Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

Viral–bacterial co-infections in the respiratory tract

Lauren O Bakaletz

Preceding or concurrent viral respiratory tract infection can predispose to secondary bacterial co-infection throughout the airway. The mechanisms by which viruses promote these superinfections are diverse and replete. Whereas we understand much as to how viruses damage the airway and dysregulate both innate and acquired immune responses which, in turn, supports bacterial growth, adherence and invasion into normally sterile sites within the respiratory tract, new information regarding these co-infections is being gained from recent advances in microbiome research and our enhanced appreciation of the contribution of bacterial biofilms, among others. The advanced understanding obtained by continued research efforts in all aspects of viral–bacterial co-infections of the respiratory tract will allow us to devise novel approaches for disease prevention as well as to develop more effective therapeutics.

Address
Center for Microbial Pathogenesis, The Research Institute at Nationwide Children's Hospital and The Ohio State University College of Medicine, Department of Pediatrics, 700 Children's Drive, Columbus, OH, 43205, USA

Corresponding author: Bakaletz, Lauren O (Lauren.Bakaletz@nationwidechildrens.org)

Current Opinion in Microbiology 2017, **35**:30–35

This review comes from a themed issue on **Host–microbe interactions: bacteria**

Edited by **Samuel Miller** and **Renée Tsolis**

http://dx.doi.org/10.1016/j.mib.2016.11.003

Viral–bacterial co-infections throughout the respiratory tract

In healthy persons, seasonal influenza usually resolves without consequence, however each year approximately 200 000 hospitalizations and 36 000 deaths occur in the U.S. alone [1]. At greatest risk for secondary bacterial pneumonia are children under the age of 1, adults over 65, pregnant women and individuals of any age with comorbid illnesses [2]. Longstanding evidence for the role of influenza virus in bacterial pneumonia derive from studies of the four well-documented pandemics of the last 100 years. Whereas *Streptococcus pneumoniae* (Spn) was the predominant bacterial pathogen associated with both the 1918 and 1968 pandemics, *Staphylococcus aureus* accounted for 44% of deaths in 1957. In the most recent pandemic (2009), interestingly the majority of deaths were now in persons under 65 [3•] with *Streptococcus pyogenes*, *Haemophilus influenzae* and other Gram negative rods identified as causative agents in addition to Spn and *S. aureus*. Despite the introduction of antibiotics and influenza vaccines in the period between the 1918 and 1957 pandemics, death from secondary bacterial pneumonia remains a significant problem and in fact, in part due to the rapid aging of the U.S. population, associated mortality has increased [2].

Multiple additional infections of the airway are predicated on a bacterial superinfection either subsequent to, or concurrent with, an ongoing upper respiratory tract (URT) viral infection due to influenza A, influenza B, respiratory syncytial virus (RSV), rhinovirus (RV), human coronavirus, parainfluenza virus and adenovirus (AV), among others [4]. Viral 'colds' predispose to bacterial rhinosinusitis in both adults and children [5,6] and are among the most common infections seen in primary care [7]. In one prospective longitudinal study in children, 8% of viral URTI were complicated by acute bacterial rhinosinusitis [6]. Spn, *H. influenzae*, *Moraxella catarrhalis*, *Staphylococci* and respiratory anaerobes predominate in both acute and chronic rhinosinusitis. In otitis media, or middle ear infection, virtually any URT virus, as well as some enteroviruses, can predispose the middle ear to invasion by bacteria that normally reside in the nasopharynx (NP) [8,9]. The predominant bacterial pathogens of OM are Spn, nontypeable *H. influenzae* and *M. catarrhalis*. Whereas the URT viruses are unique in terms of specific histopathology and nature of the evoked immune response, the net effect of all viral infections that lead to OM is compromise of the protective functions of the Eustachian tube and thus there is a bounty of evidence to support the parental lore that '*my kid gets a cold and a week later has an ear infection*' [10].

A positive association between viral RTI and bacterial superinfection has also been demonstrated in rhinitis [11,12], RSV-induced bronchiolitis [13], and acute expiratory wheezing [14]. Cystic fibrosis, an autosomal inherited disease that affects >60 000 persons worldwide is characterized by recurrent and chronic RTI [15] that are exacerbated by infection with common respiratory tract viruses [16]. *Pseudomonas aeruginosa* and *S. aureus* are the predominant causative agents of these exacerbations. Both viral and bacterial infections are also associated with exacerbations of chronic obstructive pulmonary disease (COPD) [17–19] with COPD expected to rank as the

third leading cause of death worldwide by 2030 (WHO, http://wwwwhoint/respiratory/copd/burden/en/.2015). A wide variety of URT viruses have been implicated as playing a role in bacterial exacerbations of COPD due to the 'usual suspects': *H. influenzae*, Spn, *M. catarrhalis*, *S. aureus*, *P. aeruginosa* and *Enterobacter* spp. In further support, a recent study [20] found that 15 days after experimental RV infection of subjects with COPD there was a sixfold increase in both the 16S copy number and a 16% rise in the number of proteobacterial sequences detected in sputum compared to baseline values obtained from sputum collected before RV inoculation, with *H. influenzae* predominating.

Mechanisms for viral predisposition to bacterial superinfection of the respiratory tract

Much of what we have learned to date has been gleaned from animal models which have shown that complex molecular mechanisms underlie the ability of viruses to predispose to bacterial superinfection (see Table 1). For detailed description, readers are referred to several reviews [21,22•]. Briefly however, as a general outcome, viral infection can induce destruction of the airway both histologically and functionally. Depending on the virus, the histopathology induced can be relatively mild or severe and include evidence of cell loss, goblet cell hyperplasia, altered mucus secretion and/or biochemistry, disruption of surfactant, reduced ciliary beat frequency, dis-coordinated mucociliary clearance function and reduced oxygen exchange [23]. Each of these effects has long been associated with potential mechanisms by which viruses predispose the respiratory tract to bacterial superinfection. Additional specific mechanisms associated with viral-bacterial co-infection are discussed in greater detail below.

Augmented bacterial adherence and colonization

Depending on the virus, bacterial species/strain and experimental system used, viral infection has been shown to promote bacterial adherence and airway colonization via a number of mechanisms. Using a ferret model, Peltola *et al.* [24] reported that influenza viruses of any subtype increased colonization of the NP by Spn, however only specific subtypes were associated with development of bacterial sinusitis or OM. These findings contribute to our understanding of why bacterial complication rates are greater during seasons when a particular influenza subtype predominates. As to mechanism, influenza viral neuraminidase has been shown to expose host cell receptors used for bacteria adherence due to its sialidase activity which alters epithelial cell surface carbohydrate moieties [1,23] and is also known to enhance bacterial adherence via activation of TGF-β which induces upregulation of expression of fibronectin and integrins to which bacteria bind [25••]. Moreover, stimulation of type I interferons (IFNs) by influenza virus leads to decreased production of the chemokine CCL2 resulting in impaired recruitment of macrophages (required for pneumococcal clearance) thereby promoting Spn colonization in mice [26]. Influenza virus also primes mice for pneumonia due to *S. aureus* [27] where both bacterial and viral titers are enhanced during co-infection. The investigators of this latter study hypothesized that viral titers increase after bacterial co-infection due to enhanced virus release from infected cells, but that bacterial titers increase due to alveolar macrophage (AM) impairment [28].

Other URT viruses also enhance bacterial adherence to both primary and immortalized epithelial cells with distinct differences noted amongst epithelial cell types in terms of response to infection with RSV, parainfluenza virus-3 or influenza virus [29]. Novotny and Bakaletz [30] recently showed that both RSV and AV induced upregulated expression of the cell surface glycoprotein intercellular adhesion molecule 1 (ICAM-1) by primary respiratory tract epithelial cells and that ICAM1 served as a cognate ligand for the Type IV pilus of nontypeable *H. influenzae*, thus promoting adherence of this Gram negative pathogen. RSV infection also enhances adherence of *P. aeruginosa* to both normal and CF epithelial cells [31] and this effect can be extended to Gram positive

Table 1

Mechanisms by which viruses predispose to secondary bacterial infection
Damage to airway epithelium/induction of hyperplasia/cell loss/exposure of basement membrane
Diminished ciliary beat frequency/disruption of mucociliary clearance/altered mucus rheology
Increased receptor availability on epithelial cells promotes augmented bacterial adherence
Dysregulated activation, migration and function of antigen presenting cells (alveolar macrophages, dendritic cells, tissue resident macrophages and T-cells)
Disruption of phagocyte function
Abnormal expression of antimicrobial/host defense peptides
Virus-induced type I interferons alter the phenotype of the immune response
Enhanced production of inflammatory mediators (cytokines, chemokines, acute phase reactants)
Generalized immunosuppression that leads to immune paralysis
Virus-mediated release of bacteria from biofilms
Viral dysregulation of nutritional immunity
Virus induced alteration of the microbiome with increase in pathogens associated with secondary infections