Review Article

Current Status of Community-Acquired Pneumonia in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Objective: Worldwide, community-acquired pneumonia (CAP) is a common infection that occurs in older adults, who may have pulmonary comorbidities, including chronic obstructive pulmonary disease (COPD). Although there have been clinical studies on the coexistence of CAP with COPD, there remain some controversial findings. This review presents the current status of COPD in CAP patients, including the disease burden, clinical characteristics, risk factors, microbial etiology, and antibiotic treatment.

Data Sources: A literature review included full peer-reviewed publications up to January 2018 derived from the PubMed database, using the keywords "community-acquired pneumonia" and "chronic obstructive pulmonary disease".

Study Selection: Papers in English were reviewed, with no restriction on study design.

Results: COPD patients who are treated with inhaled corticosteroids are at an increased risk of CAP and have a worse prognosis, but data regarding the increased mortality remains unclear. Although *Streptococcus pneumoniae* is still regarded as the most common bacteria isolated from patients with CAP and COPD, *Pseudomonas aeruginosa* is also important, and physicians should pay close attention to the occurrence of antimicrobial resistance, particularly in these two organisms.

Conclusions: COPD is a common and important predisposing comorbidity in patients who develop CAP. COPD often aggravates the clinical symptoms of patients with CAP, complicating treatment, but generally does not appear to affect prognosis.

Key words: Chronic Obstructive Pulmonary Disease; Community-Acquired Pneumonia; Morbidity; Treatment

Introduction

Worldwide, community-acquired pneumonia (CAP) is a common group of infectious diseases that result in substantial health and economic burden.[1] CAP affects about 2–13/1000 community-dwelling people each year, and remains a leading cause of hospital admissions, morbidity, and mortality in developed countries, especially for older people, with hospitalization rates of between 20% and 60%.[2-4] Chronic obstructive pulmonary disease (COPD) is characterized by long-term worsening airflow, resulting in shortness of breath, cough, and sputum production. The clinical diagnosis of an acute exacerbation of COPD (AECOPD) is made when the patient with COPD experiences a sustained increase in sputum production, cough, or dyspnea for 24–48 h.[2-4] Among all patients with CAP, those aged ≥65 years account for about one-third, but they are responsible for more than half of all health costs due to this disease.[5] COPD is one of the most common comorbidities in patients with CAP, characterized by persistent respiratory symptoms. Worldwide, COPD was reported to be the third-most common cause of death in 2008, and the morbidity from COPD is projected to rise by 2020.[6,7]

The aim of this review was to present the current status of CAP in patients with COPD, including the disease burden, clinical characteristics, risk factors, microbial etiology, and antibiotic treatment.

Disease Burden and Morbidity of Community-Acquired Pneumonia Associated with Chronic Obstructive Pulmonary Disease

Patients who are suffering from COPD are at an increased risk of infection from CAP compared with patients with

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.230727

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Received: 20-12-2017 **Edited by:** Qiang Shi

How to cite this article: Liu DS, Han XD, Liu XD. Current Status of Community-Acquired Pneumonia in Patients with Chronic Obstructive Pulmonary Disease. Chin Med J 2018;131:1086-91.

normal pulmonary function. COPD was an independent risk factor for developing severe CAP, with an odds ratio (*OR*) of 1.91.[8] COPD was a frequent comorbid condition in patients with CAP with reported rates of between 15% and 42%.[9-11] A large retrospective study has shown that the incidence of CAP in patients with COPD was 22.4%, with a 95% confidence interval (*CI*) of 21.7–23.2/1000 person-years.[12]

Clinical Outcome of Community-Acquired Pneumonia Associated with Chronic Obstructive Pulmonary Disease

Previously published studies have shown that the primary clinical outcome for all-cause mortality included the length of stay in the hospital, admissions to the Intensive Care Unit (ICU), as well as the demand for mechanical ventilation.[13] Although worse prognosis for patients with both CAP and COPD has been shown, there remains controversy in the published literature.[13,14] Several studies have been undertaken to examine the impact of COPD on the clinical outcome for patients, who developed CAP, with the majority of studies showing that COPD increased mortality in patients with CAP and prolonged the hospital stay in patients who were successfully treated for CAP.[9,15-17] However, some other studies have shown that COPD had no relationship with patient mortality in CAP, length of stay in the hospital, as well as more frequent admission to the ICU.[10,13,14,18-20]

Two studies have shown that COPD was associated with reduced mortality among patients with CAP.[15,21] These varying results may be due to several reasons that include variations in study design and the target populations assessed, the varying use of inhaled corticosteroid therapy, varying underlying comorbidities, including COPD, and the timing and frequency of patients who seek medical evaluation and treatment.[22-24] Therefore, more future prospective and controlled studies are needed that can divide patient populations by comorbidity, treatment, and other subgroups to verify the effect of COPD on the prognosis of patients with CAP.

Clinical Characteristics of Community-Acquired Pneumonia Associated with Chronic Obstructive Pulmonary Disease

A key previously published prospective study on the clinical features of patients with CAP and COPD has shown that these patients were more likely to have a cough ($P = 0.001$), expectoration ($P < 0.001$), purulent sputum ($P < 0.001$), dyspnea ($P < 0.001$), tachypnea ($P < 0.001$), and respiratory failure on hospital admission ($P < 0.001$).[11] Conversely, those patients in the group with CAP only, fever, diarrhea, headache, arthromyalgias, multilobar infiltrates, pleural effusion, empyema, and bacteremia were more common presentations.[11] Patients with CAP who had chronic respiratory disorders and who were then treated with inhaled corticosteroids tended to have a reduced incidence of parapneumonic pleural effusion.[25] Both *in vitro* and clinical studies suggested different inflammatory responses in patients with CAP, either with or without COPD, such as raised levels of the inflammatory biomarkers, C-reactive protein (CRP), and procalcitonin (PCT), with levels being similar in each group.[17,26,27] However, the levels of CRP and PCT were different between patients with CAP and COPD compared with patients with AECOPD, and a previously published study has also shown increased serum levels of CRP, PCT, tumor necrosis factor-α, and interleukin (IL)-6, IL-1, and IL-8 in patients with CAP and COPD compared with patients with AECOPD.[28] One study conducted by Pizzini *et al*.[29] calculated that CRP, PCT, and neopterin (NPT) levels were significantly increased in patients with CAP compared with the patients with AECOPD, whereas the CRP/NPT ratio was lower. The CRP/NPT ratio was considered to discriminate between AECOPD, CAP, and CAP with COPD, with a cutoff ratio of 0.346 (sensitivity, 65% and specificity, 79%).[29]

The pneumonia severity index (PSI)[30] and the CURB-65 score[31] are often used to assess patients with CAP. Crisafulli *et al*.[17] reported that patients with CAP who also had COPD, had increased levels of these scores, with the mean PSI score of 86.0 ± 37.4 in the CAP only group and 100.4 ± 28.7 in patients with CAP and COPD ($P < 0.001$). However, there was no significant difference between the classes of I to V for the PSI and CURB-65 sores between the two groups, respectively.[17]

Risk Factors for Community-Acquired Pneumonia Associated with Chronic Obstructive Pulmonary Disease

General risk factors for CAP, tested in previous studies, have mainly focused on factors that include gender, age, smoking history, body mass index (BMI), COPD severity, comorbid conditions, and COPD therapy.[11,12,14,27,32-36] Müllerova *et al*.[12] demonstrated that for patients with COPD, patient age ≥65 years, BMI ≥25 kg/m^2, and severe COPD (requiring nebulized oxygen therapy) were associated with increased rates of occurrence of CAP. However, the current smoking status and a moderate history of COPD had no significant association with the incidence of CAP.[12] There was an increased risk of CAP in patients with COPD, which coexisted with other diseases, such as congestive heart failure, dementia, peptic ulcer, peripheral vascular disease, and connective tissue disease (*OR* 1.4, 95% *CI*, 1.2–1.6; *OR* 2.6, 95% *CI*, 1.9–3.8; *OR* 1.2, 95% *CI*, 1.1–1.4; *OR* 1.3, 95% *CI*, 1.1–1.6; and *OR* 1.2, 95% *CI*, 1.0–1.3; respectively).[12] There was no significant association with a diagnosis of diabetes mellitus.[12]

Moreover, medications used to treat some comorbidities may be associated with an increased risk of infection, for example, treatment with proton pump inhibitors are reported to be strongly associated with CAP (*OR* 5.0, 95% *CI*, 2.1–11.7).[12] However, a case-controlled study has not confirmed this conclusion.[37] A recently published study showed that angiotensin-converting-enzyme (ACE) inhibitors could reduce the risk of pneumonia and decrease pneumonia-associated

mortality.[38] Similarly, a study from the UK recently reported that the use of ACE inhibitors reduced the 30-day mortality risk for CAP.[39] A recently published retrospective cohort showed that noninvasive ventilation and shorter length of stay in the ICU were associated with reduced mortality from CAP.[40]

The use of inhaled corticosteroids is likely to reduce airway inflammation and neutrophil recruitment, thus reducing the severity of CAP, but can cause an impaired systemic inflammatory response, leading to an increase in bacterial load.[41] Therefore, the use of inhaled corticosteroids is reported to be associated with increased risk of pneumonia.[32] Cascini *et al*.[42] have shown that patients treated with inhaled corticosteroids, no matter whether there is combined treatment with long-acting beta-agonists, had an increased risk of CAP. Almirall *et al*.[43] reported that a combined treatment arm (salmeterol and fluticasone) were easier for patients with CAP to tolerate than tiotropium bromide. However, patients with COPD with CAP and who are treated with inhaled corticosteroids are more likely to have drug-resistant pathogens.[44]

However, the impact on patient prognosis of inhaled corticosteroids on patients with CAP and COPD remains controversial. Some studies have shown that patients with COPD treated with inhaled corticosteroids have reduced mortality after developing CAP,[45,46] but other studies have not shown any impact on outcome following treatment.[14,43,47,48] It is possible that treatment with inhaled corticosteroids modulates the inflammatory response in patients with pneumonia, but the reasons for these effects on patients' survival remain unknown, and require further study.

Vaccination can be a preventive strategy, particularly in the elderly, to prevent pneumococcal and influenza infections and published studies have shown that these vaccinations can reduce patient morbidity, hospitalization, and mortality in patients with CAP.[49,50] A previous study has reported that the risk of CAP was reduced by 50% for patients who were vaccinated when compared with patients without vaccination.[51] Torner *et al*.[18] described in their study that pneumococcal vaccination significantly reduced 30-day mortality for CAP (*OR* 0.68, 95% *CI*, 0.48–0.96; $P = 0.03$) and influenza vaccination was slightly protective (*OR* 0.72, 95% *CI*, 0.51–1.02; $P = 0.06$). Therefore, offering both pneumococcal and influenza vaccination to the elderly with COPD may improve 30-day mortality for patients who develop CAP.[18] Gómez-Junyent *et al*.[11] reported previous pneumococcal vaccination improved the prognosis of patients with COPD and CAP. However, there are still some controversies from some authors regarding the effectiveness of vaccination in patients with COPD, for example, Skull *et al*.[52] showed no benefit of vaccine in the prophylaxis of CAP for COPD in the general population.

After many years of clinical patient follow-up, Müllerova *et al*.[12] showed that the probability of developing CAP in unvaccinated patients was increased. However, in an adjusted multivariate model, there was no significant relationship between vaccine use and reduced risk of CAP, probably, due to the small number of deaths registered within 30-day CAP hospital admission in this study, but despite this, the use of vaccination for patients with COPD has been written into some CAP and COPD clinical guidelines.[53,54] The Global Initiative for Chronic Obstructive Lung Disease indicated that vaccination for the influenza virus was more helpful to the older patients with COPD, and recommended that the pneumococcal conjugate vaccine 13 and pneumococcal polysaccharide vaccine 23 should be used for all the patients with COPD who are 65 years of age or more.[53]

Microbial Etiology of Community-Acquired Pneumonia Associated with Chronic Obstructive Pulmonary Disease

Among patients with CAP, *Streptococcus pneumoniae* has been shown to be the most common infectious bacterial cause, but CAP can also be caused by atypical organisms that include *Legionella*, and Gram-negative bacteria including *Pseudomonas aeruginosa*.[55-57] A recent study showed that *S. pneumonia* was the most common causative agent in the patients with CAP when compared with the patients with CAP and COPD, while *Haemophilus influenzae* were more common in the group of patients with CAP and COPD (5.6% vs. 26.0%, $P < 0.001$).[58] The frequencies of pathogens are usually the same between age groups. However, for *S. pneumonia,* the incidence of CAP has been shown to be 20.9–28% in patients <65 years of age and 19.9–85% in patients ≥65 years of age and *H. influenzae* were isolated more often in elderly patients aged ≥65 years, and this association requires recognition by physicians.[59]

Exacerbation of COPD by pneumonia in patients on high-dose inhaled corticosteroids (>1000 μg beclomethasone per day) had an increased rate of positive sputum bacterial culture when compared with patients on a low dose or medium dose of inhaled corticosteroids (50% vs. 18.2%, $P = 0.02$).[60] Among patients with CAP and COPD, *S. pneumoniae* remains the most common cause, but *H. influenzae*, *Moraxella catarrhalis*, and *P. aeruginosa* are also often isolated in CAP.[10,11,61] Infection with *P. aeruginosa* has been shown to be associated with an older patient population and regular oral corticosteroid therapy.[60] Due to chronic bacterial colonization, the etiological diagnosis of pneumonia can be challenging for sputum culture diagnosis, as in 4–15% of patients with COPD, *P. aeruginosa* was isolated from sputum in patients without pneumonia.[62] Therefore, the isolated rates of *P. aeruginosa* in sputum may be overstated.

Clinical Characteristics of Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Community-Acquired Pneumonia

Huerta *et al*.[28] reported that *S. pneumonia* was more prevalent in patients with combined CAP and COPD

compared with patients with AECOPD (43% vs. 10%, $P < 0.001$) and that infection with *H. influenzae* was more common in AECOPD (19% vs. 5%, $P = 0.04$), but there was no difference between the two groups for the incidence of infection with *P. aeruginosa.* In patients with AECOPD and concomitant pneumonia, bacterial pathogens have been reported to be more commonly isolated etiological agents when compared with viruses, which has been supported by a prospective study that reported that the overlap between viral and bacterial etiologies was low.[60] Mohan *et al*.[63] showed that the prevalence of viral respiratory infections among patients with AECOPD was up to 34.1%, and included infection by picornavirus (17.3%) and influenza virus (7.4%). Picornavirus was found to be the most common virus associated with CAD in Western countries; influenza virus was found to be the most common virus associated with CAD in Asia.[63] The findings of another prospective study showed that in patients with AECOPD, viral pneumonia was more common and was these patients had an increased rate of coinfection with bacteria, especially with pneumococcal pneumonia.[16]

Atypical Infectious Agents and Antimicrobial Resistance in Community-Acquired Pneumonia Associated with Chronic Obstructive Pulmonary Disease

Atypical infections, including *Legionella pneumophila*, have been described in patients with CAP and with COPD. Gómez-Junyent *et al*.[11] showed that *L. pneumophila* is more often found in patients in the CAP only group, compared with patients with CAP and COPD (6.5% vs. 2.1%, $P < 0.001$). In another study, atypical organisms were not detected by any measure or scale.[60] Other studies have shown that atypical microorganisms may be the main pathogens in patients with CAP and COPD.[9,64]

Due to frequent courses of antimicrobial treatment, patients consistent with CAP and COPD might be more susceptible to infection with antimicrobial-resistant organisms, and this has been supported by a study showing that pathogens in patients with AECOPD expressed higher rates of antimicrobial resistance, but patients with CAP and COPD had no significant association with infection by drug-resistant pneumococci.[65] Differences in antimicrobial resistance can now be demonstrated using various techniques, including the analysis of different serotype distributions in patients who have CAP as well as COPD and AECOPD.

Antibiotic Treatment of Community-Acquired Pneumonia Associated with Chronic Obstructive Pulmonary Disease

Treatment for CAP should be individualized for each patient with COPD, who is likely to have different disease severity and comorbidities. At this time, current clinical CAP and COPD guidelines have not recommended specific treatment guidelines for CAP in patients with COPD. However, in one study, younger patients (<65 years) received fewer beta-lactams and more quinolones than older patients (≥65 years) (beta-lactams: 62.5% vs. 81.3% and quinolones: 28.2% vs. 17.1%, respectively); in contrast, macrolide use was similar between the two groups (32.6% vs. 31.4%, respectively).[66] The most commonly used combination therapy is combining beta-lactam with a macrolide or quinolone. For patients with CAP and with COPD, the most frequent antibiotic regimens are β-lactams alone or a combination with a macrolide, β-lactam plus fluoroquinolone, fluoroquinolone alone, and β-lactam/β-lactamase inhibitor.[66] A retrospective cohort study showed that there was no difference in effectiveness between the use of fluoroquinolones and β-lactam/β-lactamase inhibitors for the treatment of outpatients with CAP and COPD.[67] Another study reported that data on antibiotic treatments did not differ with the presence or the absence of COPD.[9]

However, it is common to see the antibiotic modification and changes of combinations in patients with COPD and CAP, particularly when treated in the ICU.[40] Therefore, physicians should be aware of the increasing trend for bacteria; resistance in this patient population. Of particular note is the use of empirical antibiotic regimens in patients diagnosed with COPD, at least 90 days before hospitalization or has been prescribed antibiotic therapy in the past 3 months, where *P. aeruginosa* is often isolated.[68] Because inappropriate antibiotic treatment has repeatedly been linked with worse clinical outcome in patients with CAP associated with COPD. Patients with COPD should receive the appropriate antipseudomonal coverage.

Conclusions

COPD can lead to an increased risk of developing CAP, which is associated with a poorer prognosis. There is a need for physicians to pay attention to the association between CAP and COPD, as demands for diagnostic accuracy increase, and pressures on health economics and cost of care continue to increase, with more stress on medical resources and social and community patient support. Patients with COPD are more commonly older, male, and more likely to suffer from respiratory failure, severe pneumonia, comorbidities, and the effects of treatment with inhaled corticosteroids. Vaccination may be protective for patients with COPD who are more likely to develop CAP. Regarding the most common bacterial pathogens in CAP, infection with *S. pneumonia* is the most common, followed by *P. aeruginosa*. COPD is a common and important predisposing comorbidity in patients who develop CAP, and often aggravates the clinical symptoms of patients with CAP, complicating treatment, but generally does not appear to affect prognosis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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社区获得性肺炎合并慢性阻塞性肺疾病研究现状

摘要

目的：社区获得性肺炎（CAP）是世界范围内常见的感染性疾病,常发生于老年人中，这类病人往往合并肺部疾病，其中包括慢性阻塞性肺病（COPD）。虽然已有许多相关CAP合并COPD的临床研究，结果仍存在一些争议。本文的主要目的是对以下方面进行回顾和总结：疾病负担、临床特征、危险因素、微生物病原学和抗生素治疗。
数据来源：综述包括来自2018年1月之前PubMed数据库中全部同行评审的文献，使用关键词“社区获得性肺炎”和“慢性阻塞性肺病”。
研究选择：对相关英文文献进行综述，研究类型无限制。
结果：COPD应用吸入性糖皮质激素治疗可能导致发生CAP的风险升高，且往往预后较差，但在病死率方面存在争议。肺炎链球菌仍被认为是最常见的细菌，但铜绿假单胞菌也很重要，临床医生应密切关注抗菌药物耐药性的发生，特别对于这两种细菌。
结论：COPD为患者常见且重要的合并症，往往导致CAP的发生。COPD加重CAP患者的临床症状，使得治疗变得复杂，但对于预后往往影响不大。