

## Recent advances in our understanding of *Streptococcus pneumoniae* infection

Charles Feldman<sup>1\*</sup> and Ronald Anderson<sup>2</sup>

Addresses: <sup>1</sup>Division of Pulmonology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown, 2193, Johannesburg, South Africa; <sup>2</sup>Department of Immunology, Faculty of Health Sciences, University of Pretoria, 5 Bophela Road, Arcadia, Pretoria, 0083, South Africa

\* Corresponding author: Charles Feldman (charles.feldman@wits.ac.za)

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### Abstract

A number of significant challenges remain with regard to the diagnosis, treatment, and prevention of infections with *Streptococcus pneumoniae* (pneumococcus), which remains the most common bacterial cause of community-acquired pneumonia. Although this infection is documented to be extremely common in younger children and in older adults, the burden of pneumonia it causes is considerably underestimated, since the incidence statistics are derived largely from bacteremic infections, because they are easy to document, and yet the greater burden of pneumococcal pneumonias is non-invasive. It has been estimated that for every bacteremic pneumonia that is documented, three non-bacteremic infections occur. Management of these infections is potentially complicated by the increasing resistance of the isolates to the commonly used antibiotics. Furthermore, it is well recognized that despite advances in medical care, the mortality of bacteremic pneumococcal pneumonia has remained largely unchanged over the past 50 years and averages approximately 12%. Much recent research interest in the field of pneumococcal infections has focused on important virulence factors of the organism, on improved diagnostic and prognostication tools, on defining risk factors for death, on optimal treatment strategies involving both antibiotics and adjunctive therapies, and on disease prevention. It is hoped that through these endeavors the outlook of pneumococcal infections will be improved.

### The burden of pneumococcal disease

A number of significant challenges remain with regard to the diagnosis, treatment, and prevention of infections with *Streptococcus pneumoniae* (pneumococcus) [1]. Pneumococcal infections are particularly common in younger children and in older adults and may be divided broadly into invasive and non-invasive disease; the former refers to infections in which the microorganism is isolated from normal sterile body sites, such as the blood or the cerebrospinal fluid [1]. Pneumonia is one of the most common clinical presentations of pneumococcal infection and may itself be invasive (i.e. bacteremic) or non-invasive. Importantly, since much of our understanding of the burden of pneumococcal pneumonia comes from studies of bacteremic infections (because

they are easy to identify), it needs to be recognized that the true adult burden of pneumococcal pneumonia, when extrapolated from bacteremic cases alone, seriously underestimates the true overall burden of pneumococcal pneumonia. Studies undertaken to develop a conceptual and quantitative strategy for estimating the burden of non-bacteremic infections have suggested that for every bacteremic case there are three non-bacteremic infections [2].

Management of pneumococcal infections is potentially being compromised by increasing resistance of the pathogen to antibiotics commonly used to treat these infections [3-5]. However, there has been considerable debate about the true impact of current levels of

antibiotic resistance, particularly intermediate resistance, on the outcome of pneumococcal infections in patients treated with the different antibiotic classes. In the case of pneumococcal meningitis, poorer outcomes are much more likely to occur in the presence of antimicrobial resistance; however, the situation is less clear-cut with infections such as pneumonia [3]. In general, most researchers suggest that, in the case of community-acquired pneumonia (CAP), the use of appropriate  $\beta$ -lactam agents in adequate doses is unlikely to be associated with a poorer outcome but that this is not the case with regard to macrolide resistance (particularly high-level macrolide resistance) or with regard to fluoroquinolone resistance, in which failure of antibiotic therapy in patients treated with these classes of agents in the presence of antibiotic resistance is much more likely to occur [3-5].

In the US and Europe, pneumococcal disease carries a high clinical and economic burden, particularly in adults at least 50 years of age, and the mortality of invasive pneumococcal disease has remained unchanged at about 12% since the 1950s despite advances in antibiotic therapy and the introduction of pneumococcal vaccination [1]. In the case of human immunodeficiency virus (HIV) infection in the setting of sub-Saharan Africa, pneumococcal disease is second only to *Mycobacterium tuberculosis* infection as a cause of mortality [6]. The present article will review some of the recent advances that have been documented in our understanding of the diagnosis, management, and prevention of pneumococcal infection, concentrating particularly on patients with CAP.

### Community-acquired pneumonia and pneumococcal infection

Lower respiratory tract infections—and, in particular, pneumonia—remain a major cause of morbidity and mortality throughout the world, being the leading infectious disease cause of death [7,8]. Despite routine microbiological testing, the microbial etiology of CAP is not always identified, but with current laboratory investigations a diagnosis usually can be made in up to 60% of patients [9]. Studies investigating CAP etiology have consistently documented that *S. pneumoniae* (the pneumococcus) is the most common microbial cause in the vast majority of cases [9]. This holds true whether the severity of the infection is such that the patient may be treated in the community or whether hospitalization or even intensive care unit admission is required. It is also irrespective of the severity of the infection as determined objectively by the use of a severity-of-illness score, such as the pneumonia severity index [9]. More recently, it is being increasingly recognized that both seasonal and pandemic influenza may be complicated by secondary

bacterial infection, frequently by the pneumococcus. For example, one study of 128 patients during the recent H1N1 swine-origin influenza A virus pandemic documented bacterial co-infection in 42 cases (33%), and the pneumococcus was the most frequently isolated pathogen (26 cases, 62%) [10]. Other studies have confirmed the pneumococcus as one of the common bacterial secondary infections in association with critical illness associated with the 2009 influenza A (H1N1) infection [11-13].

### Pneumococcal virulence factors

The pneumococcus is a formidable adversary, possessing an array of virulence factors that it uses not only for concealment but also to evade and frustrate host defenses. The consequence is the creation of a pro-inflammatory milieu in the lower airways, which, as opposed to being protective, predisposes to inflammation-mediated tissue damage, favoring extra-pulmonary dissemination of the pneumococcus. The most significant of these pneumococcal virulence factors, which were recently described in detail elsewhere [5], and the mechanisms used to promote concealment from or evasion of host defenses (or both) are summarized in Table 1. It is well recognized that the polysaccharide capsule of the pneumococcus is an important virulence factor of the microorganism, and on the basis of differences in the immunochemistry of the capsule, it has been documented that there are more than 90 pneumococcal serotypes [14]. The importance of knowledge of these different serotypes is that it has been recognized more recently that certain serotypes are more virulent than others, are more likely to be associated with invasive disease or certain clinical disease presentations (or both), and are more likely to be associated with a poorer outcome when causing infection [14-17]. Furthermore, ongoing surveillance for the circulating serotypes is important in both the development and use of pneumococcal vaccines, such as the pneumococcal conjugate vaccine [14-17].

**Table 1. Major pneumococcal virulence factors**

Factor	Activity
Polysaccharide capsule	Attachment to respiratory epithelial cells (pro-adhesive), evasion of host defenses
Hydrogen peroxide	Pro-invasive, evasion of host defenses
Pneumolysin	Pro-invasive, evasion of host defenses
Pneumococcal surface adhesin C	Pro-adhesive, pro-invasive, evasion of host defenses
Pneumococcal surface protein A	Evasion of host defenses
Pneumococcal surface protein C	Pro-adhesive, pro-invasive, evasion of host defenses

### Diagnosis and prognostication of pneumococcal pneumonia

As indicated above, despite fairly extensive microbiological investigation, the microbial etiology of CAP is identified in 60% of patients or less. Clearly, more effective diagnostic tools are required for determining likely etiology. More recently, it has been recognized that determination of the pneumococcal load by using quantitative polymerase chain reaction (PCR) may be a useful tool for the diagnosis of pneumococcal infection and also for assessment of severity of infection and for its prognostication [1,18,19]. An earlier study quantified *S. pneumoniae* DNA levels in blood by real-time PCR in 93 patients with confirmed pneumococcal CAP [18]. A positive *S. pneumoniae* PCR was associated with a significantly higher mortality, risk for shock, and need for mechanical ventilation (MV). Logistic regression with appropriate adjustments documented bacterial load as being independently associated with septic shock (adjusted odds ratio [aOR] 2.42, 95% confidence interval [CI] 1.10 to 5.80) and need for MV (aOR 2.71, 95% CI 1.17 to 6.27), whereas bacterial loads of at least  $10^3$  copies per mL (occurring in 29% of patients) were associated with a significantly higher risk of septic shock (OR 8.00), need for MV (OR 10.50), and hospital mortality (OR 5.43). A more recent study documented that detection of pneumococcal DNA in the serum was associated with more severe disease and that there also appeared to be a dose-response effect with increasing bacterial loads being associated with increasing disease severity [19]. The authors did not find a similar association between bacterial load and disease severity with the use of sputum specimens, except for in one specific subgroup of patients, namely those who were previous or current smokers [19].

### Cardiac complications in patients with community-acquired pneumonia, including pneumococcal community-acquired pneumonia

It has been recognized for some time that a relatively high incidence of cardiac events occurs in patients with CAP, involving up to a quarter of adults admitted to the hospital, and that the occurrence of such complications may be related to poorer short-term patient outcomes [20–22]. These complications may occur even in patients without underlying cardiac disease, and also in patients at low risk of complications, based on a low severity-of-illness score [22]. Among the cardiac complications documented is new-onset, or worsening, cardiac failure, new or worsening arrhythmia, or myocardial infarction [21]. In one study of 170 pneumococcal pneumonia patients who were admitted to a hospital for management of their infection, 33 cases (19.4%) had one or more of these cardiac complications [23]. An important

additional finding was that among these pneumococcal pneumonia patients who had a cardiac event, there was a significantly higher mortality than among patients without such events ( $P < 0.008$ ). In a more recent study of 3,921 patients with CAP, of whom 315 (8%) had one or more acute cardiac events, multivariate analysis documented factors associated with these events, and among these parameters was pneumococcal etiology [24]. The authors derived a prediction rule based on these variables which could allow bedside evaluation of the likelihood of acute cardiac events [24]. Interestingly, in one study of 6,171 patients with CAP, of whom 175 (3%) developed acute coronary syndromes (ACSs), prior exposure to the polyvalent polysaccharide pneumococcal vaccine was independently associated with a 58% reduction in ACS events (adjusted hazard ratio 0.42, 95% CI 0.27 to 0.66) [25].

Sensitivity analysis suggested that these findings were related, at least in part, to a “healthy vaccinee” effect, and the authors concluded that because of this confounding the benefits of pneumococcal polysaccharide vaccine (PPV) were more likely to be much smaller than the initial analysis suggested but that the sensitivity analyses could not refute the existence of some, perhaps small, protective benefit of PPV [25]. It is now commonly recommended that CAP patients who are not reaching clinical stability in response to appropriate therapy should be evaluated for a possible cardiac event since early recognition and treatment of these events may improve patient outcomes.

### Antimicrobial treatment of pneumococcal community-acquired pneumonia

A myriad of guidelines have been developed globally describing the optimal management of CAP, including a consideration of the most appropriate antibiotic therapy [26]. Although differences are found in the recommendations from the different regions, recommendations usually include a  $\beta$ -lactam or a macrolide, or a fluoroquinolone, either alone or in certain combinations [26,27]. Many guidelines recommend that in more severely ill, hospitalized patients with CAP, the choices of antibiotic therapy are either a  $\beta$ -lactam and macrolide combination or a fluoroquinolone alone. There is some debate as to whether these two alternative regimens are equally effective, and the data are somewhat contradictory. In a study among outpatients with pneumonia, patients receiving guideline-concordant therapy were less likely to die within 30 days than those receiving non-concordant treatment, and within the former group, those receiving macrolides were less likely to die compared with those treated with a fluoroquinolone alone (aOR 0.28, 95% CI 0.09 to 0.86;  $P = 0.03$ ) [28].

A systematic review and meta-analysis by the same author among hospitalized patients with CAP documented that macrolide-based regimens were associated with a 22% reduction in mortality compared with non-macrolide-containing treatments, but the benefit was not seen in randomized controlled trials or in patients receiving guideline-concordant therapy, suggesting that guideline compliance was more important than the choice of antibiotic class [29]. Macrolide-based regimens were documented to be associated with better patient outcomes among patients hospitalized with bacteremic pneumonia (including pneumococcal pneumonia) [30]. In a recent systematic review and meta-analysis of critically ill patients with CAP, which retrieved 28 observational studies involving almost 10,000 patients, macrolide use was associated with a significant 18% relative and 3% absolute reduction in the mortality of patients compared with non-macrolide therapies [31]. Combination therapy has been shown to be of greater benefit compared with monotherapy in bacteremic pneumococcal CAP and in severely ill hospitalized patients with pneumococcal bacteremia [27,32].

The reason that macrolide combination regimens may be associated with better outcomes is uncertain and may be multifactorial in origin. Possibilities include the following:

- Cover for atypical pathogens
- Cover for polymicrobial therapy
- Cover for antimicrobial resistance
- Antibiotic synergy
- Anti-inflammatory, immunomodulatory activity of macrolides.

Many investigators, including these authors, believe that this may relate to the alternative activities of the macrolides, and the use of macrolides, in this fashion, as adjunctive therapy is described in more detail below.

#### **Adjuvant anti-inflammatory strategies in severe pneumococcal disease**

As mentioned above, a significant percentage of patients with severe pneumococcal disease will die, despite the implementation of ostensibly effective antibiotic therapy. This is due, at least in part, to misdirected inflammatory responses orchestrated by the pneumococcus which not only disrupt epithelial and endothelial barriers but also counteract the harmonious interactions

between antibiotics and host defenses which optimize the eradication of microbial pathogens [33]. In addition, the invasion of host cells, especially epithelial and endothelial cells [34], as well as erythrocytes [35], protects the pneumococcus against  $\beta$ -lactam antibiotics, which in comparison with more lipophilic agents such as macrolides are poorly taken up by eukaryotic cells [36]. Bactericidal antibiotics, such as  $\beta$ -lactams, may also exacerbate harmful inflammatory responses by causing disintegration of the pneumococcus, resulting in the release of pro-inflammatory cell wall components such as lipoteichoic acid and peptidoglycan, as well as the cytotoxin pneumolysin [37].

The primary goal of adjunctive anti-inflammatory therapy in severe pneumococcal disease is therefore to optimize antibiotic therapy and survival. Although many varied strategies have been tried, those considered to have the greatest potential are macrolide antibiotics, in particular, as well as corticosteroids and statins [5,38].

#### **Macrolide antibiotics**

As mentioned earlier, combination therapy with a  $\beta$ -lactam and a macrolide is recommended in patients with more severe pneumococcal disease. Although this approach can be justified solely on the grounds of microbiological criteria, macrolides, in addition to their primary antimicrobial activities, also possess anti-inflammatory properties that are believed to contribute to their therapeutic efficacy in severe pneumococcal disease.

Macrolides possess an unusual, dual mechanism of anti-inflammatory activity targeting both the pathogen and inflammatory cells of the host. In the case of the former, macrolides via their primary, selective inhibitory effects on bacterial protein synthesis suppress the production of pneumococcal adhesins, invasins, cytotoxins, and immunosubversins. In addition, because they are bacteriostatic as opposed to bactericidal, macrolides do not cause abrupt, potentially pro-inflammatory disintegration of target pathogens.

Neutrophil-mediated inflammation is the major target of the secondary anti-inflammatory activity of macrolides, unrelated to antimicrobial activity. Neutrophils are the predominant type of leukocyte in the circulation. They are small phagocytic cells that circulate in a relatively quiescent state and are rapidly mobilized to sites of infection, a process that is orchestrated via regional, pro-adhesive alterations to vascular endothelium. These cells use an array of indiscriminate, toxic reactive oxygen species and proteases to eliminate ingested pathogens. If inappropriately activated, however, these same

neutrophil-derived antimicrobial agents have the potential to cause considerable tissue damage [39].

Macrolides inhibit neutrophil influx by suppressing the synthesis of the neutrophil-mobilizing chemokines/cytokines interleukin-8 and tumor necrosis factor by various types of structural cells (epithelial cells, fibroblasts, and smooth muscle cells) in the airways as well as by resident lung macrophages [40,41]. These effects appear to be achieved via interference with mechanisms involved in the transcription of genes encoding these pro-inflammatory proteins [40-43].

Evidence that the anti-inflammatory activities of macrolides are operative *in vivo* has been derived from both experimental animal studies and clinical studies in humans. In the case of the former, two studies are particularly noteworthy. In the first of these, in which the investigators used a murine model of secondary pneumonia caused by an antibiotic-sensitive strain of the pneumococcus following influenza virus infection, significantly improved survival was observed in animals treated with azithromycin (macrolide) or clindamycin (macrolide-like agent) alone or in combination with ampicillin ( $\beta$ -lactam) relative to those treated with ampicillin alone [44]. Improved survival in the azithromycin/clindamycin-treated groups was associated with a reduction in indices of pulmonary inflammation and tissue damage [44]. More recently, others using a murine model of primary pneumococcal pneumonia caused by an antibiotic-resistant strain of the pneumococcus reported essentially similar findings when comparing responses to treatment with ampicillin alone and in combination with azithromycin [45]. Although the secondary anti-inflammatory activity of azithromycin is likely to have contributed to the positive outcome in both of these studies, primary antimicrobial activity cannot be excluded, even in the setting of antibiotic resistance [46,47].

In the clinical setting, justification for combination antibiotic therapy of CAP, most commonly a  $\beta$ -lactam with a macrolide, is based on a series of observational studies, prospective and retrospective, undertaken between 1999 and 2010 [5,48]. The efficacy of combination therapy, which was associated with significantly lower in-hospital and intensive care unit mortality, was attributed to improved antimicrobial coverage, encompassing pathogens that were not susceptible to  $\beta$ -lactams. Although broadening of antimicrobial coverage explains, in part, the benefit of combination therapy, several noteworthy studies have documented the apparent involvement of macrolide-mediated anti-inflammatory activity. In these studies, macrolide therapy was associated with significantly increased survival in patients

with (i) pneumonia and severe sepsis caused by macrolide-resistant pathogens, predominantly Gram-negative bacteria [49]; (ii) pneumonia caused by antibiotic-resistant strains of the pneumococcus, the so-called "*in vivo-in vitro* paradox" [50]; and (iii) acute lung injury secondary to pneumonia irrespective of the causative pathogen [51].

Although macrolides appear to be ideal adjuncts to  $\beta$ -lactams in the therapy of severe pneumococcal disease, acceptance of this strategy is not universal [52-54] and will depend on the acquisition of convincing data from large multicenter, prospective, randomized, controlled clinical trials. One such trial, currently ongoing, is the CAP-START trial (Community-Acquired Pneumonia-Study on the Initial Treatment With Antibiotics of Lower Respiratory Tract Infections - NCT01660204). This trial, which involves 2,100 CAP patients admitted to one of seven Dutch hospitals, is designed to assess the comparative efficacy of therapy with a  $\beta$ -lactam alone or combined with a macrolide, and fluoroquinolone monotherapy, with all-cause mortality 90 days after hospital admission as the primary outcome (NCT01660204). It seems important, however, that such trials address the issue of subgroups of patients most likely to benefit from macrolide therapy, specifically those at the highest potential risk from the adverse consequences of neutrophilic inflammation. These include patients who smoke and those with pneumonia secondary to influenza infection, a combination of these risk factors, or acute lung injury.

### **Corticosteroids**

These are broad-spectrum anti-inflammatory agents that are commonly recommended for the adjunctive therapy of penicillin-susceptible meningitis [55]. The situation with regard to corticosteroid use in meningitis, though somewhat controversial, appears to be more clear-cut than is the case with patients with CAP. When all the evidence is taken into account, it appears that corticosteroid use in patients with acute meningitis may be associated with a lower mortality in adults and with fewer neurological and auditory sequelae in both adults and children, in high-income countries, and particularly in the subset of cases specifically with pneumococcal meningitis [56-59]. Earlier studies involving relatively small numbers of adult patients with severe CAP [60-62], and more recently in children [63], reported a benefit of adjunctive intravenous corticosteroid therapy with respect to duration of hospital stay or mortality or both. Somewhat disappointingly, however, the promise of this adjunctive strategy has not been confirmed in one large, randomized, double-blinded, placebo-controlled trial in adults with severe CAP [64] or in another large

retrospective study [65]. Although the reasons for the apparent lack of efficacy of systemic administration of corticosteroids are unknown, it is noteworthy that neutrophils are relatively insensitive to the anti-inflammatory actions of corticosteroids [66]. In addition, it was recently reported that high levels of the endogenous corticosteroid, cortisol, are predictive of critical disease and mortality in patients with severe CAP [67].

A definitive answer on the adjunctive role of systemic administration of corticosteroids in severe CAP is likely to emerge on completion of three ongoing stringently controlled clinical trials: one in the US (Extended Steroids in CAPe-ESCAPE) (NCT01283009) and two others in Spain (NCT00908713) and Switzerland (NCT00973154).

### **Statins**

These pharmacological agents inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, an activity which underpins their therapeutic efficacy in controlling hypercholesterolemia in the prevention of cardiovascular disease and stroke. Statins, however, also possess secondary anti-inflammatory properties which are achieved via (i) interference with G-protein receptor-mediated signaling mechanisms in immune and inflammatory cells [68] and (ii) induction of the enzyme heme oxygenase-1 which, in turn, mediates the synthesis of anti-inflammatory proteins [69]. Both mechanisms have the potential to control harmful neutrophilic inflammation.

Statin use for the prevention of cardiovascular disease has been reported in a number of largely retrospective studies to confer a significant survival advantage on patients with bacterial CAP (reviewed in [70,71]) as well as in those with documented pneumococcal disease [72]. Although these protective effects of statins may result from their secondary anti-inflammatory activity, other mechanisms have also been proposed. These include protection against acute cardiac events triggered by pneumonia [70] as well as possible interference with the cytotoxic and pro-inflammatory activities of the cholesterol-binding pneumococcal toxin, pneumolysin [5].

Given the limitations of the largely observational studies reported to date, together with the uncertainty surrounding the exact therapeutic mechanisms involved, randomized controlled studies are essential to conclusively establish a link between current statin use and reduced mortality from CAP [71,73].

### **Immunization strategies**

Pneumococcal vaccine development is targeted primarily at the anti-phagocytic, polysaccharide capsule, the major

virulence determinant of the pathogen. The existence of about 94 immunogenic capsular variants (serotypes), however, has complicated vaccine development. The number of serotypes covered in polysaccharide-based vaccines is therefore determined by serotype virulence and prevalence. Two types of vaccine are currently available, those which contain a cocktail of unconjugated purified capsular polysaccharides and those in which the capsular polysaccharides are conjugated to a carrier protein to enhance immunogenicity. Of these vaccine types, those in current use are the pneumococcal polysaccharide vaccine 23 (PPV23), which contains unconjugated pneumococcal capsular polysaccharides from 23 different serotypes, and the more recently developed conjugate vaccine, PCV13 [74]. The latter vaccine contains capsular polysaccharides from 13 prevalent serotypes conjugated to an attenuated, common protein carrier immunogen, diphtheria toxin cross-reactive material 197 (CRM197) [74].

In addition to coverage of the predominant serotypes causing pneumonia and invasive pneumococcal disease, immunogenicity in high-risk groups is the primary criterion for vaccine efficacy. These include the very young and the elderly in particular as well as smokers, HIV-infected persons, and other high-risk groups associated with secondary immunosuppression. Limitations of PPV23 include poor efficacy in the very young and the elderly, who because of immature and senescent immune systems, respectively, respond poorly to unconjugated pneumococcal polysaccharides [74,75]. The efficacy of PPV23 for adults in high-risk groups is enhanced when preceded by PCV13 in a so-called "prime-boost" strategy, with the two vaccines being administered at least 8 weeks apart [76].

Currently, PCV13 appears to be the most effective pneumococcal vaccine, having been introduced into childhood immunization programs in many countries. It is also licensed for use in other high-risk categories and for adults who are 50 years old or older. Importantly, in a very recently completed multi-center, double-blind, placebo-controlled trial to which 84,496 older Dutch patients (65 years old or older) were recruited (the CAPITA trial: Community-Acquired Pneumonia Immunization Trial in Adults), PCV 13 was found to be protective against a first episode of vaccine-type CAP and invasive disease [77].

On a cautionary note, the widespread use of PCVs has raised concerns about "serotype replacement", meaning nasopharyngeal colonization with non-vaccine serotypes which, in turn, can cause active infection. Although this appears to have been an issue with first-generation PCVs, specifically PCV7 [78], it is likely to be less so with the

newer extended-coverage vaccines, PCV13 and PCV15, which include the most invasive serotypes of the pneumococcus [79]. Nonetheless, given the potential of vaccine-induced selective pressure to promote nasopharyngeal colonization with capsular-switch, penicillin-resistant variants, continued vigilance is essential [80,81]. Pipeline and future vaccines are focused largely on highly conserved pneumococcal proteins as well as whole-cell vaccines, which may provide much broader, serotype-independent protection [74].

## Conclusions

Much progress is being made in our understanding of the pneumococcus and of pneumococcal infections. The true burden of disease is now better recognized. New molecular mechanisms of investigation may well pave the way for better identification of the presence of pneumococcal colonization and of active infections. Additional factors that may be associated with poorer outcome of infections, such as cardiac complications, are being better recognized, and aspects of more optimal treatment, both with antibiotics and with adjunctive therapies, are being delineated. Additional strides in disease prevention in both children and adults, with the development of more effective vaccines, are taking place. It is hoped that all these advances in our understanding of the disease will ultimately lead to a better outcome among the patients.

## Abbreviations

ACS, acute coronary syndrome; aOR, adjusted odds ratio; CAP, community-acquired pneumonia; CI, confidence interval; HIV, human immunodeficiency virus; MV, mechanical ventilation; OR, odds ratio; PCR, polymerase chain reaction; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

## Disclosures

Charles Feldman has acted on the advisory boards of, and received honoraria for presentations and received support for congress travel from, pharmaceutical companies marketing and manufacturing macrolide antibiotics—Pfizer and Abbott—and pneumococcal vaccines (Pfizer). Ronald Anderson declares that he has no disclosures.

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