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Chronic obstructive pulmonary disease and risk of infection

Czynniki ryzyka infekcji w przewlekłej obturacyjnej chorobie płuc

Abstract

This review article focuses on the risk of infections in patients with chronic obstructive pulmonary disease (COPD). Throughout the years there have been a number of studies describing the risk of pulmonary infections in patients with COPD, whereas only few studies have focused on the risk of infection outside the lungs.

With increasing severity of COPD the risk of respiratory tract infection also increases. The impairment of the innate immune system is most likely responsible for both the colonization of respiratory tract with bacteria and for an increased risk of infection with new strains of bacteria causing acute exacerbations. Also lung infections like pneumonia, lung abscess and empyema are more often seen in patients with COPD than in healthy subjects. With regard to extrapulmonary infections, it seems that COPD patients are not at higher risk of infection compared with subjects without COPD.

It is concluded that COPD is significantly associated with an increased risk of various respiratory tract infections, but not with infections outside the respiratory system.

Pneumonol. Alergol. Pol. 2009; 77: 284–288

Introduction

Chronic obstructive pulmonary disease (COPD) is a major health problem being among the top ten leading causes of mortality worldwide [1, 2]. In addition, in most countries COPD is related to large use of health care resources [3]. In daily clinical practice, an exacerbation of COPD is a very common cause for an acute visit to the general practitioner or to an emergency room and especially during the cold months of the year also an important cause for admission to hospital. In addition, it is now recognized that the frequency of exacerbations plays an important role for the perception of quality of life for the COPD patient [4, 5]. Therefore, there has been an increased focus on acute exacerbations in COPD, including their natural history, their causes and the possibility of prevention. Since respiratory tract infections are responsible for more than 50% the COPD exacerbations, a number of studies have focused on importance of infection and our knowledge on this topic has expanded substantially over the recent years [6].

In the last decade, there has also been a change in the perception of COPD, which in addition to pulmonary involvement, is now defined also to exhibit extra-pulmonary manifestations including a low-grade systemic inflammation [7]. Therefore, it can be hypothesized that in addition to predisposing to pulmonary infections COPD also promotes extra-pulmonary infections. The topic of this brief review is to describe the relationship between COPD and infections, both pulmonary and extra-pulmonary.

Epidemiological studies

The relationship between COPD and subsequent infection has been studied in a number of studies in the epidemiological setting. These studies often comprise samples of the general population including individuals with COPD. The advantage of this approach is a large number of cases and a possibility of a comparison between participants with and without COPD. The weakness is the fact that the

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Praca wpłynęła do Redakcji: 28.01.2009 r.

ISSN 0867–7077

enrolled subjects are not particularly well-characterized with regard to the nature of their lung disease and that the observed infections are based on reports from hospital records or self-reports and that microbiological findings are often not available.

The seminal study of Fletcher and coworkers, who followed almost 800 men for from 1961 to 1969 in London focused on decline in lung function, respiratory symptoms, smoking and respiratory tract infections had a profound influence on our understanding of natural history of COPD and is often regarded as the prototype of such studies [8]. Among many important findings from this study is the fact that especially presence of chronic mucus hypersecretion (phlegm) predisposes to respiratory tract infection [8]. This finding has also been reported in other cohorts. Already more than 30 years ago, Jedrychowski using information on absence from work among employees of a fertilizer factory in Krakow, found that symptoms of chronic bronchitis were a strong predictor of absence from work due to chest infections [9]. In The Copenhagen City Heart Study, where we followed a large cohort of almost 15 000 individuals selected from the general population including patients with COPD, we could show that mucus hypersecretion contributed to the risk of death from COPD and that this was mediated by respiratory infections in individuals with most severe disease [10, 11].

Using the same cohort we observed that reduction of lung function (expressed as FEV_1 in percent of the predicted value) was significantly associated with an increased risk of hospitalization from pneumonia [12]. Other epidemiological studies using similar methods have also reported that lung function reduction (and presence of chronic lung disease) predicts an increased risk of pulmonary infection, in particular community-acquired pneumonia [13, 14].

In spite of the recent focus on systemic manifestations of COPD, there are almost no studies investigating the risk of extra-pulmonary infections in patients with COPD. We recently used the Copenhagen City Heart Study database to study such possible association [15]. In this study we linked the information on the severity of COPD (according to GOLD classification) assessed by spirometry in 1976–1978 with the number of hospital admissions during a follow-up period of more than 25 years in order to estimate the risk of hospital admissions due to all infectious diseases. Based on the classification of World Health Organization International Classification of Diseases we investigated following categories of infectious diseases: diarrhoeal diseases, hepatitis, HIV/AIDS, influenza, lower respiratory tract infection, meningitis, other viral infection, parasitic infection, pulmonary abscess/ /pyothorax, sepsis, skin infection, tuberculosis, urinary tract infection and upper respiratory tract infection. During the follow-up period, we observed a total of 3333 infectious disease hospitalizations. The time to first hospitalization because of infection decreased with increasing GOLD stage and persisted after the statistical adjustment for background characteristics including age, gender, smoking, alcohol consumption, comorbidity and socioeconomic status (Figure 1). Compared with participants without COPD as the reference group, the Cox proportional hazards model yielded following adjusted relative risks for infectious disease hospitalisation: 1.06 (95% CI: 0.92–1.23) for GOLD stage 1, 1.39 (1.24–1.56) for GOLD stage 2, and 2.21 (1.84–2.64) for GOLD stage 3 and 4, respectively, P = 0.001). In a sub-group analysis focusing on different types of infection, the increased risk was associated with lower and upper respiratory tract infections, pyothorax, and tuberculosis but not with influenza, sepsis, skin infections, urinary tract infections, diarrhoeal disease or other infectious diseases (Table 1). Thus, this recent analysis confirmed a higher risk of pulmonary infections in COPD, but did not show an increased risk of hospitalization from extra-pulmonary infections [15]. This finding was surprising to us, as we expected that some of the extra-pulmonary infections by worsening the general condition of the patients

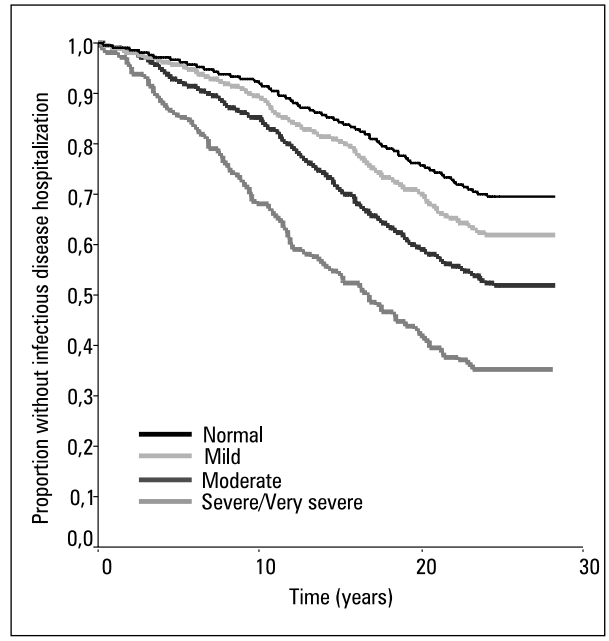

Figure 1. Time to infectious disease hospitalization in The Copenhagen City Heart Study Cohort according to GOLD stage. Log rank test: P = 0.00001 (adapted from [15])

Table 1. Incidence and risk of infectious disease hospitalization in The Copenhagen City Heart Study cohort followed for 25 years after initial diagnosis of COPD (adapted from 15)

	No COPD N = 10190	Mild COPD GOLD stage 1 N = 708	Moderate COPD GOLD stage 2 N = 1156	Severe or very severe COPD GOLD stage 3 N = 335	Significance
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	P value*
Lower respiratory tract infection[1], n = 1411	1.0	1.2 (1.0–1.5)	2.0 (1.7–2.3)	3.3 (2.6–4.1)	< 0.0001
Upper respiratory tract infection[2], n = 312	1.0	0.95 (0.54–1.67)	1.98 (1.42–2.75)	5.26 (3.55–7.78)	< 0.0001
Influenza[6], n = 64	1.0	0.93 (0.29–2.96)	1.27 (0.55–2.97)	1.89 (0.46–7.75)	0.78
Pulmonary abscess /pyothorax[3], n = 54	1.0	0.91 (0.28–2.96)	1.32 (0.55–3.17)	6.02 (2.57–14.11)	< 0.001
Tuberculosis[4], n = 64	1.0	1.11 (0.39–3.11)	2.28 (1.18–4.40)	3.11 (1.19–8.15)	0.02
Urinary tract infection[6], n = 714	1.0	0.96 (0.69–1.33)	0.93 (0.70–1.24)	1.16 (0.69–1.95)	0.89
Sepsis[5], n = 197	1.0	1.39 (0.83–2.35)	0.92 (0.53–1.60)	1.50 (0.61–3.72)	0.48
Skin infection[1], n = 401	1.0	1.01 (0.65–1.56)	1.07 (0.75–1.51)	0.67 (0.30–1.51)	0.77
Diarrhoeal disease[6], n = 261	1.0	1.36 (0.83–2.23)	1.10 (0.69–1.76)	2.31 (1.14–4.69)	0.09
Other infections[6], n = 844	1.0	1.01 (0.77–1.34)	1.04 (0.84–1.30)	1.08 (0.74–1.56)	0.97

N — number of participants; n — number of hospitalizations; RR — relative risk; CI — confidence interval
*P value for adjusted relative risk; [1]Adjusted for sex, age, income, education, smoking, productive cough, alcohol intake and diabetes mellitus; [2]Adjusted for age, income, education, smoking, productive cough, and alcohol intake; [3]Adjusted for sex, age, smoking, productive cough and diabetes mellitus; [4]Adjusted for sex, age, and productive cough; [5]Adjusted for sex, age, income, alcohol intake, productive cough and diabetes mellitus; [6]Unadjusted

with advanced COPD would have provoked admissions to hospital as a result of a lower threshold for admission to hospital.

Clinical studies

Contrary to epidemiological studies, the clinical studies often comprise patients with well-characterized COPD and include more detailed information on the type of emerging infections. During the last decade, particularly the East London Study of COPD where Wedzicha and coworkers have followed a cohort of patients with severe COPD, and two Spanish studies (EFRAM and DAFNE) have provided new insight into the natural history of exacerbations in COPD and the role of infection [16–18].

The infectious triggers of COPD exacerbations comprise both virus and bacteria. Both types of microorganisms can trigger inflammatory reactions that result in clinical exacerbation with dyspnea and increased amount of sputum, but it seems that pronounced sputum purulence is a marker of bacterial infection [19, 20]. Some studies report that the incidence of respiratory viral infections increases in frequency almost two-fold from mild COPD to moderate and severe COPD [21]. The studies also suggest that the inflammatory response to viral infection is greater in COPD, thus resulting in more prolonged clinical symptoms [22]. There is evidence that viral infection predispose to secondary bacterial infections and that both types of microorganisms by interacting make the exacerbations associated with presence of both virus and bacteria more severe [23].

The airways of patients with COPD, especially severe COPD, are often colonized with bacteria. The bacteria in question are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and in the most advanced disease *Pseudomonas aeruginosa* [6]. Low lung function and current smoking are strongly associated with both high frequency of exacerbations and with risk of colonization and chronic infection [24, 25]. The perception some years ago was that exacerbations were mainly caused by an increased load of already present bacterial strains in the airways, but newer studies suggest that exacerbations more likely are precipitated by infections with new bacterial strains which initiate an inflammatory response [26].

Underlying mechanisms and consequences of pulmonary infections in COPD

In health, a well functioning mucociliary apparatus, airway and alveolar macrophages together with secreted products comprising IgA, mucins and antimicrobial peptides constitute an effective defense system of the lower respiratory tract. In COPD, several of these lines of defense are not functioning optimally and this promotes bacteria to achie-

ve a foothold in the lower airways. It seems that smoking itself affects host defenses negatively [25, 27]. Although one could anticipate that presence of undiagnosed bronchiectases would increase the exacerbation frequency, this was not the case in the East London Study, although lower lobe exacerbations were associated with more severe exacerbations and more profound bacterial colonization [28].

The colonization or chronic infection of the airways promotes a vicious circle impairing host defenses and promoting further infections [6]. In the East London Study, colonization/chronic infection was associated with frequent exacerbations and predicted an accelerated decline of FEV_1 [29].The latter finding, although in contrast to the findings of Fletcher et al. [8], has also been reported in a large intervention trial, The Lung Health Study [30], where participants with repeated exacerbations experienced a steeper FEV_1 decline than those without exacerbations. In fact, it has been estimated that exacerbations may account for up to 25% of the reduction in FEV_1 over time [30, 31]. Additionally, a rapid FEV_1 decline over time is associated with more frequent episodes of lower respiratory infection [32]. Thus it seems that the vicious cycle of infection and damage of the innate immune system may lead to faster progression of COPD [33].

Prevention of infectious exacerbations of COPD

Because of the large influence on patients' well-being and the course of COPD, there has been great interest in treatments that can prevent infectious exacerbations in COPD.

In this context, stopping smoking is an important tool. In addition to having a beneficial effect on the decline of lung function, stopping smoking also reduces mucus hypersecretion making the airways less susceptible to infections [8, 34].

Immunization against influenza can reduce the number of exacerbations during winter months substantially and is recommended for all patients with COPD [7, 35]. In general, the evidence for the effect of pneumococcal vaccine for prevention of infectious exacerbation in COPD is less clear than for influenza vaccination, yet also this type of immunization may be of value in COPD population [36].

Most studies of the effects of pharmacotherapy were not particularly designed to study infectious episodes in COPD, but rather to study exacerbations as such. There are a number of studies in the literature investigating possible effects of inhaled corticosteroids, long-acting bronchodilators, combination of both, mucolytics and phospodiesterase-4-inhibitors, with regard to prevention of COPD exacerbations [37–42]. Although all these compounds can reduce the number of exacerbations by approximately 20–30%, the mechanism behind this effect, although unknown, is unlikely to be a prevention of infections as such, but rather an elevation of the lung function and modification of the inflammatory response to infections and other triggers of exacerbations. Surprisingly, inhaled corticosteroids, although reducing COPD exacerbations as such, have been shown in both a controlled trial [38] and in a pharmacoepidemiological study [43] to be associated with an increased risk of pneumonia.

A more direct approach with regard to prevention of bacterial exacerbation is prophylactic treatment with antibiotics. Although a Cochrane review has only showed minor benefits from prophylactic antibiotic therapy, this could be caused by the fact that most of the studies included in this analysis were quite old and used old-fashioned antibiotics [44]. Macrolides have both anti-inflammatory and antibacterial action and studies suggest that daily treatment result in fewer and shorter exacerbations of COPD [45, 46]. Further studies using modern antibiotics for prophylaxis in subgroups of COPD patients with frequent exacerbation are ongoing and results are awaited with great interest.

In addition to above mentioned measures, perhaps also some simple advice on daily living, may reduce the number of chest infections. Most importantly, since especially viruses spread by coughing, sneezing and direct contact, it is wise for COPD patients to minimize contacts with people with obvious signs of airway infection (including taking care of their grandchildren with "snotty noses"!). Since cold weather has been shown to lead to bronchoconstriction and is also known to lead to increased numbers of exacerbations [47, 48], the patients should avoid cooling of their bodies, by wearing appropriate cloths while being outdoors, and even avoid going outdoors in if the weather is particularly cold.

Conclusion

COPD is significantly associated with an increased risk of various respiratory tract infections, in particular infectious episodes in the lower airways, but not with infections out site the respiratory system. These lower airway infections are responsible for the majority of acute exacerbations of COPD and are very likely to contribute to the faster progression of the disease. A number of non-pharmacological and pharmacological measures can be undertaken to reduce the number of infectious episodes in COPD and to reduce the deleterious effects of these infections.

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