patients with CAP [6].

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Clinical Characteristics and Risk Factors

Patients with COPD have an increased risk of pneumonia, but data are limited on the disease phenotypes most susceptible to pneumonia. In the large TORCH study, risk factors for pneumonia were age ≥55 years, forced expiratory volume <50 % predicted in 1 s, COPD exacerbations in the year prior to the study, worse Medical Research Council dyspnea scores, and body mass index <25 kg/m^2 [7]. In a US cohort, pneumonia hospitalization risk was associated with older age, male gender, comorbid conditions, smoking status, and an impaired level of lung function [8]. Overall, people with normal lung function had the lowest pneumonia hospitalization rate (1.5 per 1000 person-years) and those with Global Initiative for Obstructive Lung Disease (GOLD) stage 3 or 4 COPD had the highest rate (22.7 per 1000 person-years).

After adjusting for other potential confounding factors, COPD severity (GOLD stage) was independently associated with an increased risk of pneumonia. In the analysis of 2008 UK National COPD audit data, 16 % of the COPD patients

had pneumonia [9]. These patients tended to be older (mean ages 75 vs 72 years), more likely to come from care homes, with more disability, higher BMI and comorbidity, lower albumin, but higher urea levels, and less likely to be current smokers. In another COPD cohort that showed age >65 years, comorbidities including congestive heart failure (OR 1.4, 95 % CI 1.2–1.6) and dementia (OR 2.6, 95 % CI 1.9–3), prior severe COPD exacerbations requiring hospitalization (OR 2.7, 95 % CI 2.3–3.2), and severe COPD requiring home oxygen or nebulized therapy (OR 1.4, 95 % CI 1.1–1.6) were significantly associated with risk of CAP [3••]. A retrospective study from Taiwan showed that increased age, lower body mass index, lung cancer, bronchiectasis, and inhaled corticosteroid containing treatment were associated with an increased risk of CAP in COPD patients [10]. In a very recent study which consisted of two pooled, one-year randomized exacerbation trials (n=3255), a cluster analysis was used to identify distinct patient groups at the greatest risk of pneumonia [11]. Five clusters were identified. Patients at greater risk of pneumonia had more severe obstruction (forced expiratory volume in 1 s (FEV_1)/forced vital capacity <46 %) and either a body mass index <19 kg/m^2 (hazard ratio 7.8, 95 % CI 4.7–13.0) or a pneumonia history and greater comorbidities (hazard ratio 4.8, 95 % CI 3.0–7.7) relative to the cluster with the lowest pneumonia risk.

Patients with COPD who are hospitalized with CAP are most likely to have previously received antibiotic therapy and have more severe respiratory failure and more severe pneumonia than those without COPD [12–21]. They also tend to be associated with more comorbidities such as cardiovascular diseases and diabetes mellitus, more systemic or inhaler corticosteroid use, more acidosis, and more alcohol abuse. A recent prospective trial showed that COPD patients with CAP had higher FEV_1 compared with patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) without pneumonia [22]. However, patients with AECOPD had more readmissions, and patients with CAP had more prior episodes of pneumonia. Chills, pleuritic pain, sputum purulence, and CRP levels at day 1 were independent clinical predictors of CAP with COPD.

Inhaled corticosteroid use has also been associated with an increased risk of pneumonia in COPD patients [23••]. Inhaled corticosteroid use has important immunomodulatory effects in airways with COPD [24], and there is an increased bacterial load especially when associated with a high-dose of inhaled corticosteroid [25]. These factors may explain an enhanced risk of pneumonia in COPD patients.

Specific immunologic characteristics of inflammatory response in COPD patients with CAP are not well known. Patients with CAP and COPD may present with stronger inflammatory response than patients with AECOPD [22]. These patients had significantly higher serum levels of C-reactive protein (CRP), procalcitonin, tumor necrosis factor alpha, and interleukin (IL)-6 than patients with AECOPD. On the other hand, patients with CAP and COPD had significantly lower serum levels of tumor necrosis factor alpha, IL-1, and IL-6 compared with the CAP-only group [26]. In a recent study, Ferrer et al. showed that the previous use of inhaled corticosteroid (ICS) in patients hospitalized for CAP was associated with a reduced systemic inflammatory response without any impact on mortality [27].

Microbial Etiology

Etiological diagnosis of pneumonia may be difficult in COPD because chronic colonization confounds the interpretation of sputum culture results. For instance, *Pseudomonas aeruginosa* has been isolated from sputum in 4 to 15 % of adults with COPD without pneumonia [28]. Treatment based on respiratory tract cultures may lead to over treatment. COPD and smoking also increase serum titers to *Chlamydia pneumoniae*, rendering serological diagnosis for this infection difficult to interpret, especially when single titers are used for diagnosis [29].

Streptococcus pneumoniae remains to be the most common cause of CAP in COPD [30]. However, because of alterations in the lung microbiome in COPD, pathogens such as *Haemophilus influenzae*, *Moraxella catarrhalis*, and *P. aeruginosa* may play a larger role in the development of CAP in these patients [30].

CAP caused by gram-negative bacilli and *P. aeruginosa* is an uncommon diagnosis. The presence of very severe COPD with concomitant bronchiectasis and repeated courses of antibiotics predisposes these patients to pneumonia caused by *P. aeruginosa* [31]. *P. aeruginosa* as a CAP etiology in COPD patients has been shown to be associated with older age (84.9 vs 76.3, p<0.01), moderate to severe disease, and those patients who were treated regularly with oral corticosteroid [17, 18].

Infectious etiology could be established in 21.3 to 78 % of the COPD patients with CAP [12–21]. Diagnostic yield was lower in two retrospective studies than in prospective studies [14, 15]. COPD subjects with acute exacerbation and pneumonia on high-dose ICS (>1000 μg beclomethasone equivalent per day) had a higher rate of positive sputum bacterial culture than those on low-medium dose of ICS (50 vs 18.2 %, p=0.02) [18]. Also, there was a trend towards a higher rate of positive sputum bacterial culture among the subjects with FEV_1<50 % predicted than those with FEV_1≥50 % predicted (42.2 vs 14.3 %, p=0.04). On the other hand, subjects on ICS had a higher rate of positive viral etiologies (26.3 vs 5.8 %, p= 0.02). The most common isolated pathogen in COPD patients with CAP is *S. pneumoniae* followed by *H. influenzae*,

C. pneumoniae, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and viruses. Liapikou et al. showed that patients with COPD had more infections attributable to *P. aeruginosa*, but fewer infections attributable to *L. pneumophila* than non-COPD patients ($p<0.01$ and $p=0.04$, respectively) [12]. In the study, *P. aeruginosa* was more associated with pulmonary complications and chronic use of ICS. Rello et al. showed that *P. aeruginosa* was isolated with significantly higher frequency in COPD patients than in non-COPD patients (14.6 % vs 0.8, $p<0.05$) [13]. *P. aeruginosa* has been indicated by five of ten studies assessing CAP in the COPD subjects as being the first or second etiological agent [13, 14, 16–18]. Two of these studies comprised patients with severe CAP requiring intensive care [13, 16]. In one study, *P. aeruginosa* was the fourth most identifiable cause of CAP [12]. On the other hand, the rest of four studies revealed that *P. aeruginosa* was not one of the leading pathogens [15, 19–21].

Bacteria seem to be more common than viruses as the etiological agents in patients with AECOPD and concomitant pneumonia, whereas the overlap between viral and bacteria etiologies is also low [18]. A prospective study from Israel, which compared pneumonic acute exacerbations vs nonpneumonic AECOPD revealed a significantly higher rate of viral etiologies in the pneumonic group, especially in relation to parainfluenza virus type 2 and adenovirus [21]. The pneumonic acute exacerbation group also had a significantly higher rate of bacterial etiologies, particularly pneumococcal.

Atypical agents have been presented in varying percentages in COPD patients with CAP. In a study from Hong Kong, atypical organisms were not detected by either serology or NPA viral PCR [18]. In contrast to this study, other studies showed that atypical microorganisms may be the leading pathogens [15, 17, 19, 20]. A study from Spain showed that there was a close association between severity of airway obstruction and etiologic agent [19]. In the study, *C. pneumoniae* was much more frequent in patients with more severe COPD (one vs eight cases). Some opportunistic organisms such as *Nocardia asteroides* and *Aspergillus fumigatus* can also be seen as an etiologic agent in COPD patients with CAP if they are using oral or inhaled corticosteroids [19].

A positive blood culture has been detected in 2.4 to 15 % of the COPD patients with CAP [12, 14, 15, 19, 20]. The most frequent microorganisms were *S. pneumoniae*, *H. influenzae*, *Streptococcus viridans*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus mitis*, and *Klebsiella pneumoniae*. In one study, bacteremic pneumococcal pneumonia was presented less frequently with shock and had a lower mortality rate in COPD patients than in non-COPD patients [32]. In another study, COPD was found more frequently in patients with bacteremic pneumococcal pneumonia than those with pneumonia with a different etiology [33].

Patients with COPD receive frequent courses of antimicrobial treatment, which might be associated with a higher prevalence of resistant organisms. However, a prospective laboratory-based study showed that in patients with pneumonia, COPD as an underlying disease was not associated with more drug-resistant pneumococci [34]. In contrast, isolates causing AECOPD showed higher rates of resistance than those causing pneumonia. In another study, two out of the eight patients (25 %) related to *S. pneumoniae* were resistant to penicillin, whereas none of the *H. influenzae* isolates showed β-lactamase activity [18]. Different serotype distributions in patients with pneumonia and AECOPD can explain the differences in antimicrobial resistance. Certain serotypes of *S. pneumoniae* may be involved in COPD patients with CAP. For instance, serotypes 1, 3, and 7F were more frequent in one study [34]. Another study showed that serotypes 1, 3, 4, 5, and 8 were associated with pneumonia episodes in COPD subjects, while serotypes 16F and 11A were associated with AECOPD episodes [35].

Prognosis

Although COPD is considered a risk factor for the development of CAP, it has not been included in the two most common scoring systems currently used nor has it been included in the modified British Thoracic Society rule [36, 37]. The prognostic role of coexistence of COPD and CAP is still unclear. A number of clinical and epidemiological studies have been carried out in order to determine whether COPD was a predictor of increased mortality in patients hospitalized with CAP. Some studies of patients with COPD have reported increased mortality risks [9, 13–15, 21], but other studies and one meta-analysis have not [12, 17, 20, 38]. Possible mechanisms that may contribute to poor CAP outcome in COPD include the presence of resistant bacteria, which were perhaps not properly treated from the outset, as well as reduced lung reserve [29]. Factors that might be associated with decreased mortality include prior immune experience with related bacterial pathogens that may have protective effects, enhanced airway inflammation, and the use of inhaler or systemic corticosteroids [39].

A prospective study which consisted of 249 consecutively hospitalized patients with COPD showed that in-hospital and long-term outcomes (1 year) were similar for both patients with CAP with COPD and CAP with AECOPD [22]. A study from Scandinavia revealed that the length of hospital stay was increased and the usage of noninvasive ventilation was more frequent, but no significant increase in the in-hospital mortality was

found for pneumonic AECOPD when compared with AECOPD [40]. Other comorbidities may influence the prognosis in COPD subjects with CAP. A cohort consisting of 17,140 elderly COPD patients who were hospitalized for pneumonia showed that prior cardiovascular disease was independently associated with increased long-term mortality in COPD patients with pneumonia [41•].

The impact of inhaled corticosteroid on pneumonia prognosis is also controversial. Some studies have shown that COPD patients who were on inhaled corticosteroid have less mortality after developing CAP as compared with patients with COPD without prior inhaled corticosteroid use [42, 43], but others have not shown any impact on outcome [27, 38, 44, 45]. A small cross-sectional study from the USA showed that prior inhaled corticosteroid use was associated with higher severity of illness at admission and higher incidence of antimicrobial-resistant pathogens, particularly in those COPD patients hospitalized with CAP [46].

Antibiotic Treatment

Treatment data are not available in most of the studies conducted in COPD patients with CAP. The most frequently prescribed regimens in the available four studies were β-lactam alone or combination with macrolide, β-lactam plus fluoroquinolone, fluoroquinolone alone, and β-lactam/β-lactamase inhibitors. Antibiotic modification seems common in COPD patients with CAP especially those who were hospitalized in the intensive care unit (ICU) [13, 16, 19]. The main reasons for the antibiotic changes due to etiologic agents were therapeutic failure and antibiotic resistance issues. In one study, which was done in COPD patients with severe CAP, 14 (15.7 %) out of the 89 COPD patients with microbiological diagnosis received inadequate empirical therapy and 8 (57.1 %) died compared with 19 deaths (25.7 %, $p<0.05$) in COPD patients with adequate empirical therapy [13]. In the study, a total of 45.4 % COPD patients received empirical anti-pseudomonal therapy and the ICU mortality rate (32.5 %) was similar to episodes receiving other regimens. No difference in ICU mortality rate was observed between COPD patients who received combination therapy or monotherapy (30.4 % vs 29.3, $p=0.95$).

A post hoc analysis of two large studies of CAP in hospitalized patients showed that in patients with COPD as well as in the overall study population, the efficacy of ertapenem was comparable to that of ceftriaxone (90 vs 90 %) [47]. In this study, response rates in patients with COPD were slightly lower than the rates in patients without COPD, but the difference was not statistically significant.

Neither European CAP nor COPD guidelines recommend any specific treatment for COPD patients with CAP [1, 48–50]. In the recent Infectious Diseases Society of America/American Thoracic Society Guidelines for CAP, presence of COPD as a comorbid condition puts CAP patients in a high-risk group [31]. Treatment with a respiratory fluoroquinolone or a β-lactam plus a macrolide is recommended for outpatient setting. Among inpatients with CAP and COPD, the same choices are applicable. For severe CAP requiring ICU admission, combination therapy consisting of a β-lactam with either a fluoroquinolone or a macrolide is recommended. These recommendations can apply to the majority of patients with CAP, but physicians should be aware to identify patients who are at increased risk for bacteria resistant to these empirical antibiotic regimens. For instance, patients with COPD who were prescribed antibiotic treatment in the previous 3 months or hospitalized during the previous 90 days may be at risk for drug-resistant pneumonia. In two guidelines, severe COPD has been implicated as a major risk factor for *P. aeruginosa* and empirical antibiotic treatment is recommended to cover this microorganism [31, 49]. There is no doubt that CAP due to gram-negative bacilli predisposes to a very severe illness associated with increased mortality if early and effective treatment is not established. Therefore, appropriate anti-pseudomonal coverage should be considered in COPD patients, especially those who are hospitalized in the ICU or have risk factors for resistant bacteria.

Conclusions

In summary, patients with COPD are at higher risk of developing CAP than patients in the general population. Controversy exists as to whether the prognosis of pneumonia is altered by preexisting COPD. COPD patients with CAP are generally older, predominantly male, more likely to have comorbidities, respiratory failure, and more severe pneumonia. *S. pneumoniae* remains to be the most common cause of CAP in COPD. In the presence of very severe COPD with concomitant bronchiectasis, exposing to frequent antibiotic courses, receiving routine oral corticosteroid treatment, and hospitalizing in the intensive care unit predisposes these patients to pneumonia caused by *P. aeruginosa*. If there is no *Pseudomonas* risk, a respiratory fluoroquinolone or a β-lactam plus a macrolide is recommended.

Compliance with Ethics Guidelines

Conflict of Interest Aykut Cill has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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