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REVIEW

Pneumolysin as a potential therapeutic target in severe pneumococcal disease

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Summary Acute pulmonary and cardiac injury remain significant causes of morbidity and mortality in those afflicted with severe pneumococcal disease, with the risk for early mortality often persisting several years beyond clinical recovery. Although remaining to be firmly established in the clinical setting, a considerable body of evidence, mostly derived from murine models of experimental infection, has implicated the pneumococcal, cholesterol-binding, pore-forming toxin, pneumolysin (Ply), in the pathogenesis of lung and myocardial dysfunction. Topics covered in this review include the burden of pneumococcal disease, risk factors, virulence determinants of the pneumococcus, complications of severe disease, antibiotic and adjuvant therapies, as well as the structure of Ply and the role of the toxin in disease pathogenesis. Given the increasing recognition of the clinical potential of Ply-neutralisation strategies, the remaining sections of the review are focused on updates of the types, benefits and limitations of currently available therapies which may attenuate, directly and/or indirectly, the injurious actions of Ply. These include recently described experimental therapies such as various phytochemicals and lipids, and a second group of more conventional agents the members of which remain the subject of ongoing clinical evaluation. This latter group, which is covered more extensively, encompasses macrolides, statins, corticosteroids, and platelet-targeted therapies, particularly aspirin.

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Introduction: the burden of pneumococcal infection

There have been several studies published in the recent literature attesting to the high clinical and economic burden of community-acquired pneumonia (CAP) in both developing and developed countries, with associated considerable morbidity and mortality.[1–4] Furthermore, review of the worldwide literature indicates that currently the microbial aetiology of CAP can be established in up to 60% of cases of CAP, with *Streptococcus pneumoniae* (the pneumococcus) being the most common bacterial cause overall, irrespective of whether the cases are mild enough to be treated in the community, or whether admission to hospital or even the intensive care unit (ICU) is required.[5] While pneumococcal infections may be invasive (organism present in normally sterile sites) or non-invasive, it is clear that the burden of both invasive and non-invasive pneumococcal disease in adults is determined primarily by the presence of pneumonia.[6] However, while much is known about the incidence rates for CAP and invasive pneumococcal disease (IPD) in adults in developed countries,[6] there is much less information on the burden of pneumococcal disease in adults in the developing world.[7]

There are a number of challenges remaining with regard to pneumococcal infections, not least of which are the limitations of the current diagnostic tools, particularly those for detection of non-bacteraemic infections, such that the incidence of pneumococcal pneumonia is most likely to be significantly underestimated.[8] One systematic review and meta-analysis concluded that for every case of bacteraemic pneumonia there were likely to be at least three additional non-bacteraemic infections.[9] Another systematic review of the burden of PCV-preventable pneumococcal disease in the United Kingdom indicated that it continues to be high despite the impact of PVC13 and that estimates of IPD cases represent a fraction of the total pneumococcal disease burden.[10]

Other important issues include the need for defining host risk factors for pneumococcal infections in adults and their possible association with mortality, as well as the role of the various serotypes in severity of illness and outcome and, lastly, the impact of various aspects of antibiotic treatment on mortality.[8] It is concerning that despite all advances in medicine, the case fatality rate for patients hospitalised with IPD has remained constant in the region of $\sim$12% since the 1950s.[8]

Risk factors for pneumococcal infections

Much has been written recently specifically about risk factors for pneumococcal infections.[11–15] Older age, or ageing, possibly associated with immunosenescence, places individuals at risk for developing pneumococcal infections.[15] A range of lifestyle factors (smoking, alcohol, being underweight, regular contact with children and poor dental hygiene) and underlying comorbid conditions (chronic respiratory disorders, especially chronic obstructive pulmonary disease; asthma; cardiovascular and cerebrovascular conditions; Parkinson's disease; epilepsy; diabetes mellitus; dementia; HIV infection; chronic renal and liver disease) not only increase the risk of pneumococcal infections, but may also impact negatively on both short-term and long-term outcomes following pneumococcal pneumonia.[11,13] Patients with asplenia or splenic dysfunction, such as occurs in patients with sickle cell anaemia, are at significantly increased risk of fulminant infections with various microorganisms, and particularly the pneumococcus.[16–19] It is important to recognise that some adults, particularly those $\geq$65 years, may have multiple comorbid conditions and that the odds ratios for acquiring IPD in individuals with two or more comorbid conditions may be comparable with those of conditions classified as being very high risk for development of CAP and IPD.[14]

Complement deficiencies predispose patients to infections with encapsulated bacteria, such as the pneumococcus, and polymorphisms in the human mannan-binding lectin gene (MBL2) have also been linked to increased susceptibility to pneumococcal infections.[16] Immunoglobulin deficiencies have also been noted to be frequent in patients with pneumococcal infections, being particularly associated with IPD.[20] Most toll-like-receptors and interleukin (IL)-1 receptors signal through myeloid differentiation primary response 88 (MyD88) and IL-1 receptor-associated kinase 4 (IRAK-4) and infants and young children with deficiencies in both these proteins are highly susceptible to IPD.[21,22] Furthermore, patients with deficiencies of two proteins involved in the nuclear factor κB (NF-κB) signalling pathway, namely NF-κB essential modulator (NEMO) and IκBκ, have also been documented to increase susceptibility to infections with the pneumococcus.[21] Lastly, environmental factors, such as the occurrence of influenza and other viral infections places individuals at risk of secondary bacterial infections in the lungs, particularly pneumococcal infections.[12]

Virulence determinants and the pathogenesis of pneumococcal infections

A myriad of review articles has been published recently, describing in detail the multiple virulence factors of the pneumococcus, as well as the pathogenesis of pneumococcal disease, a detailed description of which is beyond the scope of this manuscript.[15,23–27] The obligatory first step in the pathogenesis of pneumococcal infections is colonisation of the nasopharynx by the microorganism, with the factors that govern colonisation having been fairly well characterised, including the anti-phagocytic polysaccharide capsule, the pore-forming cytolysin, pneumolysin (Ply), surface adhesins, several of which also subvert complement deposition, pilus proteins, biofilm formation, and various enzymes.[24,25,27] It is also important to note that the presence of other microbes in the nasopharynx can also influence pneumococcal colonisation and invasion.[24,25]

Development of IPD necessitates the translocation of the microorganism from the nasopharynx to the disease sites, including the lungs, bloodstream and meninges alone or in combination.[26] The exact mechanisms underlying the transition of the pneumococcus from colonisation to invasion are incompletely understood and the subject of much study.[27] However, at these disease sites, a complex interaction occurs between various pneumococcal virulence