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Improving therapeutic strategies for secondary bacterial pneumonia following influenza

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Summary

Secondary bacterial pneumonia following influenza is an old problem which is re-emerging. Despite rapid advances in our armamentarium of antimicrobials, the case-fatality rate for this frequent complication of influenza remains high. In some settings, common treatment options may actually contribute to poor outcomes, as rapid lysis of pathogenic bacteria on the backdrop of an activated immune system responding to influenza may lead to inflammatory damage in the lung. An understanding of the interrelated contributions of the antecedent viral infection, the invading bacteria, and the host immune response is necessary to formulate an appropriate therapeutic approach. Prevention and resolution of these fulminant infections will require new approaches including alternate treatment strategies, combination therapies targeting several aspects of the pathogenic process, and, potentially, immunomodulation. In the not-so-distant future, strategies aimed at disarming pathogens without eliminating them may be more effective than our current treatment paradigms.

Since the discovery of antibacterial sulfonamides in the 1930s, the only accepted treatment paradigm for bacterial pneumonia has been to kill the invading organisms as quickly and thoroughly as possible. Despite a rapid expansion over the ensuing decades of our armamentarium of drugs developed to accomplish this goal, pneumonia continues to be a common and deadly problem worldwide. Part of the reason for this is the role influenza viruses play in the pathogenesis of pneumonia, both increasing the incidence of clinically significant pneumonia and worsening the severity of disease [1]. This interaction between influenza and bacterial pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus* was first recognized in 1803 by Laennec and came into sharp focus during the great Spanish Flu pandemic of 1918–1919, during which 40–50 million persons died, many from secondary bacterial pneumonia [1,2]. Over the last decade, influenza and pneumonia together have ranked as the 7th leading cause of death in the United States for all persons and the 5th leading cause of death for children [3]. In the developing world, the problem is even more acute, as respiratory tract infections are the leading cause of death in children outside of the neonatal period [4]. As a measure of this disparity, the mortality rate for pneumonia in children in developing countries is more than 25 times higher than in the United States [3,4]. It is clear from these sobering statistics that new approaches are needed.

One of the potential reasons for this startlingly high death toll from a common clinical problem is the effect of influenza on the pathogenesis and response to therapy of bacterial pneumonia.

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Scadding was the first to note this in 1937 when he described a case series of patients with secondary bacterial pneumonia and noted that mortality was much higher when the two entities were combined than when they afflicted individuals separately [5]. This view was supported by careful epidemiologic studies during the 1957 pandemic, when it was shown that the severity of illness and case fatality rate from pneumonia when influenza was a co-pathogen simultaneously with a bacterial pathogen was higher than in cases where the two infections were separated by some distinct period of recovery [6]. Furthermore, the development of antibiotics appears to have had little impact on the outcome of bacterial pneumonia complicating influenza, as it has been noted that the mortality rate from secondary bacterial pneumonia has not changed from the pre-antibiotic era [5] through the early antibiotic era [7] to the modern era [8].

A mouse model of secondary bacterial pneumonia following influenza was developed by one of the authors of this perspective (JAM) to test specific hypotheses regarding this interaction [9] and evaluate potential new treatment strategies [10]. Data from this model support the concept that traditional therapy of secondary pneumococcal pneumonia is suboptimal in combined infections, as mice treated with ampicillin, a beta-lactam antibiotic, were unable to survive pulmonary infections despite clearance of bacteria from the lungs [8]. In this Perspective we will highlight the limited pre-clinical and clinical data on the topic of treatment of secondary bacterial pneumonia following influenza and speculate as to the directions future therapeutic interventions might take. Adding urgency to this quest to understand and develop new treatment paradigms is the emergence of community-associated strains of methicillin-resistant *S. aureus* (CA-MRSA) which are readily capable of cooperating with influenza viruses to cause fatal pneumonias. An apparent increase in the incidence of these co-infections has recently led the Centers for Disease Control of the United States to issue a Health Advisory on the subject [11].

Treatment of complicated infections is complicated

Since Austrian and Gold demonstrated the efficacy of penicillin in the treatment of adults with pneumococcal pneumonia more than 40 years ago [12], penicillin or other beta-lactam agents have been considered to be the treatment of choice for most patients with pneumococcal pneumonia. The general goal of treatment has been to eliminate pathogens as rapidly as possible, so bactericidal agents have been preferred. The Infectious Diseases Society of America /American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults [13] continue to specifically recommend beta-lactam agents as definitive therapy for pneumococcal pneumonia, including that complicating influenza. However, the recent emergence of clinically significant pneumococcal resistance to penicillin and the third generation cephalosporins (cefotaxime, ceftriaxone) [14], has resulted in failures of beta-lactam therapy in the treatment of pneumococcal meningitis and, rarely, septic arthritis.

The impact of beta-lactam resistance on the outcome of pneumococcal pneumonia, however, remains controversial [15]. Although some treatment failures have been reported, intravenous administration of high doses of beta-lactams is successful in most patients with uncomplicated pneumococcal pneumonia regardless of resistance patterns [15,16]. The few documented treatment failures appear to be associated with infections caused by pneumococcal strains with very high minimum inhibitory concentrations (MICs 4 μg/ml or greater for penicillin, 2 μg/ml or greater for cefotaxime / ceftriaxone [16] or cefuroxime [17]. For this reason, concordance between the choice of antibiotic and the resistance pattern of *S. pneumoniae* is usually not the most important factor in clinical outcome for patients with pneumococcal pneumonia [18, 17].

On the other hand, beta-lactam agents will routinely fail in the treatment of pneumonia and other serious infections caused by CA-MRSA. Until recently, MRSA were important causes of nosocomial pneumonia but were rarely associated with community-acquired pneumonia. This changed with the emergence and dramatic spread of CA-MRSA in the United States and other parts of the world [19,20,21]. Unlike the previous experience with community-acquired pneumonia caused by methicillin-susceptible staphylococci, the marked recent increase in pneumonia caused by CA-MRSA strains has not been limited to young infants, instead affecting children [19,22], adolescents [22] and adults [23].

While inadequate antibiotic coverage may certainly lead to treatment failure in bacterial pneumonia (e.g., that caused by MRSA), success in treatment of pneumonia often may be more related to host factors or the presence of co-pathogens. Age is the greatest predictor of mortality, coupled with inter-related factors such as underlying chronic medical conditions and multi-lobar involvement. Involvement of multiple lobes and bacteremia are both associated with more fulminant presentations, and are more commonly seen in association with influenza. We have suggested that one effect of influenza virus co-infection may be to accelerate the tempo of the pneumococcal infection, facilitating spread throughout the lung and invasion of the bloodstream before the host can mount an appropriate immune response [8]. Austrian and Gold argued that treatment of fulminant cases during the early period prior to development of specific immunity was ineffective [12], which may help explain the higher case fatality rates during co-infection with influenza virus since these infections tend to be rapidly progressive and complex. Fulminant and necrotizing pneumonia has long been associated with *Staphylococcus aureus*, and again these infections may be particularly severe in patients infected with influenza [24].

Prevention may be easier than cure

Since severe secondary bacterial pneumonia is often refractory to treatment, the best approach may be to prevent co-infections altogether by targeting one or more of the components of the interaction. Vaccination is clearly the preferred means to prevent such infections. Use of seasonal inactivated influenza vaccine has been demonstrated to decrease the incidence of hospitalization and death for influenza and pneumonia [25], and use of a conjugate pneumococcal vaccine has been shown to prevent virus-related lower respiratory tract infections [26]. In unvaccinated patients, however, treatment of the preceding influenza infection may be the only way to positively impact development of bacterial superinfections. Data from the mouse model support this idea. Treatment of influenza virus infected mice with the neuraminidase inhibitor (NAI) oseltamivir prevented most secondary bacterial pneumonias [10,8], and slowed the progression of those infections which did develop, allowing cure with ampicillin [8]. Antiviral therapy could be initiated as late as 5 days after infection with a positive effect on secondary bacterial disease and survival in the model. This is an important point, as current recommendations for use of the NAI class of drugs suggest use only in the first 48 hours of clinical symptoms, as the effects on the viral illness itself are minimal after virus has spread throughout the lungs. In mouse studies, improved outcomes were mediated by abolition of the influenza virus neuraminidase's support for bacterial adherence in the lung, not by a decrease in viral titers as is the goal in therapy of primary influenza [10,8,27]. Inhibition by rimantadine, a member of the adamantane class of influenza antivirals which targets the M2 ion channel, did not mediate similar effects [8].

In humans, analyses of clinical trials of NAIs suggest similar effects. Studies of NAIs in both children and adults have shown lower rates of otitis media, sinusitis, pneumonia, and antibiotic use in patients receiving therapy [28,29]. Meta-analyses of NAI trials support the utility of these drugs in the prevention of secondary complications of influenza, with the caveat that the most vulnerable groups such as the elderly and those with high-risk conditions have been poorly

studied thus far. Similar benefits on secondary complications of influenza have not been seen with the adamantane drugs amantadine and rimantadine [30]. There are no data from humans at present addressing the question of whether late therapy of influenza has an effect on secondary complications independent of the effect on the primary illness, as was seen in the mouse model [10,8]. However, in the setting of high risk patients, in whom complications such as bacterial pneumonia are common and potentially deadly, the low rate of side effects from NAIs and the promising pre-clinical data may make a case for treatment regardless of the timing relative to the primary infection. Recent guideline support this suggestion, “treatment of antigen- or culture-positive influenza with antivirals in addition to antibiotics is warranted, even if the radiographic infiltrate is caused by a subsequent bacterial superinfection.” [13]

Another situation where treatment with NAIs may be indicated is after the development of the secondary bacterial infection. One prominent finding in the pre-clinical model is elevated viral titers during the super-infection, which may contribute to worse outcomes. Louria et al. suggested this was the factor mediating worse outcomes in patients co-infected with influenza virus and *S. aureus*, arguing that these severe pneumonias were poorly responsive to antibiotics because the viral pneumonia was worsened by the bacteria [6]. Antiviral therapy may diminish this secondary viral burst during combined infection, allowing better outcomes when combined with antibacterial treatments.

Are we using the wrong antibiotics?

We have made the argument above that treatment of severe secondary bacterial pneumonia with beta-lactams is not always an effective strategy. One poorly understood aspect of severe lung infections is the contribution of the host inflammatory response to disease and death. In pre-clinical models the inflammatory response is needed to control bacterial infections [31], but too much inflammation leads to lung damage and increased mortality [32]. An emerging concept in the study of severe infections is that a balance of anti- and pro-inflammatory activity is necessary for resolution of infection and survival [33]. Rapid lysis of bacteria using agents such as beta-lactams which target and disrupt the bacterial cell wall releases pro-inflammatory components containing pathogen-associated molecular patterns (PAMPs) which are recognized by the innate immune system, triggering an inflammatory burst [34,35]. In a setting where an intense inflammatory process is already underway, such as during influenza, the augmented response may be more detrimental that curative. Parallels can be drawn to the pathogenesis of meningitis, where inflammation within the closed space bounded by the skull is the cause of most of the associated morbidity [35].

One potential solution to this problem is killing the bacteria without lysing them. Compared with beta-lactams, exposure of pneumococci to non-lytic antibiotics (including macrolides, clindamycin, or rifampin) results in diminished release of proinflammatory components of the organism [35] - including virulence factors containing PAMPs such as pneumolysin, lipoteichoic acid and bacterial DNA. Macrophages exposed to pneumococci in the presence of clindamycin (compared with beta-lactam antibiotics) produce and secrete less TNF-α and nitric oxide [36]. A similar reduction in the magnitude of the macrophage inflammatory response is observed when these cells are stimulated with other gram-positive cocci (e.g, *S. aureus, Streptooccus agalactiae*) in the presence of clindamycin or other non-lytic antibiotics alone or in combination with beta-lactams [37,38]. Nau et al. have demonstrated the potential relevance of these observations in a rabbit model of pneumococcal meningitis: treatment with a non-lytic antibiotic such as rifampin (compared with ceftriaxone) resulted in the reduced release of LTA and other bacterial products into the CSF [35], diminished accumulation of TNF-α and other host cytokines in the CSF, and, most importantly, reduced mortality [35] in these animals. Limited data from these investigators suggests that the benefits of rifampin therapy in this model are preserved when used in combination with ceftriaxone [35]. A possible

parallel with these animal studies comes from a recent clinical study of Memphis children with pneumococcal meningitis: we found that children receiving early therapy with vancomycin and a beta-lactam agent had a worse outcome with higher rates of hearing loss [39].

In the setting of severe lung infections where the inflammatory response may be a significant contributor to pathology, these observations provide a rationale for alternative approaches to the standard cell-wall active agents currently in clinical use. Testing this theory in the mouse model of secondary bacterial pneumonia has shown promising results. Mice with pneumococcal pneumonia following influenza can be clinically cured using a protein synthesis inhibitor such as clindamycin or a macrolide such as azithromycin, but do not survive if treated with the cell wall active agent ampicillin [40]. Combination therapy beginning with clindamycin and adding ampicillin 24 hours later gave similar results. Although this strategy has not been tested in combined viral-bacterial pneumonia in humans, it has been (indirectly) assessed in complicated pneumococcal pneumonia. Two retrospective studies [41,42] and one prospective, multicenter trial [43] have concluded that the addition of a macrolide to a beta-lactam results in a significant reduction in mortality (compared with beta-lactam therapy alone) in adults with bacteremic pneumococcal pneumonia. One issue requiring further study is how much of this benefit is derived from the mechanism of action, how much from potential anti-inflammatory effects of the compound, and how much from treatment of unrecognized co-pathogens [44]. Nonetheless, initial therapy with an antibiotic unlikely to induce rapid lysis and inflammation followed by more specific therapy designed to eradicate the organism may be a tenable approach to severe lung infections.

Is there a role for immunomodulation?

An increasing appreciation for the role of the immune response in the pathogenesis of severe lung disease has fueled study of immunomodulation as a potential new strategy. In some cases, such as sepsis or bacterial pneumonia, this would be an adjunct to treatment of the underlying cause. In others, such as acute respiratory distress syndrome where the inciting pathogen may have been eliminated but the disease process continues to evolve, restoration to a baseline state may be the desirable outcome. Influenza viruses stimulate an intense pro-inflammatory reaction in the lung manifest by infiltration of neutrophils, monocytes, and T-cells and driven in part by the expression of the short immunostimulatory protein PB1-F2 [45]. This response is exaggerated with certain highly pathogenic influenza viruses such as H5N1 strains infecting humans in Southeast Asia [46], and it has been suggested that control of the cytokine storm is a necessary adjunct to inhibition of the virus [47]. Study of rare genetic defects suggests such an approach may be feasible. Patients with deficiencies in components of innate immune pathways, such as interleukin-1 receptor associated kinase 4 (IRAK-4), are susceptible to invasive infections from pyogenic bacteria, but typically do not manifest symptoms or signs of disease even with serious and widespread infections [48]. If such a state could be induced while treating an infection with rapidly effective antimicrobial agents, better outcomes might be possible.

Several attempts have been made to intervene in this manner in the context of sepsis (reviewed by Vincent et al., [49]) or ARDS [50]. Many of the approaches seek to neutralize toxins and/or inflammatory mediators and are rational extensions of previous studies performed *in vitro* and/or in animal models. Though some clinical trials employing immunomodulatory strategies for patients with suspected sepsis, meningitis, or ARDS have yielded encouraging results (steroids for *Haemophilus influenzae* meningitis in infants and pneumococcal meningitis in adults; activated protein C for treatment of selected adults with sepsis), the majority of such studies have yielded inconsistent (steroids for ARDS) or frankly disappointing (anti-TNFα therapy for sepsis) findings. The generally disappointing outcome of these studies is likely

related to the heterogeneity of patients, pathogens, and clinical stage of illness that greatly complicates studies of patients with sepsis or septic shock [49].

In the lung, an intense inflammatory state arises during secondary bacterial pneumonia following influenza, characterized by strikingly elevated levels of pro-inflammatory cytokines, chemokines, and a massive influx of neutrophils and monocytes [51]. In the mouse model targeted inhibition or deletion of the pro-inflammatory cytokine TNF-α or the neutrophil chemokine MIP-1α worsened disease and mortality, indicating the inflammation is essential for control of the infection [52]. Deletion of the pro-inflammatory PB1-F2 protein from the inciting virus by reverse genetic methods, however, greatly reduced the incidence and the severity of secondary bacterial pneumonia [45]. Thus, in a manner analogous to the downstream effects of inhibition of the viral neuraminidase [10], inhibition of the PB1-F2 protein by antibodies or small molecule therapeutics either alone or in conjunction with other inhibitors may reduce the secondary complications of influenza.

Perspective

The history of our interactions with pathogenic microorganisms has to this point been one of antagonism. Over millennia we have developed a complex and sensitive immune system to identify and eliminate harmful bacteria and viruses. In the last century, however, this contest between humans and bugs has changed, as we have introduced foreign substances, e.g. antibiotics, into the fight. This strategy may in some ways work against the innate controls which we have evolved, as the inflammation induced by lysis of bacteria triggers or amplifies our innate responses beyond what is needed for pathogen clearance, leading to poor outcomes. Our immune system does not have a means to recognize that these invading pathogens are going to abruptly disappear, nor a ‘switch’ to turn itself off when it is suddenly unneeded. Even if we were to develop means to control the unintended consequences of pathogen elimination, this evolutionarily “new” strategy of using antibiotics is being countered by the pathogens in the form of resistance, which is developing at a greater pace than we can produce new lethal compounds. In the short term, more research is needed into alternate antibiotic strategies that effectively eliminate pathogens without causing rapid lysis and the resulting inflammatory response.

A better strategy may be to learn to live with the bugs rather than attempt to eliminate them. While pathogenic interactions get most of our attention, the great majority of interactions with microorganisms are mutualistic, resulting in harm to neither the pathogen nor the person [53]. In fact, most so-called pathogens including *S. pneumoniae* and *S. aureus*, the primary bacteria that cooperate with influenza virus to cause secondary pneumonias, live as commensals throughout most of their life cycles. We propose further study of what makes these bacteria pathogens, particularly in situations where they are likely to convert from commensals to invaders, such as during an infection with a respiratory virus or following damage to the respiratory tract (e.g., cigarette smoking). While it can be argued that study of virulence is a major effort in the field, most of these studies are done in “clean” systems, without the critical influence of factors that might modulate disease. Typically these experiments are done in the context of searching for ways to eliminate organisms rather than co-exist with them.

In the context of dual infection, it may be factors that are important to the interaction between the potential pathogens that need targeting, not the pathogens themselves. If we understand and can interfere with several of the specific interactions between influenza virus and *S. pneumoniae*, for example, influenza may just result in a bad “cold” and pneumococcus may remain a harmless commensal, instead of together representing a leading cause of death. Perhaps active immunization strategies, passive immunotherapy, or small molecule therapies can be devised which target an array of virulence factors such as the influenza A virus PB1-

F2 and the pneumococcal pneumolysin. Without expression of potent virulence factors in the context of a co-infection, most pneumonias will be prevented by our innate immune controls, and those that do occur can be treated without the complication of an excessive inflammatory response. Just as we now supplement milk and orange juice with calcium, future strategies may include substances that modulate the expression of virulence factors crucial to pathogenicity as a part of our diets, encouraging mutualistic interactions rather than pathogenic relationships. We are not terribly far from understanding the basics of pathogenicity for many organisms – it is the shift in focus of the research community to study commensality and the conditions that create opportunities for pathogenicity that is needed going forward.

Executive Summary

Complicated pneumonia continues to be difficult to treat

- Despite advances in medical care and numerous new antibiotics, the case fatality rate for complicated bacterial pneumonia has not decreased appreciably since the introduction of penicillin.

- Antecedent infections with influenza virus plays some role in this, as the virus appears to worsen the clinical presentation, the tempo of progression, and the host immune response to the pneumonia.

Treatment with cell wall active agents may contribute to poor outcomes

- Lysis of bacteria may contribute to detrimental host inflammatory responses, particularly when the immune system has been primed by antecedent viral infection.

Preventing or treating the viral infection helps

- Vaccination and treatment with neuraminidase inhibitors to prevent or dampen the viral infection appears to be a good strategy in both pre-clinical and clinical studies of complications following influenza.

Alternative treatment for bacterial pneumonia may be preferable

- Pre-clinical and clinical studies of complicated pneumonia suggest use of non-cell wall active agents either alone or as adjuncts to beta-lactam therapy may decrease the inflammatory response, preventing the immune-mediated lung damage that contributes to the pathogenesis of severe pneumonia.

- Study of this approach specifically during secondary infections following influenza is only in the early pre-clinical stages, but appears promising.

Novel approaches are needed

- An improved understanding of the complex interactions between virus, bacteria, and the host may lead to strategies targeting the pathogenic interactions, rather than the pathogens themselves.

- The future may hold a more holistic approach where modulation of the immune response or modification of the interactions of potential pathogens with the human host leads to commensality rather than disease.

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Abbreviations

MRSA, ; CA-MRSA, ; NAI, ; ARDS, ; PAMPs, ; MIC, .