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POSSIBLE MECHANISMS UNDERLYING BACTERIAL-VIRAL INTERACTIONS IN RESPIRATORY DISEASES: A REVIEW

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Abstract

Background: Respiratory diseases are frequent and economically significant problems in both humans and animals. The potential losses resulting from decrease in average daily gain and feed efficiency, as well as the cost of preventing or treating these diseases are substantial. Although synergistic relationships between bacteria and viruses have been documented to aggravate these diseases, the pathogenic mechanisms remain poorly understood.
Materials and method: For this review, PubMed and Google search engines were used to select about 45 publications on bacterial-viral interactions in respiratory conditions. Studies on animal models were also included in the review. The publications were compared and summarized using a narrative review approach and findings were described qualitatively.
Results: Respiratory diseases are exacerbated by interactions between bacteria and viruses in both humans and animals. Possible mechanisms underlying this synergism were found to include, among others, increased bacterial adherence due to viral infection, reduction of mucociliary clearance, diminished chemotaxis, immature phagocytes and decreased surfactant levels.
Conclusion: Interactions between bacteria and viruses make management of respiratory diseases difficult. However, exploration of the highlighted mechanisms responsible for this synergism in the development and production of novel antimicrobials and vaccines against these pathogens is crucial to improving management, prevention and control of respiratory infections. This may be particularly beneficial in this era of increasing antibiotic resistance.

Key words: Bacterial-viral interactions, respiratory diseases, adherence, mechanisms

Introduction

It has been appreciated for over a century that viral respiratory infections are often accompanied by bacterial complications.. This association came into focus as the influenza pandemic of 1918 took some 40 to 50 million lives (Potter, 1998), many because of secondary bacterial pneumonia (Metersky et al., 2012; Peltola and McCullers, 2004).This outbreak was the genesis of investigations into the epidemiology and pathology of bacterial-viral interactions that continue till today. The first epidemiological studies that focused on bacterial-viral interactions during respiratory infection were conducted in the late 1920s (Noble and Brainard, 1928; Webster and Clow, 1978) and had the common goal of detecting changes in the throat bacterial flora during viral respiratory disease. Sanford et al. (1978) were the first to introduce an adherence assay to verify increased susceptibility of mammalian cells to bacterial adherence as a result of viral infection. They exposed monolayers of Madin-Darby canine kidney (MDCK) cells to various streptococcal strains. Indeed, the adherence of group B *Streptococcus* and various streptococcal species was found only in the cells infected with influenza virus and not in the membranes of uninfected cells. Yet, these bacteria were not recognized to be human pathogens associated with increased morbidity during influenza epidemics.

In subsequent adherence studies with *Staphylococcus aureus*, however, pre-infection of MDCK cells with influenza A virus significantly enhanced adherence (Davison and Sanford, 1981). This effect varied depending on the virus and bacterial strains being tested. Respiratory diseases constitute a frequent and economically significant problem in animals and humans with the potential losses due to decreased average daily gain and feed efficiency, and cost of preventing or treating them from being substantial (McCullers, 2006; Nolte, 2008). Respiratory disease caused by virus or bacteria alone can be aggravated by a number of management and environmental factors such as stress and unfavourable temperature. Numerous researchers (Galina et al., 1994; Weeks-Gorospe et al., 2012) have also shown that respiratory disease can be exacerbated by interactions of viruses and bacteria in pigs. These interactions have also been noted in humans (Kleemola et al., 2005) and other animals (Emikpe et al., 2010).

Despite astounding progress over recent decades in the molecular microbiology of viruses and bacteria considered separately, the detailed mechanisms of the process leading from viral to bacterial infection have remained largely unknown (Peltola and McCullers, 2004).

Epidemiology

Several steps are involved in the development of bacterial respiratory infections. Bacteria must first adhere to epithelial surfaces and establish colonization of the nasopharynx before invading and spreading to the middle ear, paranasal sinuses or lungs. Epidemiologic and clinical studies show that the first step in the process, adherence and colonization of nasopharynx, is facilitated by viral infection. In an otitis media study, pneumococcal carriage was 49% and 41% respectively in infected children aged 2 to 24 months with or without otitis media, as against 21% in the same children during healthy visits (Syrjanen et al., 2001). Similar results for *Pneumococcus* and other bacteria were obtained from other studies in young children (Heikkinen and Chonmaitree, 2003).

Invasion and delocalization are also facilitated by prior viral infection. A close association has been reported between laboratory-documented viral upper respiratory infection and acute otitis media (Heikkinen and Chonmaitree, 2003; Vesa et al., 2001). Research has shown that

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the highest incidence of acute otitis media is observed between 3 to 4 days after the onset of respiratory symptoms (Kleemola et al., 2005). In most cases, acute otitis media can be regarded as a secondary bacterial infection during a viral respiratory infection. The causes of viral infections associated with acute otitis media include respiratory syncytial virus (RSV), influenza A and B, para-influenza virus (PIV) types 1, 2 and 3, adenoviruses, rhinoviruses, enteroviruses and coronaviruses. Although sinusitis has classically been considered to be a bacterial disease, recovery of viruses from sinus aspirates both alone and in conjunction with bacteria suggests a role for viruses in the pathogenesis of bacterial sinusitis (Peltola et al., 2006). Rhinovirus, influenza virus and para-influenza virus were most frequently involved. Most sinusitis is thought to arise as a complication of viral infections of the respiratory tract (Kleemola et al., 2005); however, definitive studies on both the clinical and research levels are needed. The most striking and severe example of the prevalence of bacterial infections after viruses is the massive number of pneumonia deaths recorded during the influenza pandemic of 1918. During the 1918 (Metersky et al., 2012) and 1968 (Sharrar, 1969) pandemics, *Streptococcus pneumoniae* was the most frequently isolated bacterium. More recently, severe pneumococcal pneumonia was associated with preceding influenza A (H1N1) infection in children (McCullers, 2006; Weinberger et al., 2012). In this article, we reviewed how some respiratory viruses and bacteria can combine to cause disease, their possible mechanisms of interaction and probable consequences of such interaction.

Possible Mechanisms

It is clear that multiple mechanisms for synergism between viruses and bacteria exist although the relative contributions of each are yet to be determined (Peltola and McCullers, 2004). Recent research has suggested certain explanations for the mechanisms of bacterial-viral interactions and these include:

Increased bacterial adherence due to viral infection

Bacterial adherence to cells of the respiratory tract is an initial step in bacterial infection. Plotokowski et al. (1986) found that viral infection alters surface membrane receptors of respiratory epithelium, which modifies the micro-environment of the basal layer and basement membrane of the epithelium. The modified environment allows bacteria to proliferate, a phenomenon called "opportunistic adherence" (Ramphal et al., 1980). For instance, influenza A infection in Chinchillas caused damage to ciliated epithelial cells in the Eustachian tube (Pettigrew et al., 2011). That, together with nasopharyngeal congestion, can lead to dysfunction of the tube and development of otitis media. Also, presentation of new receptors during regeneration and remodeling of the airways after viral infection provides an environment conducive to bacterial adherence and invasion (McCullers and Bartmess, 2003).

Destructive virus enzyme (role of neuraminidase in synergy between viruses and bacteria)

Some viruses such as influenza virus use specific enzymes (e.g. neuraminidase) that may destroy some of the mucous glycoproteins that normally prevent bacterial attachment and infection of epithelial cells (McCullers and Bartmess, 2003). Many cellular structures that can act as bacterial receptors are covered by sialic acids on cell surface carbohydrates. If sialic acids are cleaved by neuraminidase (NA), bacteria may be able to adhere and invade. In contrast to neuraminidase produced by the influenza virus, a role for bacterial NA in pathogenesis has not yet been clearly established. Although Soong et al. (2006) were unable to establish respiratory infection in mouse model using a mutant of *Pseudomonas aeruginosa*, exogenously administered bacterial NA have been reported to increase adherence of Pneumococcus to chinchilla tracheal (Tong et al., 1999), Eustachian tube (Tong et al., 2001) and middle ear (Linder and De Maria, 1992) epithelia in organ perfusion models. Furthermore, whereas a NA-deficient mutant of *Pneumococcus* had reduced the ability to alter the carbohydrate structures in the Chinchilla nasopharynx (Tong et al., 2001), another chinchilla study with lectin probes showed that sequential influenza A virus and *S. pneumoniae* infection caused more pronounced changes in carbohydrate structures than either pathogen alone, suggesting that NAs of both these pathogens act synergistically in altering the carbohydrates to facilitate pneumococcal invasion (Tong et al., 2002).

Reduction of mucociliary clearance

Viruses may diminish mucociliary clearance by reducing the production of bactericidal substances. This mechanism has been proposed as part of the interaction of hog cholera virus (HCV) and *Pasteurella multocida*. Iglesias and Pijoan (1980) studied the effect of a strain of HCV vaccine on cilia destruction of *P. multocida* by using tracheal explants collected from embryonic pigs. The tracheal explants were infected *in vitro* with a vaccine suspension of HCV and later P. multocida type D. Hog cholera virus affected the bactericidal activity of tracheal explants against *P. multocida*, reducing lysis of the bacterium to 58% at 24 hours after viral infection and to 44% during the following 24 hours. The authors suggested that the damage caused by the virus may be responsible for bacterial colonization of the lungs by altering epithelial cell bactericidal secretions. Also, influenza virus infection is accompanied by cytological changes in the ciliated columnar epithelium leading to necrosis of the bronchial epithelial lining in addition to cellular lesions in the alveoli (McCullers and Rehg, 2002).

Diminished chemotaxis

Certain viruses seem to diminish the chemotactic response of cells to invading organisms. Chemotaxis is a phenomenon by which the release of certain substances mobilizes macrophages and other cells to inflammatory sites. Cheung et al. (2002) found that influenza virus decreases the chemotactic responsiveness of normal peritoneal macrophages. Therefore, viruses may also depress the migratory activity of polymorphic alveolar macrophages (PAM) in the lung. This inflammatory response to viral infection could up-regulate expression of molecules that bacteria can utilize as receptors. Incubation of cultured epithelial cells with cytokines that are produced during viral infections (e.g. tumor necrosis factor-alpha and interleukin-1-alpha) promoted attachment and invasion of *Pneumococcus* (Kadioglu and Andrew, 2004). One proposed mediator of this process is the reeptor for platelet activating factor (PAF-R), a ubiquitous G-coupled protein to which phosphorylcholine expressed on the surface of the *Pneumococcus* can adhere (Gosink et al., 2000). The expression of PAF-R is up-regulated by inflammatory cytokines (Cundell et al., 1995) and has been shown to be an important factor in the transition from the blood to the cerebrospinal fluid during induction of meningitis (Orihuela et al., 2004).

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Immature phagocytes

The alveolar macrophage is the replication site of such swine viruses as pseudorabies virus and porcine reproductive and respiratory syndrome virus (PRRSV). It has been hypothesized that after viral infection, mature macrophages are destroyed and probably replaced by immature phagocytes that are not fully capable of bactericidal activity; consequently, bacteria can proliferate (Engelich et al., 2001). Similarly, impairment of neutrophil functions by influenza virus has been shown to correlate with development of secondary pneumococcal otitis media in the Chinchilla model (van der Sluijs et al., 2004).

Decreased surfactant levels

Bacterial infections may result when functions of immunologic cells are impaired by viral infection. In swine influenza virus infections, the function of the alveolar type-2 pneumocyte is impaired. These cells synthesize and secrete surfactant, which plays an important role in phagocytosis of microorganisms (Engelich et al., 2001). Reduction of surfactant may therefore be an additional mechanism of virus-induced macrophage dysfunction.

Immune response

Indirect effects of the virus on the host have also been considered. In experiments of viral-induced phagocytic dysfunction, the bactericidal deficiency is associated with declining viral titers and increasing antiviral immunity, suggesting decreased bactericidal function due to host response as well as virus-induced effects on macrophages (Cheung et al., 2002). Commonly, an opportunistic bacterium super-infects after a primary viral infection. Multiple mechanisms appeared to be involved in virally-induced suppression of pulmonary anti-bacterial defenses (Tong et al., 2002; Kadioglu and Andrew, 2004). For instance, influenza virus in combination with *S. pneumoniae* causes more apoptosis of neutrophils than either pathogen alone (Engelich et al., 2001). The conditions for viral enhancement of bacterial super-infections have to be appropriate and several important factors such as strain virulence, viral dose, and health status of the animal must be taken into account (McCullers and Rehg, 2002; McCullers, 2006). It is noteworthy that bacterial-viral interactions do not always begin with a viral infection and neither do they always involve secondary bacteria. Bacteria can also act as predisposing factors for viral infection, as is the case of *Pasteurella multocida* (toxin), which has been shown to intensify pseudorabies virus infection (Ostroff and Leduc, 2000). Moreover, viral and bacterial virulence factors are synergistically important in the development of diseases. It has been demonstrated with the PRRSV and *Streptococcus suis* models, that a strain of S. suis lacking a protein associated with virulence would not reproduce clinical signs of *S. suis* disease even with PRRSV pre-infection (Ostroff and Leduc, 2000).

Conclusions

Morbidity and mortality rates may be increased when a combined infection of virus and bacteria is present as compared to an infection with either agent alone. Hence, treatments with antibiotics after extensive damage had been done and bacterial colonies formed may be of little value. It may be advisable to time the administration of vaccines and antibiotics to ensure efficacy. Additionally, it may be necessary to immunize against both viral and bacterial pathogens. Therapy against bacterial agents should include both management and anti-bacterial (Leekha et al., 2011). Interactions of virus and bacteria are important in developing respiratory and other diseases, making control of these diseases difficult. Identification and exploration of the underlying mechanisms responsible for this synergism will provide targets for prevention and control of the primary agents (most commonly viral) rather than simply treating the secondary agents that cause clinical disease. Finally, understanding these mechanisms is crucial for improving the management of respiratory infections, which may be particularly helpful in this era of increasing antibiotic resistance.

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