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Management of serious pneumococcal pneumonia — Pathogenesis

Prise en charge des pneumonies graves à pneumocoque — Pathogenèse

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Introduction

Streptococcus pneumoniae (or simply "pneumococcus") has proven to be amazingly resilient, thriving despite a century of attempted serum therapies, chemotherapeutic agents and preventative vaccines designed against this microorganism. Sir William Osler's designation of the pneumococcus 100 years ago as "the captain of all the men of death" continues to hold true today. This microorganism's capacities to bind to respiratory epithelial surfaces, avoid host immune clearance, compete with co-resident airway microbial species, resist antimicrobial agents and invade the host are truly remarkable.

S. pneumoniae is a common inhabitant of the upper respiratory tract, existing primarily as a commensal bacterium along with other resident microorganisms along the respiratory epithelium. Once colonised by one of the over 90 serotypes, the new serotype will persist for weeks (in adults) or months (in children), usually without any adverse sequelae. The carrier state, which is readily detectable in 5–10% of healthy adults, 20–40% of healthy children and up to 60% of children in day care settings, is critically important in the maintenance of the organism within human populations.

Pneumococcal virulence factors

A large number of gene loci contributes to the entire complement of genes necessary for invasive pneumococcal disease. Virulence in pneumococci is a multifactorial and polygenic process; some virulence gene products only add to virulence potential in specific tissues or in the presence of other virulence genes (conditional virulence genes). An example is the pneumococcal serine-rich repeat protein (PsrP). This surface adhesin protein does not participate in colonisation or survival in blood but is essential to invasion across host alveolar membranes in bacteraemic pneumonia. Some virulence genes are expressed only when sufficient bacterial populations exist within biofilms.

The capsular antigen of pneumococci is the most important virulence determinant for this microorganism. The capsule serves multiple important roles during colonisation, invasion and dissemination from the respiratory tract. The capsule prevents mechanical clearance by mucous secretion, and facilitates the transit of the organism to the epithelial surface. Capsular polysaccharide is highly negatively charged and sterically inhibits the interaction between phagocytic CR3 receptors to iC3b, and Fcγ receptors to the Fc component of IgG fixed to cell wall antigens on pneumococci. Thick capsules (more opaque colony types) are more complement resistant and promote invasion. Paradoxically, thinner capsules (transparent phenotypes) are better for colonising mucosal surfaces owing to reduced electrostatic forces and steric hindrance when binding to epithelial cells. Pneumococci overcome this problem by phase variation in the amount of capsule produced depending upon its immediate microenvironment.

Pneumolysin is an essential virulence factor expressed by virtually all invasive strains of S. pneumoniae. This pore-forming cytotoxin is released by pneumococci as a soluble enzyme that oligomerizes on the cell surface and then lyses host cells. The toxin has many other pathophysiological properties, including the ability to inhibit the ciliary action of epithelial cells, activate CD4+ T cells, impair respiratory burst of phagocytic cells, induce the production of chemokines and cytokines, stimulate complement fixation and activate inflammation by linking to TLR4 on immune effector cells. Pneumolysin-negative mutants of S. pneumoniae are significantly less likely to produce lethal pulmonary infections than wild-type pneumococci.

Other cellular elements of S. pneumoniae that induce proinflammatory networks include the membrane phospholipid lipoteichoic acid (LTA) and cell wall polysaccharide (ligand for C-reactive protein [CRP] and classical complement pathway activation). Autolysin enhances innate

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immune responses during invasive pneumococcal infection by its lytic actions upon the peptidoglycan cell wall. Autolysin releases free peptidoglycan components, LTA and pneumolysin, all of which induce proinflammatory signals in host tissues.

Pattern recognition receptors and pneumococci in the respiratory tract

Pattern recognition receptors (PRRs) are key components of the innate immune system. They recognize conserved motifs expressed by pathogens referred to as pathogen-associated molecular patterns (PAMPs). Several PRRs contribute to the initiation of an effective innate immune response to the pneumococcus.

C-reactive protein (CRP) binds phosphorylcholine in the pneumococcal cell wall, which results in activation of complement. Human CRP exerts protective effects against lethal infection produced by intravenous injection of S. pneumoniae in mice. The generally accepted notion that binding of CRP to S. pneumoniae is a prerequisite for its protective effect was recently challenged by a study demonstrating that CRP mutants that bind neither phosphorylcholine nor intact pneumococci still protect mice against lethality after intravenous administration of S. pneumoniae. Although it remains to be established to what extent CRP contributes to an effective innate immune response to pneumococci in the lungs, it likely contributes to host defence during bacteraemic pneumonia.

Macrophage receptor with collagenous structure (MARCO) is a member of the class A macrophage scavenger receptors. MARCO expressed by alveolar macrophages is capable of binding and internalising S. pneumoniae in vitro. As a consequence thereof, MARCO-/- mice displayed a markedly reduced resistance against pneumococcal pneumonia, as reflected by accelerated growth of pneumococci and increased mortality.

Toll-like receptors (TLRs) have a central role as PRRs in the initiation of cellular innate immune responses. TLRs can be expressed on the cell surface (TLR1, -2, -4, -5 -6 and -10) or in intracellular compartments, in particular within the endosomes (TLR3, -7, -8 and -9). Viable and heat-killed S. pneumoniae are primarily recognized by TLR2. LTA is a major pneumococcal TLR2 ligand; TLR2 is essential for cellular activation by purified pneumococcal LTA. LTA released in culture supernatants of pneumococci signals via TLR2 and TLR2-deficient (TLR2-/-) mice do not develop airway inflammation upon intrapulmonary delivery of pneumococcal LTA in vivo. Other TLRs that are able to sense pneumococcal components are TLR4 and TLR9. TLR4 can transmit the proinflammatory effects of pneumolysin. In addition, S. pneumoniae contains unmethylated CpG-containing DNA that can potentially bind TLR9. The relative importance of different TLRs in host defence against S. pneumoniae in the airways has been studied in several in vivo models. Although killing and phagocytosis of S. pneumoniae by murine neutrophils are impaired in the absence of TLR2, TLR2 does not play a major role in host defence against pneumococcal pneumonia. TLR4 has been implicated in host defence against pneumococcal invasion through its capacity to recognize pneumolysin. TLR4 may play a role in defence against pneumococcal infection of the lower airways, although only TLR4-deficient mice demonstrated enhanced bacterial growth and mortality after inoculation with a relatively low infectious dose. Recent data suggest that pneumolysin-induced TLR4 signalling can compensate for TLR2 deficiency during pneumonia with S. pneumoniae: pneumolysin-deficient (but not wild-type) pneumococci showed enhanced growth in lungs of TLR2-/- mice. In an investigation that compared multiple TLR-deficient mice after intranasal infection with S. pneumoniae, only TLR9-/- mice displayed enhanced bacterial growth and dissemination and a reduced survival; in this study, the immune responses detected in TLR1-/-, TLR2-/- and TLR6-/- mice were unremarkable. In accordance with a role for TLR signalling in host defence against pneumococcal pneumonia, mice deficient for the common TLR adaptor protein myeloid differentiation primary-response protein 88 (MyD88) had a profoundly enhanced growth of pneumococci and a strongly reduced survival after intranasal infection.

The relevance of TLR signalling in host defence against pneumococcal infections in humans has been provided by the description of children with a genetic deficiency for IL-1 receptor-associated kinase 4 (IRAK4, a kinase acting directly downstream from MyD88), who are especially vulnerable for developing invasive pneumococcal disease. In addition, a single nucleotide polymorphism in the TLR adaptor protein (TIR-domain-containing adaptor protein [TIRAP]) influences host defence against S. pneumoniae in men: heterozygous carriage of a polymorphism encoding a leucine substitution at Ser180 of TIRAP (TIRAP S180L), resulting in attenuated TLR2 signalling, was associated with protection from invasive pneumococcal disease.

CD14 is a PPR that can interact with a variety of bacterial components including peptidoglycan and LTA. CD14-/- mice were strongly protected against dissemination of S. pneumoniae from the respiratory tract, which was associated with a profoundly reduced lethality. Intrapulmonary delivery of recombinant soluble CD14 to CD14-/- mice rendered them equally susceptible to S. pneumoniae as wild-type mice. Considering that TLR signalling contributes to host defence during pneumococcal pneumonia, these data suggest that S. pneumoniae specifically uses (soluble) CD14

in the bronchoalveolar compartment to cause invasive disease by a TLR-independent mechanism.

Cells involved in the innate immune response to pneumococcal pneumonia

The fact that respiratory epithelial cells are important for host defence against pneumococcal pneumonia is illustrated by studies using transgenic mice with overexpression of a degradation-resistant form of IκB-α in alveolar and bronchial epithelium. These mice, in which the expression of NF-κB-driven proinflammatory genes is inhibited in respiratory epithelial cells, demonstrated an increased growth of pneumococci upon intratracheal infection. Pulmonary surfactant is a mixture of lipids and proteins that is abundantly present in the fluid lining the alveolar epithelium. Surfactant protein (SP)-A and -D bind to S. pneumoniae, whereas the in vivo relevance of SP-A in pneumococcal pneumonia remains to be established; SP-D-/- mice displayed a reduced pulmonary clearance of intranasally administered S. pneumoniae accompanied by early bacteraemia.

Alveolar macrophages are able to phagocytose and kill S. pneumoniae and to clear pneumococci from the lower airways without the help of recruited neutrophils after infection with a low bacterial dose. Upon induction of pneumonia with a high infectious dose, neutrophils are recruited and alveolar macrophages do not play an important role in the clearance of S. pneumoniae anymore. In this case, alveolar macrophages are pivotal for phagocytosis and clearance of apoptotic neutrophils. Macrophages themselves also undergo apoptosis during pneumococcal pneumonia, which is associated with an inhibition of the inflammatory response. Moreover, macrophage apoptosis facilitates killing of S. pneumoniae and limits pneumococcal invasion into the bloodstream.

The classical concept of neutrophil migration involving selectin-mediated rolling and β2-integrin-mediated tight adhesion to the endothelium does not apply to pneumococcal pneumonia. Recently, galectin-3 has been implicated as a soluble adhesion molecule important for the recruitment of neutrophils during lung infection with S. pneumoniae. Galectin-3-/- mice recruited fewer neutrophils into their airways upon infection with S. pneumoniae, which was accompanied by an enhanced bacterial growth and dissemination. The local production of CXC chemokines also contributes to the influx of neutrophils to the primary site of infection during pneumococcal pneumonia. Several experimental studies have documented a pivotal role for neutrophils in protective immunity against S. pneumoniae pneumonia. During respiratory tract infection by serotype 3 pneumococci, antibody-induced neutropenia resulted in an increased mortality and an enhanced growth of pneumococci in postinfluenza pneumonia. In addition, depletion of neutrophils caused an enhanced bacterial growth in the lungs after intranasal inoculation with a high infectious dose of serotype 4 S. pneumoniae. Of note, a recent study has suggested that neutrophils may not be essential for host defence against pneumococcal pneumonia in all cases: depletion of neutrophils prior to lung infection with a serotype 8 pneumococcal strain resulted in prolongation of survival and less bacterial growth in blood.

Intranasal infection with S. pneumoniae resulted in an early accumulation of T cells in the lungs, a response that was dependent on the presence of pneumolysin. Importantly, major histocompatibility complex II-/- mice, which display strongly reduced CD4+ T cell numbers, demonstrated an increased pulmonary growth and dissemination of pneumococci associated with a higher mortality upon induction of pneumonia, indicating that CD4+ T cells contribute to innate resistance against pneumococcal infection.

Inflammatory mediators of innate immunity in pneumococcal pneumonia

The clearance of pneumococci from the circulation strongly depends on opsonisation by complement components and by phagocytosis of bacteria by the reticuloendothelial system. Disruption of the common C3 pathway results in a profoundly impaired resistance against pneumococcal pneumonia. Only recently the relative contribution of the three complement enzyme cascades (the classical, the alternative and the mannose-binding lectin [MBL] pathways) in host defence against pneumococcal pneumonia has been unravelled. Upon in vivo intranasal infection, both the classical and alternative pathways were required for innate immunity, as demonstrated by increased susceptibilities of both C1qa-/- and factor B (Bf)-/- mice. Nonetheless, C1qa-/- mice showed an increased lethality when compared with Bf-/- mice after intranasal infection with S. pneumoniae, suggesting that the classical pathway is the dominant complement pathway for innate immunity to pneumococci in the lungs. Moreover, C4-/- and C1qa-/- mice were similarly susceptible to infection with S. pneumoniae, indicating that a loss of the MBL pathway does not significantly affect innate immunity to S. pneumoniae.

Recognition of pneumococci by immune cells present in the respiratory tract results in the release of pro- and anti-inflammatory cytokines. For several of these mediators, a clear role in innate defence against pneumococcal pneumonia has been established. Tumour necrosis factor (TNF)-α is of particular importance in this respect. Inhibition or elimination of TNF-α strongly facilitated the growth and dissemination of pneumococci. IL-1 appears to play a similar, albeit less strong, protective role: IL-1 receptor type

I-deficient (IL-1r-/-) mice infected with S. pneumoniae displayed an increased bacterial outgrowth. Of considerable interest, treating IL-1r-/- mice with a neutralizing anti-TNF antibody made them extremely susceptible to pneumococcal pneumonia, indicating that TNF-α and IL-1 collaborate in mounting an effective immune response to pneumococcal pneumonia. Other proinflammatory cytokines important to combat pneumococci that invade the lower respiratory tract include IL-6 and IL-18, whereas the anti-inflammatory cytokine IL-10 impairs defence mechanisms during both primary and postinfluenza pneumococcal pneumonia.

Treatment recommendations for pneumococcal pneumonia

Soon after penicillin became available for clinical use in the late 1940s, the remarkable and essentially uniform activity of penicillin against S. pneumoniae made penicillin the standard of care for the treatment of community-acquired pneumonia. Penicillin-resistant strains of S. pneumoniae first appeared in the mid-1970s, and resistant clones have now spread worldwide. Intermediate and even high level resistant S. pneumoniae isolates found outside the central nervous system can still be treated with high-dose, beta-lactam antibiotics (penicillins or 3rd or 4th generation cephalosporins). Meningitis due to S. pneumoniae with even intermediate levels of resistance to pneumococci necessitates the use of other agents to assure successful outcome. Expression of antimicrobial resistance by pneumococci to macrolides, fluoroquinolones, vancomycin, sulfa-trimethoprim and a variety of other antimicrobial agents is now increasingly recognized worldwide.

One additional unresolved issue in antimicrobial therapy is the advisability using combination therapy with beta-lactam and either macrolide or respiratory fluoroquinolone for bacteraemic pneumococcal pneumonia. Several retrospective and small prospective studies have indicated a possible survival advantage to combination therapy, even when the pneumococcal isolate is found to be susceptible to penicillins or cephalosporins. It has been postulated that some in vivo synergy might exist with combination therapy. Alternatively, combination therapy might treat some unrecognized co-pathogens not covered by the beta-lactams (e.g., Mycoplasma, Chlamydophila spp. or other atypical pathogens). Finally, macrolides and fluoroquinolones might provide a survival advantage by limiting excessive inflammation in severe pneumococcal pneumonia. Convincing clinical evidence from prospective studies, and a clear explanation for the purported mechanism of protection afforded by combination therapy, will be needed before dual therapy can be generally recommended in bacteraemic pneumococcal pneumonia.

While controversy remains about the risk–benefit ratio for the use of recombinant human activated protein C in severe sepsis and septic shock, this therapy remains a consideration in selected cases of severe pneumococcal pneumonia.

Conclusion

Multiple genes and virulence factors expressed by S. pneumoniae contribute to its capacity to cause infection of the lower respiratory tract. On the host side, many innate immune pathways have been shown to be important for an adequate defence against pneumococcal pneumonia. Now that we have begun to understand the molecular pathogenesis of pneumococcal pneumonia, the challenge for the years to come will be to exploit new insights into the dynamic and complex interactions between the pneumococcus and the host, clinically.

Conflit d'intérêt : l'auteur déclare ne pas avoir de conflit d'intérêt.

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