Review Article

Risk factors for community-acquired pneumonia in adults: Recommendations for its prevention

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ABSTRACT

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in developed countries. The disease is one of the top 10 causes of death and up to the present time, standard aggressive medical care has not resulted in a decrease in mortality. Knowledge of risk factors for CAP is essential to the design of preventive measures to reduce its incidence. Preventive strategies promoting effective vaccines or identifying and acting on modifiable risk factors are of paramount importance in reducing CAP-related death. Most studies have been performed in patients referred for inpatient care or in CAP cases in which a specific pathogen has been identified, but data from population-based studies are scarcer. We present a review of the main risk factors for CAP in adults, classified in the following categories: (a) Comorbidities and their treatments, (b) demographic and socioeconomic factors, (c) lifestyle factors and (d) environmental factors. We conclude with some brief recommendations on preventive measures and vaccination.

Key words: Community-acquired pneumonia, prevention, risk factors

INTRODUCTION

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in developed countries. Knowledge of risk factors for CAP is essential to the design of preventive measures to reduce its incidence. We present a review of the main risk factors for CAP classified in the following categories:

a. Comorbidities and their treatments,
b. Demographic and socioeconomic factors,
c. Lifestyle factors, and
d. Environmental factors.

We also present a comment about vaccination and finalize with some recommendations for CAP prevention.

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COMORBIDITIES AND THEIR TREATMENT

Chronic diseases of the respiratory system like chronic obstructive pulmonary disease (COPD) play a major role in the development of CAP. These diseases represent a 2-3 fold increase in the risk of CAP in both elderly and general population.[1-5] However, risk estimates for older populations (>65 years) are higher than for the general population and one study including younger participants (<60 years) even found COPD not to be a significant risk factor for CAP.[6] These results suggest a possible interaction between chronic bronchitis/COPD and age. Several studies report that chronic lung diseases not only increase the risk of outpatient pneumonia but also the risk of CAP requiring hospitalization.[2,4,7] As for mortality associated with CAP, studies are contradictory, with some reporting no increased

risk[8,9] and with others indicating an increased risk.[7] Asthma has also been signaled as a risk factor for CAP, with five studies independently documenting an up to four-fold CAP incidence increase in asthma patients.[2-4,7,10] Nonetheless, asthma was not an independent risk factor in another three population-based studies.[3,10,11] In most studies of older people, asthma is a clear risk factor for CAP, whereas in the only study conducted of subjects of all ages >14 years[3] asthma was a nonsignificant factor, suggesting again a possible interaction with age.

The inhaled medication used by many patients with respiratory diseases may also represent a risk factor that is independent of the underlying respiratory disease and its severity.[12,13] However, the role of these drugs is not clear because the studies are heterogeneous with regard to the specific drug considered and the baseline diagnosis requiring inhaled drug treatment.[5,12] Some randomized clinical trials indicate that the use of corticosteroids may trigger a lung infection as a serious adverse event,[7,14] especially in patients with COPD.[7,9] Other authors have studied the association between beta2-agonists/anticholinergics and CAP risk, although without arriving at any clear conclusions.[13] For the sub-cohort of patients with asthma, anticholinergics showed a significant effect but steroids and beta2-agonists did not.[12] For the sub-cohort of patients with COPD, steroids were significant but beta2-agonists and anticholinergics were nonsignificant, and for the sub-cohort with chronic bronchitis, all types of steroids were nonsignificant.[12] The role of oxygen therapy in CAP is not clear, as studies have reported conflicting results. A number of population-based studies point to an association.[4,10] In a general population study, after adjusting for asthma and chronic bronchitis, oxygen therapy was identified as a risk factor.[12] However, oxygen therapy became nonsignificant in a restricted analysis of the sub-cohorts with chronic bronchitis and with COPD.[12] In a single study of elderly people, home oxygen therapy was nonsignificant after adjusting for COPD, asthma, and other factors.[4] Oxygen therapy is strongly correlated with other risk factors such as advanced chronic disorders, aging, polymedication, and institutionalization among others. It has also been associated with drying of the nasal and oropharyngeal mucosa, which, in turn, leads to superinfected lesions, difficulty in swallowing and a greater risk of aspiration.[15]

A previous upper airway infection and frequent colds have proved to be key risk factors for CAP for all age groups.[3,5,9,10,12,16] A lifelong history of pneumonia and prior hospitalizations for CAP are other well-known risk factors for CAP for all age groups[3,4,10,17] and are, furthermore, also associated with a poorer prognosis. Upper respiratory tract diagnostic and therapeutic techniques may produce contamination or affect natural aspiration barriers or may lead to the epithelial destruction of the airways and so facilitate infection.[18-21] The most studied techniques have been bronchoscopy,[22,23] nasogastric tube,[5,7,24-26] nose and throat examinations, gastroscopy, general anesthesia, tonsillectomy,[27,28] and adenoidectomy[5] However, the effect of these risk factors disappeared when adjusting for comorbidities and other confounding variables, so there is a need for more studies regarding these possible risk factors. The impact of heart failure on CAP has been widely described in both population and hospital studies.[1,2,4,6,10,11,13,17,29,30] While the reasons for this enhanced risk are not well understood, it has been postulated that alveolar fluid in the lungs of some patients promotes the multiplication of aspirated germs.[1,31] Moreover, heart failure treatments, often used in combination, have also been demonstrated to pose a possible CAP risk. Diuretics and digoxin have been studied, and also amiodarone,[10] known to be lung toxic even at low doses. Results of studies reporting a possible link between coronary artery disease and CAP are inconsistent.[1,4,10] The hypothesis regarding a possible link between coronary artery disease and pneumonia was based on the demonstration, in the early 1990s, of the presence of *Chlamydia pneumoniae* in atherosclerotic lesions of the coronary arteries.[32]

Some studies have established that diabetes increases the risk of infection due to hyperglycemia and ketosis. Some population-based studies of CAP report a significant association between diabetes and the risk of CAP,[4,29,33] whereas other studies have found no association.[1-3,5,10] Given that, results overall are inconsistent, diabetes cannot be pointed to definitively as a risk factor, even though the biological plausibility of the relationship is well established.[34]

Convulsive conditions are associated with CAP as an independent risk factor.[10] Results for various neurological conditions are not conclusive, given variations in effects, and the low prevalence of exposure in the studied populations. Population-based studies of CAP have reported an increased risk of CAP in patients with stroke and dementia.[1,4,10,11,29] Possibly attributable to dysphagia or depressed swallowing and cough reflexes. Dysphagia itself might be a risk factor for CAP in the elderly.[11,35] Studies, where dysphagia was nonsignificant, were based on populations with low exposure prevalence[36] in contrast with other studies that had higher dysphagia prevalence rates.

Gastroesophageal reflux, hiatal hernia, and gastroduodenal ulcers have not been linked to the risk of CAP[10] Association between gastric acid suppressants, and the risk of CAP had been observed.[37] The authors suggested that the reduced secretion of gastric acid ("wall acid") facilitates pathogen colonization of the upper gastrointestinal tract.[27] Other authors found no association on comparing current use against no use/past use of gastric acid suppressants.[10,13] Chronic liver disease may be associated with CAP risk. A study conducted in the elderly reported liver disease to be a risk factor for CAP[16] and a study by Fernández-Solá *et al*.,[6] also suggested that liver disease was independently

associated with CAP. In contrast, other studies conducted in more general populations found no association.[5,10] Oral pathologies are a clear risk factor for CAP. Severe periodontitis is a risk factor, whereas a dental visit in the previous 30 days was an independent protective factor for CAP[10,38] a finding that may be related to better oral hygiene.

Cancer as a risk factor for CAP has been studied in numerous published population studies.[1-5,17,29] In general, low cancer prevalence in population-based studies has meant that a statistically significant risk for CAP has not been found after adjusting for various confounders.[1-3,10,11] However, interesting results have been obtained in some studies. Thus, according to LaCroix *et al*.,[29] CAP mortality is associated with a history of cancer in women and with hospitalization for cancer in men and women. According to Koivula *et al*.,[2] immunosuppressive cancer treatments are associated with a high risk of severe CAP, hospitalization, and death. Vila-Corcoles *et al*.,[17] observed an independent risk for CAP in patients with hematological or solid organ cancers, whereas Jackson *et al*.,[4] was the only author who found a relationship between CAP and lung cancer and other serious tumors.

Recurrent bacterial pneumonia was added to the definition of AIDS in 1992, based on the fact that bacterial pneumonia rates were increased in HIV-infected individuals and were indicative of immunosuppression in this population.[39]

Other nonorgan/nonsystem specific clinical conditions may act as risk factors for CAP. Numerous studies have established that previous hospitalization is a risk factor for CAP.[10] Fedson *et al*.,[40] hypothesized that previous hospitalization could be a good marker for identifying persons with an increased risk of acquiring pneumonia and also that immunization on discharge (pneumococcal vaccination) could be a highly cost-effective prevention measure. Lipsky *et al*.,[1] suggest that the association between previous hospitalization and CAP may be due to increased exposure to multiple adverse circumstances. Disability may be a risk factor for CAP, including at low and intermediate levels of dependence.[10,11] Other studies found no association between CAP risk and being bedridden[36] or the score for activities of daily living. Regarding body mass index (BMI), low weight has been observed to be a major risk factor for CAP, possibly due to the fact that low weight is an indicator of malnutrition or of an underlying disease. Indeed, malnutrition has been associated with an increased risk of CAP[36] and with an increased risk of death from pneumonia. Being overweight or obese, has not been reported to imply a risk for CAP. An increased risk of CAP in individuals who had experienced significant weight gain during adulthood was observed, however, in a prospective study by Baik *et al*.,[41] studies have also shown that obesity can impair the immune function.[42] Nonetheless, further evidence regarding a possible link between obesity and CAP risk is required.

As for drugs, the immunosuppressive effect of oral corticosteroids, which increases vulnerability to and the severity of infections, has been widely described in the literature.[43] However, because results from different studies are to some degree inconsistent, studies with greater statistical power are necessary.[1,3-5,10,17] In relation to antibiotic use, several reviews have pointed to inappropriate antibiotic use increasing bacterial resistance to common antibiotics and also altering the normal bacterial flora of the host.[10,36] Nonetheless, no population-based studies of risk factors for CAP have found any association between taking antibiotics and CAP.[10,36]

DEMOGRAPHYC AND SOCIOECONOMIC FACTORS

Age is widely reported to be a significant risk factor for CAP, with the risk growing, especially for older people as they age. In studies conducted of subjects of all ages, only results for the oldest age brackets were significant[3,41] and in the only study conducted in young people,[41] age was not a significant factor. This would suggest a possible nonlinear effect, with older age as a risk factor for CAP. The role of gender as a risk factor for CAP is not clear, as study results are inconsistent. In four studies conducted in older people, being male was a risk factor in two studies[4,17] but was nonsignificant in the other two studies.[2,13] In the only study including subjects of all ages, being male was a protective factor for CAP.[26] There is no evidence that ethnicity plays a role as a risk factor for CAP.

Overcrowding, defined as more than 10 people living in a household, has been reported as a risk factor for CAP. A low education level has also been reported to represent a higher risk for CAP compared to higher education levels.[10] A low education level is also associated with specific dietary and hygiene habits and conditions that favor the development of CAP. In fact, education loses its effect once adjustments are made for comorbidity and for occupational status.[10] Being married or in a partnership is a protective factor in comparison to being single, widowed or separated.

LIFE STYLE FACTORS

Abundant evidence attests that tobacco is the main modifiable risk factor for CAP. It has been estimated that the risk of pneumonia increases between 50% and 400% in smokers[41] and that between 15% and 30% of CAP cases could be avoided if smoking was eliminated.[44] Multivariate analyses have shown that smoking has a direct effect on pneumonia onset that is independent of the effect of chronic bronchitis, COPD, and heart failure, with which it is also closely associated. The risk of CAP is as high in ex-smokers as in smokers in the 2 years after giving up; thereafter, risk tends to fall with years of abstinence.[5,41] The impact of passive smoking is still not well understood; although most studies have observed no significant effect in the overall population, an effect has been described for people aged 65 and older.[45]

The effect of alcohol on CAP is not clear, as studies have reported differing findings. Nonetheless, several studies agree that a high level of alcohol consumption (>40-80 g/day) is a risk factor for CAP. A study by Koivula *et al*.,[2] demonstrated a very important independent effect of alcoholism. Another study found an independent effect of alcohol only for men with high levels of alcohol consumption (>40 g/day of pure alcohol);[5] from this cut-off point, a dose-response relationship was observed, with no effect observed for moderate drinkers (<40 g/day pure alcohol), even if intake was daily. In this study, multivariate analysis revealed an effect of consumption of >80 g/day of pure alcohol, independent of smoking, chronic bronchitis, heart failure or chronic liver disease. Other authors have also concluded that heavy alcohol consumption (more than 100 g/day for men and 80 g/day for women) is an important risk factor for CAP in middle-aged people.[6] A US cohort study found no association between low or moderate alcohol consumption and CAP.[41] Other authors have come to a similar conclusion,[1,5,29] probably due to insufficient statistical power and the choice of relatively low cut-off points.

ENVIRONMENTAL FACTORS

There is abundant evidence of the effect of occupational exposure on the respiratory system,[46] most especially there is evidence of the involvement of certain substances associated with environmental pollution in the pathogenesis of major chronic lung diseases such as bronchitis,[47] bronchiolitis,[48] asthma,[49] COPD,[50] and lung cancer.[51] Nonetheless, very few studies have studied the effect of environmental substances on CAP. Soot, crystal silicon, cadmium, and cotton dust, among others, can cause COPD[50] — itself a major risk factor for CAP, — but it is not known whether the dust of these and other substances may directly lead to the development of CAP. No association has been described between CAP and occupational contact with fumes, gases, vapors, gasoline, oil, hydrocarbons, organic and inorganic fibers or ionizing and nonionizing radiation. What has been described is an independent effect resulting from recent (previous month) exposure to dust.[52] A case–control study by Palmer[53] concluded that metal fumes, especially iron, reversibly predisposes to CAP. One study shows that construction and industrial work (carpentry, painting, etc.,) is a risk factor for CAP, whereas administrative work is a protective factor.[52] The relationship between exposure to dust and the aforementioned occupations seems obvious. Referring specifically to working conditions, an association has been reported between CAP and sudden workplace changes in temperature; this effect is, moreover, independent of chronic bronchitis and respiratory infection experienced in the previous month.[51] It is likely that although the body adapts to prolonged cold, sudden changes in temperature that do not enable gradual adaptation may represent true risk factors for CAP. An analysis stratified by age showed that sudden temperature changes have a more important effect on people aged over 65 years.[10] Living or working with children aged under 15 years is also an independent risk factor for CAP. Regarding pets, it has been observed that living with cats, dogs or birds increases the risk of CAP; furthermore, the risk of CAP increases in line with the number of pets in the home. The effect of contact with domestic animals is independent of other housing conditions and comorbidity. A stratified analysis showed a significant interaction between chronic bronchitis and having birds in the home (a doubled effect).[10]

VACCINATION

Vaccination against pneumococcal disease with the pneumococcal conjugate vaccine (PCV-13) has been shown to be effective and is recommended for high-risk patients and elderly subjects, as *Streptococcus pneumoniae* is the most frequently isolated pathogen from patients with CAP.[54] A recently published trial involving 84,496 adults aged 65 years and older reports significant efficacy for the prevention of vaccine-type pneumococcal, bacterial and nonbacterial CAP, and vaccine-type invasive pneumococcal disease.[55] A 23-valent pneumococcal polysaccharide vaccine has been recommended for the routine vaccination of adults aged >65 years old and for patients at increased risk of CAP. However, there is little evidence that it is effective in elderly people or adults with chronic diseases.[56] In elderly patients, results for pneumococcal vaccination were inconclusive, with two publications regarding the same cohort[17] reporting vaccination as a protective factor and as a nonsignificant factor (in both cases adjusted for influenza vaccination). A third study with patients >65 years (also adjusted for influenza vaccination) deemed pneumococcal vaccination to be nonsignificant. However, our review of observational studies can only shade partial light on the role of vaccines, which can only be fully explored through randomized clinical trials.

The role of influenza vaccination as a protective factor for CAP is also unclear. A single general population study (>14 years) found it to be a protective factor for the whole cohort (adjusting for asthma and chronic bronchitis),[10] but to be nonsignificant in the sub-cohorts of COPD patients and of asthma patients.[12] The only study of elderly patients found vaccination to be nonsignificant.[17]

RECOMMENDATIONS FOR COMMUNITY-ACQUIRED PNEUMONIA PREVENTION

- The most frequently observed comorbidities associated with CAP are COPD, chronic bronchitis, asthma, and heart failure. We only can point to the need for heightened awareness of the risk of CAP in these patients and for appropriate management of these diseases.
- Smoking is a clear risk factor for CAP, so smoking cessation must be strongly recommended. Likewise,

passive smoking at home has been shown to be a risk factor for CAP in subjects >65 years old. Avoid exposure to tobacco smoke is also highly recommended.

- Poor oral health is related with CAP, so oral hygiene habits, which also include regular visits to the dentist, may be an effective CAP-prevention measure.
- CAP is increased in individuals with low BMI, so good nutritional and dietary practices could prevent it.
- Certain working and environmental conditions (such as contact with dust and sudden changes of temperature) have been shown to be modifiable risk factors for CAP. These factors must be avoided in exposed populations.
- In the elderly, oropharyngeal dysphagia is a major risk factor for CAP, as an impaired swallow response and delayed airway protection favor tracheobronchial aspirations and pneumonia. We propose universal screening for oropharyngeal dysphagia in elderly patients admitted with CAP and the adoption of strategies to assess and treat this condition when aspiration is suspected.
- Close and regular contact with children with respiratory tract infection has been related with an increased risk of CAP in adults. Protection against transmission is recommended.
- Pneumococcal vaccine is recommended for the routine vaccination of adults. Vaccination against *S. pneumoniae* with 13-valent PCV-13 seems to be the most promising field for improvement in the management of pneumococcal infections in elderly subjects. People with risk factors for CAP may also benefit from this vaccine.

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