Chapter

Examining the Executioners, Influenza Associated Secondary Bacterial Pneumonia

Timothy R. Borgogna and Jovanka M. Voyich

Abstract

Influenza infections typically present mild to moderate morbidities in immunocompetent host and are often resolved within 14 days of infection onset. Death from influenza infection alone is uncommon; however, antecedent influenza infection often leads to an increased susceptibility to secondary bacterial pneumonia. Bacterial pneumonia following viral infection exhibits mortality rates greater than 10-fold of those of influenza alone. Furthermore, bacterial pneumonia has been identified as the major contributor to mortality during each of the previous four influenza pandemics. *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pyogenes* are the most prevalent participants in this pathology. Of note, these lung pathogens are frequently found as commensals of the upper respiratory tract. Herein we describe influenza-induced host-changes that lead to increased susceptibility to bacterial pneumonia, review virulence strategies employed by the most prevalent secondary bacterial pneumonia species, and highlight recent findings of bacterial sensing and responding to the influenza infected environment.

Keywords: pneumonia, influenza, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Streptococcus pyogenes*, co-infection, superinfection, secondary pneumonia

1. Introduction

It starts mild. Congestion, fever, body aches, and fatigue. Influenza is infecting the respiratory tract. Seven days and relief should be on the horizon, but the days pass and the symptoms worsen. Breathing becomes laborious and the insides burn with a fire. Crackling can be heard as the stethoscope is pressed against the chest. The sequence of events to follow is all too common. Soon the lungs will be too weak to fulfill their function. The infection will disseminate, shutting down the organs in its path. Multisystem organ failure ensues and secondary bacterial pneumonia adds another mark to its resumé.

Unlike many diseases that have plagued human past, influenza continues to remain a prominent threat and leading cause of worldwide morbidity and mortality. The etiology of influenza would be task for the 20th century, but descriptions of

influenza-like diseases and pandemics begin as early as ca 410 BCE [1, 2]. Accurate reports of disease are scarce through early middle-ages, however, descriptions of an epidemic spreading through Britain in CE 664 have been attributed to influenza [3]. England, France, and Italy are thought to have experienced an influenza pandemic from 1173 to 1174. Contemporaries of this period reported "...an inflammatory plague spread... and all eyes swept following a cruel rhinorrhea" [3, 4]. A community in Florence, Italy in 1357 associated a seasonality to the abrupt onset of symptoms—fatigue, fever, and catarrh—with the changing weather of the winter months; collectively members of community termed the disease "*influenza di freddo*" or "influence from cold," giving rise to the diagnostic term, "influenza" [3, 5].

Around 1500, descriptions of influenza become more consistent. Notably, it is now accepted that during his second journey to the new world in 1493, Christopher Columbus and his crew were suffering from influenza. Upon reaching the Antilles, influenza spread from the crew to the native population killing an estimated 90% of indigenous inhabitants [6, 7]. This was the first report of influenza spreading from Europe across the Atlantic Ocean, a trait that would soon become a hallmark of its infectivity. Reports of epidemics arising throughout Europe and spreading into the Americas were observed in 1658, 1679, 1708, and 1729 and would continue into the 1800s; however, it was the devastating impact of the influenza pandemic of 1918 that would forever influence modern research and understanding on influenza associated pneumonia [3, 8].

The 1918 influenza pandemic has been referred to as "the greatest medical holocaust in history" [2]. Conservative estimates report the 1918 influenza strain led to 50 million global deaths while others suggest the death toll could have reached as many as 100 million [9]. At the time of the 1918 outbreak, the etiological agent of influenza had yet to be correctly identified. Despite this, contemporary physicians had observed that the increases in influenza mortalities were not due to influenza alone. In a letter to a colleague, Dr. Roy Grist states, "There is no doubt in my mind that there is a new mixed infection here, but what I do not know" [10]. Similarly, in reference to increases in influenza-associated deaths, Louis Cruveilheir made the infamous confession, "If grippe condemns, the secondary infections execute" [11].

In the previous decades Richard Pfeiffer had isolated a rod-shaped bacterium from the nose of flu-infected patients that he believed to be the causative agent of influenza [12]. Pfieffer named the bacterium *Bacillus influenzae* which would later come to be known as *H. influenzae* [12]. Though Pfieffer's work was widely accepted, the devastation accompanying the 1918 pandemic caused renewed vigor in influenza research that ultimately called into question the validity of Pfieffer's claims. In 1921 Peter Olitsky and Fredericck Gates took nasal secretions from patients infected from the 1918 strain and passed them through a Berkefeld filter. The filtrate, presumably devoid of bacteria, was then exposed to rabbits wherein the rabbits subsequently demonstrated symptoms indicative of an influenza infection [12, 13]. Olitsky and Gates' studies were the first to suggest the causative agent of influenza was not of bacterial origin, but their work became heavily criticized as others struggled to repeat it. It wasn't until 1929 that Richard Shope, following Olitsky and Gates' filtration method, would use lung samples from an influenza infected pig to demonstrate that the filterable agent was the cause of the influenza, thus ending the debate on bacterial influenza [12, 14]. In the same journal issue that Shope published his findings regarding the causative agent of influenza, he published a separate article describing that swine infected with influenza displayed an increased susceptibility to bacterial infection [15]. While the significance of this finding would not be fully realized for

nearly 100 years, Shope had identified the leading cause of influenza associated mortalities—secondary bacterial pneumonia.

2. Influenza pandemics and secondary bacterial pneumonia

Influenza is a prominent global pathogen responsible for an estimated 1 billion infections annually [16–18]. Despite maintaining high infection rates, mortalities due to influenza infection alone are infrequent. In most immunocompetent hosts, infections cause mild to moderate morbidities and are often resolved within 14-days of symptom onset; however, infection with influenza markedly increases host susceptibility to secondary bacterial infection [11, 19–22]. Cases such as these often display mortality rates between 10 and 15-fold greater than those of influenza alone [23–26].

Modern studies examining the samples from the four most recent influenza pandemics (1918, 1957, 1968, and 2009) demonstrated up to 95% of fatal cases were associated with secondary bacterial infections [11, 22, 27]. The dominant causative agents of this pathology have been *S. aureus* (*S. aureus*), *S. pneumoniae* (*S. pneumoniae*), and to a lesser extent *H. influenzae* (*H. influenzae*) [11, 22, 28]. Each of the previous pandemics demonstrated a unique predisposition for secondary bacterial infection with specific species. For example, bacterial pneumonia associated with the 1918 H1N1 pandemic was dominated by *S. pneumoniae*; conversely the 1957, H2N2 pandemic was dominated by *S. aureus* [28]. Both *S. pneumoniae* and *S. aureus* were highly prominent in the 1968 H3N2 related bacterial infections, however, infections with *S. pneumoniae* were slightly more common. In the most recent 2009 H1N1 outbreak cases associated with *S. pneumoniae* and *S. aureus* were nearly equivalent [28].

Comparative genetic analysis of seasonal and pandemic influenza viruses has highlighted the importance of the PB1-F2 protein in increased inflammation and susceptibility to secondary bacterial pneumonia; however, the mechanisms defining the associations between different strains of influenza and specific bacterial pathogens remain incompletely defined [29–31]. Differences between bacterial agents following antecedent influenza infection were first described in the immediate wake of the 1957 pandemic. Two distinct pathologies of bacterial infection were observed. In the first, bacterial infection arose after viral clearance and were highly dominated by *S. pneumoniae*. In the second, bacterial infection occurred during the viral infection and were predominantly caused by *S. aureus*. Patients inflicted with superinfections by *S. aureus* represented the majority of severe and fatal cases [32]. Of note, this pattern of infection sequence and outcome is consistent with current observations. It is now generally recognized that *S. pneumoniae* is the most prevalent cause of secondary bacterial infection whereas *S. aureus* has emerged as the most common cause of severe and life-threatening cases [22, 27, 33, 34].

2.1 Dysregulation of innate immunity

The prevalent etiological agents of bacterial pneumonia following antecedent influenza infection (*S. aureus*, *S. pneumoniae*, and *H. influenzae*) are common, persistent, and asymptomatic colonizers of upper respiratory tract [35–38]. Curiously, this is a trait shared by other microorganisms that are less frequent causes of secondary pneumonia such as *S. pyogenes* (*S. pyogenes*) [38, 39]. Studies examining the contributions of respiratory commensals on lower respiratory disease have revealed residents of the upper respiratory tract are frequently trafficked into the lungs via inhalation,

microaspirations, and direct mucosal dispersion [40, 41]. Despite recurrent exposure to the lower respiratory environment, and apart from a preceding influenza infection, bacterial pneumonia in immune competent adults is uncommon [21, 22, 42]. This has prompted many studies aimed at understanding influenza induced dysregulations in immune function that lead to increases in susceptibility to bacterial infection. To that end, considerable progress has been made identifying key changes within the host environment that prelude bacterial pneumonia [21, 43, 44].

In general, susceptibility to bacterial co-infection peaks 6–7 days post influenza infection and corresponds with increases in tissue damage and dysregulation of cytokine production [36, 45, 46]. In immunocompetent individuals, alveolar macrophages and neutrophils are the primary cell types responsible for controlling bacteria invading the lower respiratory tract (LRT). During influenza infection the bactericidal activity of these two cells is severely impaired [47–50]. Specifically, influenza infection can cause a ≥85% loss in alveolar macrophages numbers by day 7 of the infection [47, 51]. Aberrant interferon-gamma (IFN-γ) signaling in the macrophages that are present demonstrate impaired phagocytic activity [48]. Similarly, the incumbent infection elicits production of the regulatory cytokine IL-10 in the lung epithelia. IL-10 reduces phagocytic activity in neutrophils [36, 43, 52]. Pretreatment of mice with a neutralizing monoclonal antibody against IL-10 after viral infection, but prior to onset of bacterial infection, significantly increases mouse survival [34]. Other notable immunological changes implicated in increased susceptibility to secondary bacterial infection include disruptions in the TH17 pathway, type-I IFN production, and antimicrobial peptide production [53–59]. While these studies certainly contribute to identifying factors leading to the increased susceptibility to secondary bacterial pneumonia following influenza infection, they fail to address the direct impacts of the viral infection on the pathogenesis of these bacterial species.

2.2 Viral influence on bacterial virulence

Given the frequency of upper respiratory colonization with bacterial pathobionts and the opportunity for exposure into the lower respiratory environment, it is shocking that severe bacteria pneumonia is not more common. Moreover, it is often overlooked that these species contain a diverse repertoire of virulence factors that must be suppressed during colonization to avoid a host response. Recent models of infection have enabled investigators to begin to examine how influenza infections can promote transcriptional changes leading to a transition from asymptomatic commensal to life-threatening pathogen [26, 48, 60–63]. Identifying changes in bacterial virulence production has highlighted an important role of bacterial toxin production causing increased host tissue damage during these infections. Furthermore, these efforts have led to a more complete understanding of the mechanisms influencing susceptibility and severity of secondary bacterial pneumonia, as they not only consider the contributions of the viral infection on host immunity, but account for the contributions of the host and virus towards the pathogenesis of bacterial species.

Commensals of the anterior nares commonly grow in biofilm communities [64, 65]. Recent studies have demonstrated infection with influenza promotes biofilm dispersal and dissemination of *S. aureus* and *S. pneumoniae* into the LRT [60, 62]. Interestingly, in biofilm communities where both *S. aureus* and *S. pneumoniae* are present influenza induced dissemination was almost entirely restricted to *S. pneumoniae* [61]. This suggests interactions with influenza result in immediate transcriptional changes that trigger *S. pneumoniae* biofilm dispersal while simultaneously suppressing

S. aureus biofilm dispersal [61]. In addition, influenza can directly interact with surface of Gram-positive and Gram-negative organisms [66]. Virus bound to the surface of *S. aureus*, *S. pneumoniae*, and *H. influenzae* has been demonstrated to enhance bacterial adherence to epithelial cells [66].

One of the primary environmental factors that effects *S. pneumoniae* virulence is nutrition availability [57]. Carbohydrates are a necessary carbon source for pneumococcal growth [67]. Destruction of the epithelia tissue due to viral replication leads to increased mucus accumulation and decreased mucociliary clearance [21]. The accumulation of carbohydrate-rich mucus in the LRT promotes *S. pneumoniae* growth and production of epithelial adherence proteins [57, 62]. Intrinsic *S. pneumoniae* neuraminidase activity in combination with influenza neuraminidase activity during viral exit, desialylate the surface of host cells providing an additional carbohydrate source in the form of sialic acid [68, 69]. Continuous viral replication induces reactive oxygen species (ROS) generation from host cells. The presence of viral-induced ROS leads to an upregulation of the *S. pneumoniae* cytotoxin pneumolysin and causes enhanced necroptosis of the lung epithelium [70]. Taken together, these observations demonstrate a synergistic effect of *S. pneumoniae* growth and virulence with influenza infection.

There is substantial overlap regarding the broad effects of influenza infection on *S. pneumoniae* and *S. aureus*. Both organisms demonstrated enhanced dissemination into the lungs and upregulation of virulence genes during influenza infection [26, 61, 62, 70]. Evidence suggests that immediately upon being trafficked into the LRT, *S. aureus* forms microaggregates in the crypts of the alveolar wall [71]. These microaggregates secrete alpha-hemolysin (Hla), a toxin described to effect human alveolar macrophages and promote lung damage [72–74]. Gene regulation of *hla* is predominantly controlled by the two-component regulatory system SaeR/S and protein expression through the global gene regulator Agr [75, 76]. Agr regulates expression through quorum sensing and may be playing a role in Hla during microaggregate growth [75]. In a murine model of secondary *S. aureus* pneumonia, influenza infected mice demonstrated immediate upregulation of the *S. aureus* genes *saeR* and *saeS* and *saeR/S*-regulated toxins over mock infected mice [26]. Furthermore, mice challenged with a *saeR/S* isogenic gene deletion mutant strain of *S. aureus* displayed 100% survival compared to only 30% survival in mice challenged with wild-type *S. aureus* [26]. These data clearly demonstrate that the contributions of the bacterial pathogen towards *S. aureus* secondary bacterial pneumonia morbidity and mortality are, at minimum, of equal importance to the effects of influenza infection on host immune defenses.

3. Conclusion

A disease that has paralleled human progress throughout history is now just beginning to be understood. It is now apparent that the contributions to the increased susceptibility, morbidity, and mortality associated with secondary bacterial pneumonia following influenza infection span multiple disciplines (**Figure 1**). Undoubtedly, the effects of an influenza infection on the host immune system play a substantial role in increasing susceptibility to bacterial infection. Tissue damage, dysregulation of cytokine signaling, and suppression of phagocyte activity create an environmental niche primed for bacterial exploitation. However, more recent data have demonstrated changes in innate immune function alone are incomplete towards defining how bacteria transition from commensals to pathogens. This has prompted studies

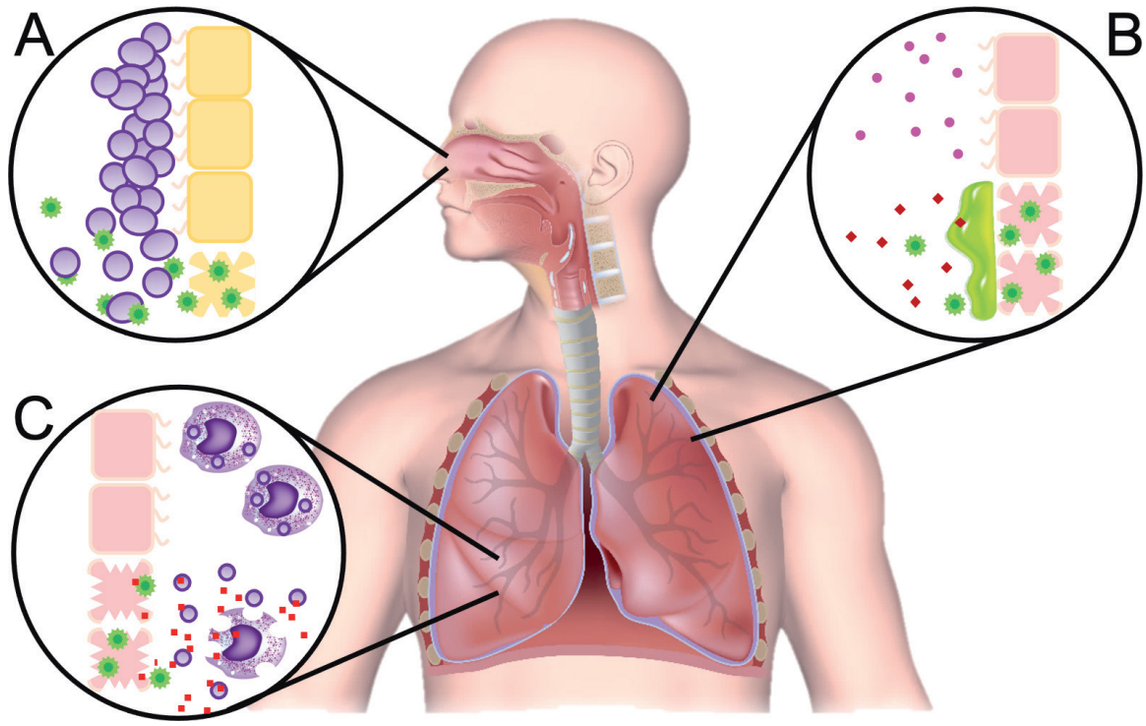

Figure 1.
Influenza infection enhances secondary bacterial pneumonia. (A) Increased dissemination into the LRT, (B) dysregulation of cytokine production and mucus accumulation, and (C) toxin production and tissue damage and reduced phagocytic function.

examining the ability of bacteria to sense and respond to the changes induced during and after influenza infection. Findings have demonstrated viral infection directly impacts bacterial pathogenesis by increasing bacterial dissemination, binding to epithelia, and upregulating virulence production. Taken together, these data indicate that a more thorough understanding necessitates additional studies to interrogate the contribution of host, viral, and bacterial interactions towards secondary bacterial pneumonia following influenza infection.

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Conflict of interest

The authors declare no conflict of interest.

Declarations

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Author details

Timothy R. Borgogna* and Jovanka M. Voyich
Montana State University, Bozeman, MT, United States of America

*Address all correspondence to: timothy.borgogna@montana.edu

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