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Postviral Complications
Bacterial Pneumonia

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KEYWORDS

• Influenza • Respiratory viruses • Bacterial pneumonia • Innate immunity • Interferons

KEY POINTS

- Pneumonia remains one of the leading causes of death in the United States and worldwide.
- Influenza and other respiratory viral infections often predispose individuals to a more severe clinical course with greater morbidity and mortality than bacterial pneumonia alone.
- Postviral bacterial pneumonia is mediated by complex interactions between viruses, normal nasopharyngeal bacterial flora, and the host immune system.
- Current management strategies are largely directed toward influenza vaccination and selection of appropriate antimicrobial agents.
- Novel diagnostic tests and therapies that address the complex pathogenesis of postviral bacterial pneumonias are needed to mitigate this potentially serious complication, particularly given the ongoing threat of influenza pandemics.

BACKGROUND

Introduction

As the so-called Spanish flu raged around the world during 1918 to 1919, the burden of morbidity and mortality resulted not only from influenza infection but also from subsequent bacterial pneumonia, accounting for more than 90% of the estimated 50 million deaths caused by the pandemic.[1–4] During the 1957 and 1968 influenza pandemics, secondary bacterial infection was associated with 50% to 70% of severe infections, with the decrease attributed to the advent of antibiotics.[5–7] Coinfection was noted in approximately 30% of those infected during the H1N1 pandemic in 2009, particularly in fatal cases.[8–11] Despite substantial advances in medicine and the availability of potent antibacterial and antiviral agents, influenza and pneumonia remain among the leading causes of death in the United States and worldwide.[12,13] The complex mechanisms underlying the pathogenesis of postviral bacterial pneumonia are incompletely understood, but involve a variety of host and microbial factors that allow secondary opportunistic bacterial infections to arise in virally infected individuals. This article reviews the current understanding of how virally infected hosts are more susceptible to bacterial pneumonia as well as the management of this important complication of viral infections.

Common Causal Organisms

Viral-bacterial coinfections are a commonly encountered clinical problem. Although the precise rates of secondary bacterial infections are difficult to quantify because of a lack of comprehensive reporting systems and the impracticality of obtaining microbiologic testing in all patients with respiratory infections, bacterial pneumonia

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is estimated to complicate from 0.5% to 6% of influenza infections, with higher rates among hospitalized patients in intensive care units and fatal cases. Influenza is one of many viral pathogens that have been associated with bacterial coinfections.[14] Human parainfluenza virus, adenovirus, human metapneumovirus, measles, respiratory syncytial virus (RSV), human rhinovirus, and coronavirus are also commonly associated with secondary bacterial pneumonia.[15–22] Of these viruses, influenza is arguably most important given its continuously evolving virulence factors and the sheer number of individuals infected on an annual basis. Given its public health importance, as well as the fact that influenza is the most extensively studied, bacterial pneumonia following influenza infections is the primary focus of this article.

Irrespective of the offending viral organism, causal agents of secondary bacterial pneumonia largely reflect colonizing nasopharyngeal flora. This finding has fueled the theory that viral infection causes impaired mucosal and ciliary clearance of these normally nonpathogenic bacteria, which enables particular bacteria to flourish and causes invasive infections. Epidemiologically, *Streptococcus pneumoniae* and *Staphylococcus aureus* (both methicillin-sensitive *S aureus* and methicillin-resistant *S aureus* [MRSA]) are most common, with *Streptococcus pyogenes* and *Haemophilus influenzae* less frequently isolated.[23–27] However, infections in humans are often polymicrobial, involving combinations of multiple viruses and/or bacteria. Common viral-bacterial coinfections are summarized in **Table 1**.

Clinical Presentation

The incidence of bacterial pneumonia mirrors the seasonal nature of viral infections, with increases during peak viral seasons.[19,28–31] Data from the 2009 H1N1 epidemic show that coinfection usually occurs within the first 6 days of influenza infection,[32,33] although it can develop up to 14 days after other viral infections. This delay likely represents the time needed for viral replication and the immunomodulatory effects of infection to occur.[34–36] Patients with secondary pneumonia tend to have a more severe, protracted course, with increased mortality compared with those without antecedent viral infection.[7,25,30,31,33,37–41] Although patients with comorbid conditions or at the extremes of age are at increased risk of complicated influenza infections, even previously

Table 1
Common viral-bacterial coinfections and their associated clinical infections in human hosts

Virus	Known Bacterial Coinfections	Associated Secondary Infections
Influenza	*S pneumoniae* *S aureus* *S pyogenes* *H influenzae* *Moraxella catarrhalis* *Neisseria meningitidis*	Pneumonia Otitis media Sinusitis Meningitis
Respiratory syncytial virus	*S pneumoniae*	Pneumonia Bronchitis/bronchiolitis
Adenovirus	*S pneumoniae* *H influenzae* *M catarrhalis*	Pneumonia
Coronavirus	*H influenzae*	Pneumonia
Human rhinovirus	*S pneumoniae* *H influenzae* *S aureus* *M catarrhalis*	Pneumonia Sinusitis Otitis media
Parainfluenza virus	*S pneumoniae* *M catarrhalis*	Pneumonia
Human metapneumovirus	*S pneumoniae*	Pneumonia Bronchitis
Measles virus	*S pneumoniae* *S aureus* *H influenzae*	Otitis media Pneumonia Tracheobronchitis

healthy patients can develop severe respiratory failure and death from bacterial pneumonias following influenza, underscoring the clinical significance of this problem.

Secondary bacterial pneumonia is one of several known infectious complications of respiratory viruses. Viral infections have also been associated with acute otitis media and bacterial sinusitis in children.[42–44] In addition, meningococcal meningitis has been reported as a complication of influenza infections.[45]

PATHOGENESIS

Several excellent reviews have been published of the current mechanistic understanding of how viral infections increase susceptibility to secondary bacterial pneumonias.[46–49] Thus, this article provides only a brief overview, with a primary focus on virally mediated effects on pulmonary host defense and subsequent impairment of bacterial clearance (**Table 2**). However, the authors acknowledge that microbiologic and epidemiologic factors can contribute to the pathogenesis of viral-bacterial coinfections.

Colonization

Colonization of the nasopharynx is generally the first step in the development of pneumonia and other bacterial infections of the upper respiratory tract, including sinusitis and otitis media.[50,51] *S pneumoniae*, *S aureus*, *H influenzae*, *S pyogenes*, and *Moraxella catarrhalis* are normal inhabitants of the upper respiratory tract in healthy human hosts, with the lower respiratory tract generally considered to have low abundance of bacteria.[52,53] Although these bacteria normally exist in an equilibrium governed by host, intermicrobial, and environmental factors,[54–56] under the appropriate circumstances, they can proliferate and become invasive. Studies have shown an inverse relationship between nasal carriage of *S pneumoniae* and *S aureus*.[55,57,58] Other groups have

Table 2
Known or suspected steps in the pathogenesis of secondary bacterial pneumonia

Immune Function	Viral-mediated Effect
Nasopharyngeal colonization	• Altered host microbiota, possibly in favor of more pathogenic organisms
Direct mucosal/epithelial damage	• Breakdown of mucin by viral and bacterial neuraminidase • Destruction of epithelium and exposure of basement membrane • Impairment of ciliary function
Enhanced bacterial adherence	• Cleavage of sialic acid → exposure of receptors for bacteria on mucosal surface
Alveolar macrophage response	• Decreased number of AMs after viral infection • Downregulation of MARCO (macrophage receptor with collagenous structure) receptor resulting in impaired phagocytosis of bacteria • Reduced chemokine expression and immune cell recruitment • Desensitization of Toll-like receptors → long-term immune defects
Neutrophil response	• Possible reduced recruitment to the lung • Decreased phagocytic function • Reduced production of reactive oxygen species • Impaired NETs function
Altered cytokine milieu	• Increased type I interferons → reduced macrophage and neutrophil recruitment to the lung • Increased type II interferons → impaired macrophage phagocytic function, possible viral skewing of neutrophils • Attenuated T_H17 cell function and decreased IL-17 secretion → increased susceptibility to *S pneumoniae*, decreased production of antimicrobial peptides

Abbreviations: AMS, alveolar macrophages; IL, interleukin; NETs, neutrophil extracellular traps; T_H, T-helper.

revealed antagonistic as well as synergistic relationships between members of the normal respiratory community (eg, corynebacteria and *S aureus*, *Corynebacterium accolens* and *S pneumoniae*, *H influenzae* and *S pneumoniae*).[59–62]

In addition, viruses can alter bacterial composition. Our laboratory recently examined changes in the nasal microbiome following intranasal administration of live attenuated influenza vaccine. Although individual hosts had disparate microbiome profiles at baseline, after vaccination, the relative abundance of staphylococcal and *Bacteroides* species was significantly increased. This finding suggests that viral stimuli can alter the host microbiota, potentially by creating a suitable environment in which an otherwise nonpathogenic organism can grow and become invasive.[63,64]

Mucosal Barrier Function and Bacterial Adherence

Disruption of the mucosal barrier is an important potentiating mechanism for secondary bacterial infection. Mucin present in the respiratory tract can be partially degraded by viral and bacterial neuraminidase.[65,66] Viral neuraminidase is tropic for the sialic acid present on respiratory epithelial cells, cleavage of which may uncover receptors for bacterial ligand, thereby promoting bacterial adhesion and infection. Furthermore, the increased availability of sialic acid in the airway has been shown to promote growth and proliferation of pneumococcus, which uses this moiety as a nutrient source.[67] In murine models, higher levels of viral neuraminidase are associated with increased severity of secondary bacterial infection, whereas treatment with oseltamivir decreases bacterial adherence to epithelial cells.[68–70]

Influenza and paramyxoviruses such as RSV can also augment bacterial adhesion by augmenting expression of receptors for bacteria on the epithelial cell surface. One example is platelet-activating factor receptor (PAFR), which binds to the phosphorylcholine present in some bacterial cell walls and facilitates bacterial invasion.[71] In a mouse model of pneumococcus pneumonia, PAFR was shown to increase total lung bacterial load, bacteremia, and mortality.[72] However, blocking this receptor did not show any benefit in an influenza coinfection model, suggesting that this mechanism is not a sufficient factor for enhancing susceptibility to secondary bacterial pneumonias.[73] Other receptors involved in adhesion, such as CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) and ICAM-1 (intracellular adhesion molecule 1), are overly expressed on pulmonary epithelial cells after viral infection as well.[74,75]

Epithelial cell death and breakdown of tight junctions resulting from viral infection can cause increased translocation of bacteria such as *H influenzae*.[76,77] In addition, certain bacterial species have a known binding affinity for the basement membrane and extracellular matrix proteins,[78–81] suggesting that breakdown of the epithelium might lead to increased translocation, although this has never been proved to be a critical mechanism during infections with less cytotoxic strains of influenza in vivo. In addition, viral respiratory infections are known to negatively affect respiratory ciliary function, thereby impairing the host's ability to mechanically clear aspirated pathogens from the lung.[82,83]

Macrophage and Neutrophil Function

Resident alveolar macrophages (AMs) play an integral role in host defense against viral and bacterial pathogens alike. As the main resident innate immune cells to encounter pathogens in the resting lung, they engage in phagocytosis and killing, antigen presentation, recruitment of other cell types, and paracrine and endocrine signaling. Viral respiratory infections are known to impair macrophage phagocytic function as well as monocyte chemotaxis to the lung early after influenza infection, and this has been proposed as a potential cause for secondary bacterial infection.[49,84–89] In mouse models of sequential influenza-bacterial infection, AMs are known to be decreased in number with increased susceptibility and mortality to secondary bacterial challenge. Influenza infection has also been shown to downregulate expression of the class A scavenger receptor MARCO on AMs, which phagocytose unopsonized bacteria in the lung.[34] Augmenting AM numbers and function by exogenous granulocyte-macrophage colony-stimulating factor in animals infected with influenza improves pneumococcus clearance following secondary bacterial challenge, increases reactive oxygen species, and decreases incidence of secondary pneumonia.[90–92]

Viral infections affect the ability of AMs to attract other cell types to the lung. Neutrophils are robustly recruited following the elaboration of chemokines by AMs and epithelial cells in the setting of invasive bacterial infection. Our laboratory has shown that macrophage expression of neutrophil chemoattractants CXCL1 (C-X-C motif chemokine ligand 1) (KC) and CXCL2 (C-X-C motif chemokine ligand 2) (MIP2) is reduced after influenza infection, with consequent diminished recruitment of neutrophils to the lung.[93] Desensitization of

Toll-like receptors (TLRs) on alveolar macrophages may partially explain the decrease in neutrophil recruitment and impaired bacterial clearance. Mice infected with influenza or RSV showed decreased activation of nuclear factor kappa-B (NF-KB) and expression of KC and MIP2, resulting in decreased neutrophil recruitment to the lung after stimulation with bacterial ligands.[94] In addition, influenza infection results in an early, prolonged decrease in PMN (polymorphonuclear cell) phagocytic function and depressed reactive oxygen species production.[92,95–98] Thus, during viral infection, multiple aspects of pulmonary innate immunity are compromised, leading to impaired antibacterial host defense.

Viral Effects on the Cytokine Milieu

Viral infection elicits a robust cytokine response via activation of TLRs and retinoic acid inducible gene (RIG-I) in immune cells and downstream upregulation of NF-KB. This response results in production of type I and II interferons (IFN) as part of the host antiviral response, and these in turn alter other cytokine-mediated effects.

Type I interferons

Predominantly comprised of multiple IFN-alpha proteins and 1 IFN-beta protein, these antiviral mediators can be secreted by multiple different immune cells and help to limit viral replication.[89,99] Induction of type I IFNs is known to increase the risk of secondary bacterial infection,[34,93,99–102] despite type I IFNs also contributing to host antibacterial response.[103] Mice deficient in the type I IFN receptor are protected against subsequent bacterial challenge after influenza infection, likely because type I IFNs inhibit KC and MIP2 production and neutrophil recruitment to the lung.[93,104] Monocyte and macrophage recruitment to the upper respiratory tract is suppressed by type I IFNs via blockade of Nod2-mediated expression of CCl2 (C-C motif chemokine ligand 2; a macrophage chemoattractant), with resultant increase in carriage of *S pneumoniae*.[100] These studies highlight the heterogeneous effects of IFNs in the immune response to pathogens.

Type II interferon (interferon-gamma)

Viral respiratory infection also stimulates IFN-gamma production, primarily by natural killer cells but also by CD4+ T-helper (T_H) cells and CD8+ cytotoxic T cells and neutrophils. In the context of secondary bacterial pneumonia following influenza, IFN-gamma has been shown to impair phagocytosis in alveolar macrophages, partially by downregulation of the scavenger receptor MARCO.[34] Inhibition of interleukin (IL)-10 results in increased neutrophil recruitment to the lung and improved clearance of *S pneumoniae*, and can salvage animals from death after sequential influenza-bacterial infection.[105,106] However, in normal hosts, exogenous administration of IL-12 results in increased levels of IFN-gamma in the lung, robust neutrophil recruitment, and improved innate pulmonary defense against *S pneumoniae*. In addition, in mouse models of *S pneumoniae* and *S aureus* pneumonia, IL-12–independent IFN-gamma production by neutrophils in the lung was shown to be essential to bacterial clearance, possibly because of IFN-gamma–regulated production of neutrophil extracellular traps (NETs).[107,108] These paradoxic findings in naive hosts versus hosts infected with influenza suggest that neutrophils recruited in the setting of viral respiratory infection are unable to mount antibacterial functions that would normally be activated by interferon-gamma, which may reflect distinct neutrophil phenotypes in the setting of viral versus bacterial infections. Unpublished data from our laboratory show striking transcriptional differences in neutrophils that are recruited to the lung in the setting of influenza and sequential influenza–*S pneumoniae* infection, compared with those recruited in the setting of *S pneumoniae* infection alone.

T-helper 17 cells and interleukin-17

Influenza infection is known to attenuate T_H17 cell–mediated immunity. Type I IFNs decrease production of IL-1β and IL-23, which are necessary for polarization of T_H17 cells.[109] During influenza–*S aureus* coinfection, there are resultant decreases in IL-17, IL-22, and monocyte chemoattractant protein-1 that correlate with reduced clearance of bacteria.[101] They also likely inhibit IL-17 secretion by gamma-delta T cells, resulting in increased susceptibility to secondary *S pneumoniae* infection.[109,110] In addition, influenza infection in mice was shown to suppress production of antimicrobial peptides in response to subsequent *S aureus* infection via a T_H17-mediated mechanism, leaving animals more susceptible to pneumonia. Exogenous administration of the antimicrobial peptide lipocalin 2 restored bacterial clearance in these animals.[111]

CLINICAL MANAGEMENT

Diagnostic Testing

Differentiating severe viral infection from viral-bacterial coinfection is a common diagnostic dilemma at the point of presentation, given the significant overlap in symptoms and laboratory markers. Microbiologic culture results take days,

whereas point-of-care influenza antigen tests are insufficiently sensitive. PCR-based panels for common respiratory viral pathogens are more sensitive and can be useful, but are expensive for routine use and are not able to distinguish between colonization versus true viral infection. Furthermore, in low-volume laboratories, results may not be available for days. On radiologic imaging, lobar consolidation with or without pleural effusion is presumed to be bacterial; however, multifocal infiltrates can represent either multilobar bacterial pneumonia or acute respiratory distress syndrome from severe viral infection alone. RSV and adenovirus have some hallmark features on computed tomography scan of the chest; however, imaging studies are generally unhelpful.[112] Increased C-reactive protein level in the blood correlates with presence of pneumonia but poorly distinguishes viral from bacterial causes.[113–115] Procalcitonin (PCT), another serum biomarker, is better able to differentiate the two.[18,116–121] In one study of coinfection, low PCT level was associated with 94% negative predictive value for bacterial infection, although in patients with shock, or in malaria endemic areas, it may be less reliable.[121,122] Thus, given the absence of rapid and reliable diagnostic tests, clinicians must always consider the possibility of secondary bacterial infection in patients presenting with severe respiratory infections during influenza season and manage them accordingly.

Vaccination

Infections caused by influenza, measles, *H influenzae*, *S pneumoniae*, and some strains of adenovirus are all considered vaccine-preventable illnesses.[123] Although influenza vaccination is universally recommended, vaccination against invasive pneumococcal infection is reserved for high-risk groups, including children, the elderly, and patients with immunosuppressive or chronic lung conditions.[124,125] Although robust evidence from randomized placebo-controlled trials is lacking, data from animal models of influenza-bacterial coinfection and observational studies in patients have indicated that influenza vaccine can reduce the morbidity and mortality associated with bacterial pneumonia.[126–134] Thus, on balance, vaccination against influenza currently represents the most effective public health strategy for reducing the incidence of secondary bacterial pneumonia. However, pneumococcal vaccination did not have the same effect in a large study of elderly patients, potentially because of replacement of covered serotypes with those not included in the vaccine.[135,136] This finding mirrors data from animal models of dual infection.[137] In contrast, vaccination against the M protein of *S pyogenes* seems to be protective against superinfection.[138] It is unknown whether vaccination against other pathogens affects the incidence or severity of secondary bacterial pneumonia.

Antibiotic Therapy

Antibiotic treatment of secondary bacterial pneumonia should mirror local guidelines for that of community-acquired pneumonia (ie, based on local patterns of antibiotic resistance), with the caveat that these patients are at increased risk of *S aureus* infection, including MRSA.[139,140] In patients with cavitation noted on imaging, severe respiratory infection requiring admission to the intensive care unit, or risk factors for hospital-acquired pathogens, treatment with either vancomycin or linezolid should be started empirically. As an aside, in a mouse model of influenza-MRSA infection, treatment with linezolid showed unique immunomodulatory effects on toxic production and lung inflammation with equivalent bacterial clearance; however, whether or not this translates to improved clinical outcomes in humans still needs to be studied.[141]

Antiviral Agents

There are 2 classes of antiviral drugs with activity against influenza: the adamantines (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir). At present, use of the adamantines has become uncommon because of high levels of drug resistance and side effects.[123,139,140,142–144] As previously mentioned, viral infection is often indistinguishable from lower respiratory tract infection. As such, during seasons of heightened influenza prevalence, empiric antiviral therapy is warranted pending the results of microbiologic testing. In ambulatory patients who have had symptoms for fewer than 48 hours, treatment with oseltamivir or zanamivir has been shown to reduce the duration of symptoms. In hospitalized patients, they may have benefit irrespective of when symptoms began.[25,145]

Given their mechanism of action, neuraminidase inhibitors should theoretically prevent or reduce the severity of secondary bacterial pneumonia. This effect has been described in animal models of disease.[69,146,147] In the pediatric population, oseltamivir use has been associated with a 44% reduction in subsequent diagnosis of otitis media.[148] Although individual trials in adult patients were not powered to detect any effect of oseltamivir on lower respiratory tract infection, a meta-analysis showed decreased incidence.[149] Inhaled ribavirin is approved for treatment of severe RSV

bronchiolitis; however, the treatment is cumbersome and the drug teratogenic, which presents a problem for hospital personnel because it is aerosolized for administration. As such, it is rarely used and its effects on secondary bacterial infection are unknown.

Immunomodulatory Agents

Given the role of inflammation in viral-bacterial coinfection and the pathogenesis of secondary pneumonia, there is significant interest in the utility of immunomodulatory drugs in this setting. Corticosteroids have been studied, and although data from mouse models show some protection against secondary pneumonia, they resulted in delayed viral clearance.[150] In patients with severe influenza infection, the results of such studies show either no benefit or possible harm to patients caused by worsened infectious complications.[151–155] As such, their use is not recommended. Other agents under active investigation include statins (coenzyme A reductase inhibitors), peroxisome proliferator–activated receptor agonists, cyclooxygenase inhibitors, macrolide antibiotics, and antibody-based therapies such as intravenous immunoglobulin and experimental monoclonal antibodies, all of which are in the preclinical stages of testing.[146]

SUMMARY

Secondary bacterial pneumonia after viral respiratory infection remains a significant source of morbidity and mortality. Susceptibility is mediated by a variety of viral and bacterial factors, as well as complex interactions with the immune system of the infected host. To date, prevention and treatment strategies are limited to influenza vaccination and antibiotics/antivirals respectively. Novel approaches to identifying the individuals infected with influenza who are at increased risk for secondary bacterial pneumonias are urgently needed, given the ongoing threat of another influenza pandemic. Given the threat of further pandemics and the heightened prevalence of these viruses in general, more research into the immunologic mechanisms of this disease is warranted with the hope of discovering new potential therapies.

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