Advances in the prevention, management, and treatment of community-acquired pneumonia

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Abstract

Despite the availability of powerful antibiotics, community-acquired pneumonia (CAP) remains one of the leading reasons for morbidity and mortality worldwide, and despite the availability of powerful antibiotics, there has been only little improvement in case fatality rates for many years. Consequently, it cannot be expected that novel antibiotics will substantially improve outcomes in CAP. Therefore, this review focuses on novel approaches that may reduce CAP-related mortality: the impact of immunomodulation by macrolides and fluoroquinolones and the prevention of CAP by pneumococcal vaccines.

Introduction and context

Despite the availability of powerful antibiotics, community-acquired pneumonia (CAP) remains one of the leading reasons for morbidity and mortality worldwide. Case fatality rates vary widely among patients with CAP. Recent data of the German CAPNETZ (competence network for community-acquired pneumonia) show that fatality rates were 0.5% for outpatients and 14% for hospitalized patients [1]. Owing to insufficient diagnostic tools, pathogens are detected in only 30-50% of hospitalized patients with CAP. In most studies, *Streptococcus pneumoniae* is by far the leading pathogen in CAP. A study using transthoracic needle aspiration showed that *S. pneumoniae* is found frequently when sputum and blood culture fail to detect any pathogen [2].

During the last decade, the case fatality rate of patients hospitalized with CAP has not really changed. Therefore, novel approaches are needed to further improve outcome in hospitalized patients with CAP. Recent advances in CAP include the recognition of anti-inflammatory strategies and prevention of CAP by vaccination.

Recent advances

Treatment

The primary rationale for the use of antibiotics in the treatment of CAP is undoubtedly their direct antimicrobial effect. But in the last two decades, growing evidence has shown that at least some classes of antibiotics possess beneficial properties that go beyond just killing of the causative agent; they appear to modulate the host's immune response. The best known and investigated are the immunomodulatory effects of macrolides and to a certain degree the immuno-relevant actions of quinolones.

Immunomodulatory properties of antibiotics were recognized firstly in macrolides more than 20 years ago, when the 5-year survival rate of patients with diffuse panbronchiolitis (DPB) could be improved from less than 50% (approximately 8% if the patient was chronically colonized with *Pseudomonas aeruginosa*) to approximately 90% by long-term administration of erythromycin, despite macrolide resistance of the involved pseudomonal strains and application in sub-antimicrobial doses [3,4]. Subsequently, great efforts have been taken to elucidate the underlying mechanisms

and have revealed interesting insights into the interference of antibiotic agents with neutrophil activation and mobilization, neutrophil apoptosis, activation of nuclear transcription factors, production of reactive oxygen species, airway mucus secretion, and bacterial bio-film [5]. Specifically, macrolides possess the ability to suppress the production and secretion of pro-inflammatory cytokines from monocytes and normal human bronchial epithelial cells through the inhibition of extracellular signal-regulated kinases (ERKs). Owing in part to direct and indirect downregulation of nuclear factor-kappa-B (NF-κB), this leads to decreased levels of interleukin (IL)-8, tumor necrosis factor-alpha (TNF-α), granulocyte-macrophage colony-stimulating factor, and IL-1β [6,7]. As a consequence of lower levels of IL-8 and other chemo-attractants and adhesion molecules (e.g., E-selectin and intercellular adhesion molecule-1), macrolides inhibit the recruitment and accumulation of neutrophil granulocytes at the site of inflammation and thus prevent the release of lysosomal enzymes and generation of reactive oxygen species and the resulting airway damage. This effect was confirmed recently by Bosnar *et al.* [8], who demonstrated that pre-treatment with azithromycin and clarithromycin prior to lipoploysaccharide (LPS) challenge in mice can significantly reduce total cell and neutrophil numbers in bronchoalveolar lavage fluid (BALF) and myeloperoxidase concentration in lung tissue.

Respiratory quinolones have also been shown to impair macrophage chemotaxis in rats and to significantly reduce transendothelial neutrophil and monocyte migration [9,10]. In addition, Weiss *et al.* [11] demonstrated that pre-incubation of LPS-activated human monocytes with moxifloxacin causes a concentration-dependent inhibition of the synthesis of IL-1β, IL-8, and TNF-α. Pre-incubation with moxifloxacin was also associated with reduced expressions of NF-κB, ERK, and c-Jun N-terminal kinase [11]. Recently, Ogino *et al.* [12] confirmed the inhibitory effect of different fluoroquinolones on LPS-induced pro-inflammatory cytokine production (IL-1β and TNF-α) in murine *in vivo* and *in vitro* experiments. In addition, they found that this effect can be attributed in particular to those fluoroquinolones with a cyclopropyl group at the N1 position (e.g., ciprofloxacin, moxifloxacin, grepafloxacin, and sparfloxacin).

Whereas the beneficial effects of macrolides in chronic pulmonary inflammatory conditions like DPB, cystic fibrosis, or bronchiolitans obliterans syndrome after lung transplantation are widely accepted [13], their impact on acute pulmonary inflammation is currently under intensive investigation. Experimental studies investigating the immunomodulatory actions of macrolides and

ketolides in murine models of acute pneumonia caused by *Mycoplasma pneumonia* and *Chlamydia pneumophilia* showed decreased concentrations of various pro-inflammatory cytokines (e.g., IL-1β, IL-8, and TNF-α) in BALF and reduced lung histological signs of inflammation, although complete bacterial eradication could not be achieved in all cases [14-16]. Therefore, it might be concluded that macrolides provide immunomodulatory effects in acute inflammation.

The first clinical evidence for the probability of immunomodulatory effects of macrolides, even in acute inflammation, was derived mainly from retrospective cohort studies evaluating the impact of an additional macrolide treatment in patients with CAP [17-19]. These studies could demonstrate that the addition of a macrolide to a beta-lactam significantly decreased the risk of death. This effect was also seen in severely ill patients with severe sepsis due to pneumonia [20]. Tessmer *et al.* [21] recently evaluated the benefit of beta-lactam/macrolide combination therapy (BLM) versus beta-lactam monotherapy in a prospective cohort study that included hospitalized patients with CAP. The authors could clearly demonstrate a significantly reduced adjusted mortality rate in patients with severe CAP (confusion, respiratory rate, blood pressure, and age [whether below or above 65 years old] score [CRB65] of at least 2) receiving BLM therapy. Interestingly, this effect was not seen in mild to moderate pneumonia (CRB65 of not more than 1). Finch *et al.* [22] demonstrated a similar clinical effect for quinolones.

In conclusion, there is strong evidence of an immunomodulatory effect of macrolides and some evidence of an immunomodulatory effect of quinolones in acute pulmonary inflammation and a subsequent clinical benefit in terms of improved outcome and survival in CAP. Unfortunately, most data derive from retrospective or non-randomized prospective trials. Hence, before the potential advantage of macrolides and quinolones in the treatment of CAP can be generally stated, prospective randomized controlled studies are required.

Statins are considered to have anti-inflammatory effects and prior use of statins has been linked to improved outcome of CAP. In a monocenter prospective observational study, Chalmers and colleagues [23] found that patients on statins had a higher severity of disease according to the pneumonia severity index but a decreased 30-day mortality (adjusted odds ratio 0.46). As a marker of inflammation, C-reactive protein was lower and decreased earlier in these patients. The authors controlled for the so-called 'healthy-user effect' by demonstrating that other drugs prescribed for cardiovascular disease had no influence on the outcome of CAP.

Another recent trial could not confirm a beneficial effect of prior statin use on the risk of CAP in a population-based cohort of older individuals (more than 65 years) [24]. In this case control study, inhabitants of nursing homes were excluded because they are more likely to suffer from certain severe comorbid illnesses, frailty, and cognitive or functional impairment and thus are at increased risk of pneumonia. Despite the increased risk of CAP, frail older people or those with more severe comorbidities are less likely to receive statins [25]. In addition, subjects receiving statins tend to practice other healthy behaviors, like physical activity or smoking cessation, and are more likely to have better functional status and comorbidity that is less severe. Hence, the authors postulate that a 'healthy-user bias' is responsible for the decreased CAP risk that has been described in earlier studies.

Since the two studies had different endpoints (outcome of CAP [23] versus risk of CAP [24]), it is difficult to draw any final conclusion from their findings. Therefore, the results of prospective randomized controlled trials that address the immunomodulatory properties of statins and that are currently under way should be awaited before allowing any definitive recommendation for clinical practice.

Whereas systemic steroids appear to be beneficial in patients with vasopressor-dependent septic shock and in patients with early severe acute respiratory distress syndrome (especially when critical illness-related corticosteroid insufficiency is present), their role as adjunctive treatment in patients with CAP remains controversial [26-30]. Confalonieri *et al.* [27] demonstrated that low-dose glucocorticoid infusion may have beneficial effects on organ dysfunction in severe pneumonia. Owing to the small sample size and some baseline imbalances, this study should be valued as a hypothesis-generating study rather than as a set of definitive results. In contrast to this study and other trials suggesting that adjunctive steroid treatment is advantageous in CAP [28], a recent randomized, placebo-controlled study could not confirm any improved CAP outcome attributed to steroid treatment [29].

Although adjunctive treatment with glucocorticoids in severe pneumonia is probably indicated, further randomized clinical trials are urgently needed to confirm the preliminary positive results and to define optimal dosage and duration of this treatment. A large (inclusion of more than 1000 patients is planned) randomized trial that was initiated by the Veteran Administration Cooperative Study Group and that will soon be under way in the US will probably define the significance of steroid application in CAP treatment.

Prevention

Recent advances in the prevention of CAP include two dynamic fields: vaccination (i.e., pneumococcal and influenza vaccination) and the recognition of the influence of prior medication and conditions (e.g., inhaled corticosteroids and smoking).

It has taken many years to successfully develop an efficacious vaccine against *S. pneumoniae*. The main reason is the low immunogenicity of polysaccharides, which are the target of opsonizing antibodies. Two types of vaccines are currently in clinical use.

One type of vaccine contains purified capsular polysaccharides from 23 of the known 91 pneumococcal serotypes (pneumococcal polysaccharides vaccine [PPV]-23). Polysaccharides induce primarily a B cell-dependent immune response and are not effective in children younger than 2 years of age (probably due to their immature immune system). The polysaccharide vaccine is known to reduce the rate of bacteremia, but numerous studies and a meta-analysis have demonstrated little or no effect on the prevention of pneumococcal pneumonia, particularly in immunosenescent or immunosuppressed patients [31]. However, a recent prospective, multicenter, randomized clinical trial showed reduction of pneumococcal pneumonia by 64% in Japanese nursing home residents and significantly reduced mortality from pneumococcal pneumonia in patients vaccinated with PPV-23 [32]. In a US cohort study analyzing over 60,000 patients with HIV, subjects who received PPV-23 had a lower rate of pneumonia (incidence rate ratio 0.8, 95% confidence interval 0.8-0.9) than patients who had never been vaccinated, independently of recent CD4 count, HIV viral load, antiretroviral therapy, and history of pneumonia [33]. In conclusion, results regarding the efficacy of PPV-23 in pneumonia remain controversial.

Pneumococcal conjugate vaccine (PCV) was designed for children younger than 2 years and initially contained capsular polysaccharides from seven serotypes. Capsular polysaccharides of PCV are conjugated to highly immunogenic proteins, resulting in B- and T-cell response with consequent mucosal immunity. Studies have shown that vaccination reduces the carrier rate for serotypes contained in the vaccine [34]. Since children are the main reservoir of *S. pneumoniae* (about 60% carrier rate), implementation of the conjugated vaccine has tremendously decreased invasive pneumococcal diseases by vaccine serotypes not only in vaccinated but also in non-vaccinated individuals (due to herd immunity). However, the decrease in disease by vaccine

serotypes has recently been accompanied by an increase of non-vaccine serotypes. This pre-placement of vaccine serotypes by non-vaccine serotypes is thought to be a consequence of selective pressure by the PCV-7. Most data on serotype replacement are from the US, where PCV-7 was introduced in 2000 [35]. In particular, the incidence of infections by frequently multiresistant isolates of serotype 19A, which has now been included in the extended PCV-13, has risen in the US within the last few years [36]. However, the role of PCV in replacement remains an issue of debate since countries that did not introduce PCV have also observed a rise in 19A and historical surveillance studies from Denmark report an increase of 19A before the introduction of any pneumococcal vaccine [37].

The impact of the conjugated vaccine on non-invasive pneumococcal pneumonia is estimated be much higher. As for the PPV-23, however, data from randomized controlled trials are still missing. Currently, the placebo-controlled Community-Acquired Pneumonia Immunization Trial in Adults (CAPITA) is investigating the prevention of a first episode of vaccine serotype-specific pneumococcal CAP by the conjugated vaccine in 85,000 Dutch community-dwelling adults who are 65 years or older [38]. The results are pending.

Recently, extended conjugated vaccines with 10 or 13 serotypes have been licensed. Serotype 3 has been recognized not only as a frequent cause of CAP in adults but also as an independent risk factor for septic shock [39]. Therefore, it should be kept in mind that only the conjugated 13-valent and PPV-23 contain this important serotype.

Patients with severe chronic obstructive pulmonary disease (COPD) are at increased risk for exacerbations and pneumonia. Results on inhaled steroids are conflicting. Whereas inhaled steroids decrease the frequency of exacerbations, a large nested case control study within a cohort of COPD patients from Quebec (175,906 COPD patients, of whom 23,942 were hospitalized for pneumonia) demonstrated clearly that inhaled steroids increase the risk for pneumonia in a dose-dependent manner [40]. In particular, doses above an equivalent of fluticasone 1000 μg/day seem to increase the risk relevantly.

In several epidemiological studies, smoking has been linked to increased susceptibility to CAP. A recent investigation uncovered one of the underlying mechanisms by demonstrating that smoking suppresses pulmonary innate host defense by impaired expression of antimicrobial peptides [41].

Implications for clinical practice

CAP remains a major public health threat. There are advances in treatment focusing on anti-inflammatory strategies. Some strategies can easily be transferred to daily practice (e.g., by using a combination therapy with macrolides or a respiratory fluoroquinolone with anti-inflammatory activities instead of beta-lactam mono-therapy in patients with more severe CAP).

However, currently, the prevention of pneumonia by vaccination seems to be the most promising field for real improvement. Since the performance of PPV-23 in this regard leaves room for improvement, much hope is based on the extended PCV and the results of the CAPITA study.

In the context of the current aH1N1 pandemic, it should be kept in mind that the majority of influenza-associated pneumonia cases are not primary viral pneumonia but secondary bacterial pneumonias. In the context of the recent pandemic, several studies analyzing influenza pandemics of the last century have been published. *S. pneumonia* and, to a lesser extent, *Haemophilus influenzae* and *Staphylococcus aureus* were the leading bacterial causes of secondary pneumonia [42,43]. In this regard, the impact of combined influenza and pneumococcal vaccine cannot be overestimated.

Abbreviations

BALF, bronchoalveolar lavage fluid; BLM, beta-lactam/macrolide; CAP, community-acquired pneumonia; CAPITA, Community-Acquired Pneumonia Immunization Trial in Adults; COPD, chronic obstructive pulmonary disease; CRB65, confusion, respiratory rate, blood pressure, and age (below or above 65 years) score; DPB, diffuse panbronchiolitis; ERK, extracellular signal-regulated kinase; IL, interleukin; LPS, lipoploysaccharide; NF-κB, nuclear factor-kappa-B; PCV, pneumococcal conjugate vaccine; PPV-23, 23-valent pneumococcal polysaccharide vaccine; TNF-α, tumor necrosis factor-alpha.

Competing interests

The authors declare that they have no competing interests.

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