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REVIEW

Virus-induced secondary bacterial infection: a concise review

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Abstract: Respiratory diseases are a very common source of morbidity and mortality among children. Health care providers often face a dilemma when encountering a febrile infant or child with respiratory tract infection. The reason expressed by many clinicians is the trouble to confirm whether the fever is caused by a virus or a bacterium. The aim of this review is to update the current evidence on the virus-induced bacterial infection. We present several clinical as well in vitro studies that support the correlation between virus and secondary bacterial infections. In addition, we discuss the pathophysiology and prevention modes of the virus–bacterium coexistence. A search of the PubMed and MEDLINE databases was carried out for published articles covering bacterial infections associated with respiratory viruses. This review should provide clinicians with a comprehensive idea of the range of bacterial and viral coinfections or secondary infections that could present with viral respiratory illness.

Keywords: bacteria, infection, risk, virus

Introduction

Viral respiratory tract infections (VRTIs) are very common in children and their presentations vary from simple colds to life-threatening infections.[1–5] The detection of a respiratory virus does not necessarily infer that the child has only a viral infection,[6] since outbreaks of VRTIs are being linked to increased incidence of bacterial coinfections.[7] The human body is usually capable of eliminating respiratory viral infections with no sequelae; however, in some cases, viruses bypass the immune response of the airways, causing conceivable severe respiratory diseases.[8] Robust mechanical and immunosuppressive processes protect the lungs against external infections, but a single respiratory tract infection might change immunity and pathology.[9]

Health care providers often face a dilemma when encountering a febrile infant or child with respiratory tract infection. The reason expressed by many clinicians is the challenge to confirm whether the fever is caused by a virus or bacterium.[10] Acute otitis media (AOM) is a usual bacterial coinfection that occurs in 20%–60% of cases of VRTIs.[11–14] In addition, almost 60% of children with VRTI have changes in the maxillary, ethmoidal, and frontal sinuses.[11,12] Moreover, in the year 1918, it was estimated that 40–50 million individuals died from the influenza pandemic, many of which were due to secondary bacterial pneumonia with *Streptococcus pneumoniae*.[15]

Search strategy and selection criteria

A search of the PubMed database and Google was carried out, using different combinations of the following terms: virus, induced, bacteria, pathogenesis, prevention, vaccine, and children. In addition, we searched the references of the identified articles for additional articles. We then reviewed abstracts and titles and included studies that were

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relevant to the topic of interest. Finally, the search was limited to studies of disease in humans that were published in English and Spanish from 1918 to the end of 2014 (Figure 1).

Airway epithelium

The epithelium (Figure 2) is usually covered by a layer of mucus that functions as a boundary.[16] Mucins, which are charged glycoproteins, are the main components of mucus.[17,18] MUC5AC and MUC5B are the most common mucins in the human sputum, and they assist the innate immune system through their anti-inflammatory and antiviral properties.[19,20] In addition, they facilitate trapping and clearance of viruses; however, overproduction of those mucins might have a paradoxical effect.[18,19]

The airway epithelium not only functions as a physical barrier but also recognizes microorganisms through pattern recognition receptors such as Toll-like receptors (TLRs),[18] nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and retinoic acid-inducible gene (RIG)-like helicases.[21,22]

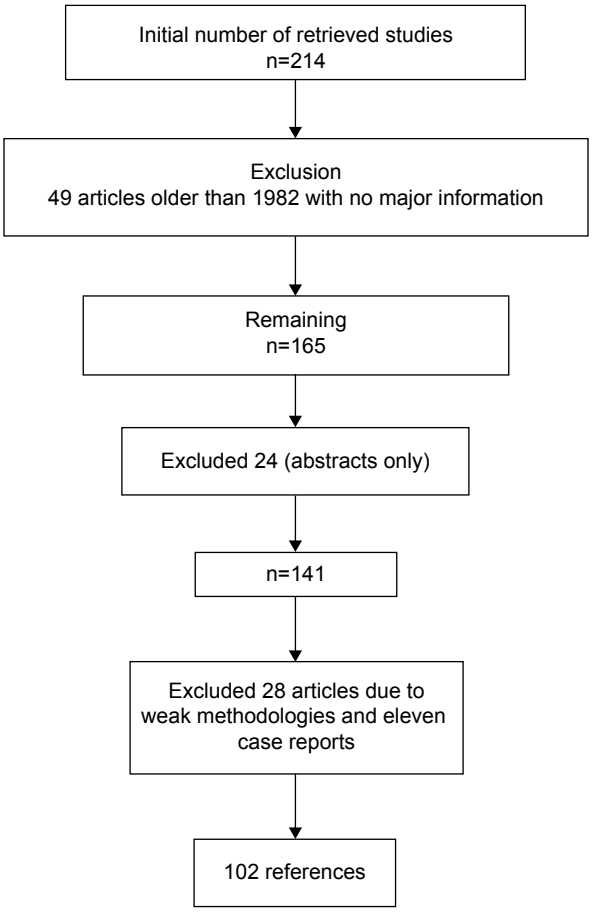

Figure 1 Flow diagram showing the selection of literature.

TLRs are single, noncatalytic, membrane-spanning receptor proteins used by the innate immune system.[23] Respiratory viruses collaborate with TLR lanes, leading to extended bacterial load in the lungs.[21,24]

In comparison, NLRs and RIG-like helicases activate innate immune responses through cytosolic sensing of viral and bacterial components.[22,25] Nod1 and Nod2, which are family members of NLRs, are induced by molecules synthesized during the production and/or degradation of bacterial peptidoglycan.[26–29] In addition, many epithelial cells express the classical antiviral interferons (INFs), especially IFN-α and IFN-β.[30,31] Moreover, the respiratory virus-infected epithelia facilitates the attraction of inflammatory cells, including natural killer cells, neutrophils, macrophages, and eosinophils from the bloodstream into the infected site.[32] Finally, the airway epithelium consists of many molecules including intercellular adhesion molecule 1 (ICAM-1), carcinoembryonic antigen-related cellular adhesion 1 (CEACAM-1), and platelet-activating factor receptor (PAF-r).[33] Viruses have an effect in modulating these receptors, leading to an increase risk of bacterial adherence; for example, rhinovirus upregulates the expression of PAF-r, leading to the binding of *S. pneumoniae* to bronchial epithelial cells.[34]

Pathogenesis of superimposed secondary bacterial infection

Different mechanisms might contribute to the debilitation in host defense of the respiratory tract against bacteria following viral infection. Some of the mechanisms have been extrapolated from studies conducted in animal models of sequential infections by respiratory viruses and several bacterial pathogens.

Virus inflicts impairment on host epithelial cells

Mammalian cells are prone to bacterial attachment during a viral illness.[8,35] Viruses can debilitate the mucociliary clearance structure, leading to the increased attachment of bacteria to mucins and colonization; moreover, the condensed mucus will impede the penetration of antibacterial material and immune cells.[36] Viruses like the respiratory syncytial virus (RSV) can damage ciliated cells, resulting in ciliostasis and, therefore, deterioration of mucociliary clearance.[37] The same concept applies to an influenza virus infection, leading to decreased tracheal mucociliary velocity and clearance of *S. pneumoniae*.[35,38] Moreover, virus-induced cell death debilitates the mechanical elimination of the

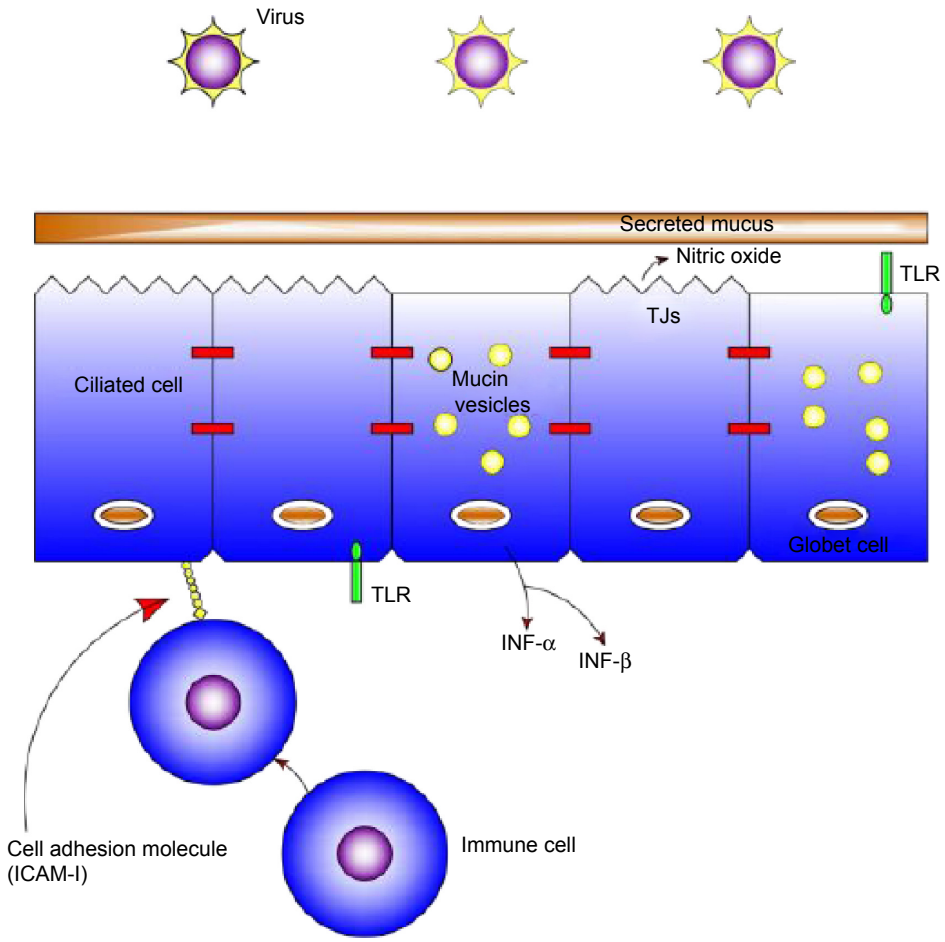

Figure 2 Airway epithelium.
Abbreviations: INF, interferon; TJ, tight junction; TLR, Toll-like receptor; ICAM-1, intercellular adhesion molecule 1.

attached pathogens and displays novice receptors for bacterial adherence.[39] Studies have shown that the RSV virus induces the adherence of *S. pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenza* to airway epithelial cells.[40–43] In addition, adenovirus and rhinovirus play the same role in the adherence of *S. pneumoniae* to the airway epithelial cells;[8,44] however, the measles virus decreases the risk of adherence of streptococcal bacteria, implying that every virus has a specific mode of changing the host cell membrane.[44] Moreover, bacterial adhesion might also be a result of the upregulation of surface receptors including PAF-r, which is involved in pneumococcal invasion.[45,46]

In patients with cystic fibrosis, bacterial adherence forms a biofilm, creating permanent airway colonization with *P. aeruginosa*.[47] Viruses such as RSV, rhinovirus, and influenza virus also lead to pneumococcal biofilm formation on the airway lining.[48] Furthermore, RSV increases the risk of adherence of *Staphylococcus aureus* and *Bordetella pertussis* to Hep-2 (human epidermoid cancer) epithelial cells.[49,50]

Virus effect on the immune system

Post-viral sustained desensitization of lung sentinel cells to TLR signals may be one possible contributor to the common secondary bacterial pneumonia associated with viral infection. For instance, TLR4 and TLR5 pathways are altered after influenza virus infection, resulting in decreased neutrophil attraction, thereby leading to increased attachment of *S. pneumonia* and *P. aeruginosa* to the airway epithelial cells.[25]

The interrelation between host cells and microorganisms during an infection induces immune responses that include the generation of proinflammatory molecules. Despite their crucial role as a bactericidal, proinflammatory cytokines such as TNF-α produced in response to infection could be detrimental to the host cells.[51] During a viral infection, TLR and RIG-I-like receptor activation induces production of type I IFNs, which can augment the inflammatory response to TLR ligands including lipopolysaccharide (LPS).[52,53] In addition, certain bacteria such as *S. aureus* integrate into the A549 respiratory epithelial cells (adeno-carcinomic

human-alveolar basal-epithelial_cells) during a respiratory viral infection by increasing the expression of ICAM-1.[54] RSV differs from influenza virus in that the former upregulates cellular receptors including CEACAM-1 and ICAM-1, which eventually leads to bacterial infection.[45] Finally, interaction between type I IFNs and Nod1/Nod2 signaling leads to bacterial recognition, but indicts harmful effects in the virally infected host.[55]

Clinical presentation

Corollary and secondary bacterial infections in patients with viral diseases are known to coexist. A study conducted by O'Brien et al[56] showed that the influenza virus (H1N1) was the culprit of the severe pneumococcal pneumonia outbreak among children that occurred in Iowa in the mid-1990s. Other studies have shown that almost one-third of children with community acquired pneumonia (CAP) had mixed (viral and bacterial) infection.[57,58] Moreover, a study in France showed that influenza virus infection was the direct cause of CAP in 12% of children.[59] Syrjanen et al[60] found in their study that the isolation of *S. pneumonia* from the nasopharyngeal area was higher during respiratory infection without concomitant AOM. Viral respiratory infection due to RSV, influenza virus (type A or B), and adenovirus increase the incidence of otitis media (OM) and recurrent OM in children.[61,62] Ruuskanen et al[63] found that there is a concrete association between AOM and 57% of children with RSV, 33% with parainfluenza type 3 virus, 30% with adenovirus, 35% with influenza A virus, 28% with parainfluenza type 1 virus, 18% with influenza B virus, and 10% with parainfluenza type 2 virus infections; the most common bacteria isolated from tympano-centesis were *H. influenzae*, *S. pneumoniae*, *Branhamella catarrhalis*, and *Mycoplasma pneumonia*. Another study showed that the rates of bacteremia and OM were 18% and 44%, respectively, in children with viral-induced bronchiolitis.[11] The highest incidence of AOM is usually 2–5 days after an upper respiratory infection.[64,65] Isolation of viruses alone from sinus aspirates or in concomitance with bacteria proposes the role of viruses in the induction of bacterial sinusitis,[62] with rhinovirus and parainfluenza viruses being the culprits.[66] The rate of bacteremia in children with acute bronchiolitis ranges from 0.2% to 1.4%.[67–75] In addition, the rate of bacterial urinary tract infection (UTI) in children with bronchiolitis can be as high as 11.4%.[67] In a recent study, Hendaus et al[76] assessed the prevalence of UTI in infants and children with bronchiolitis. The study included 835 hospitalized children with acute bronchiolitis. The results disclosed that UTI was found in 13.4% with bronchiolitis triggered by a respiratory viruses such as rhinovirus (31%), adenovirus (14%), parainfluenza virus type 4 (14%), bocavirus (10%), human metapneumovirus (10%), coronavirus (7%), parainfluenza virus type 3 (3.4%), parainfluenza virus type 2 (3.4%), parainfluenza virus type 2 (3.4%), and H1N1 (3.4%). Rittichier et al[77] have researched the effect of respiratory viruses on the risk of acquiring serious bacterial infection, including UTI. The study concluded that febrile infants with enterovirus had a coexisting rate of serious bacterial infection of 6.6%.

Role of myxovirus resistance protein 1 (MxA) in differentiating between viral and bacterial infections

The human myxovirus resistance protein 1 (MxA) is an important intermediary of the IFN-induced antiviral response against a variety of viruses. MxA expression is firmly modified by type I and type III IFNs, which also requires signal transducer and activator of transcription 1 signaling. Additionally, MxA has many characteristics similar to the superfamily of large guanosine triphosphatases.[78] MxA analysis could be beneficial to differentiate between bacterial and viral infections. Engelmann et al[79] conducted a prospective, multicenter cohort study in different pediatric emergency departments in France on the role of MxA in the diagnosis of viral infections. MxA blood values were calculated in infants and children with verified bacterial or viral infections, uninfected controls, and infections of unknown origin. A receiver operating characteristic analysis was used to verify the diagnostic performance of MxA. The study, which included 553 children, showed that MxA was significantly higher in children with viral versus bacterial infections and uninfected controls ($P<0.0001$). Additionally, MxA levels were significantly higher in children with clinically diagnosed viral infections than in those with clinically diagnosed bacterial infections ($P<0.001$).[79] Other authors have also reported the usefulness of blood MxA testing in patients with viral infections.[80,81] The use MxA in diagnosing viral infection is very promising, especially in patients who are at risk of infectious complications. Two separate studies have shown that blood MxA is beneficial in differentiating between viral illness and acute graft-versus-host disease after allogenic stem cell transplantation.[82,83]

Prevention of secondary bacterial infection

It has been recommended that treatment or prevention of a viral disease may be a superior method for diminishing

of complications from influenza.[84,85] Since viral infections might lead to secondary bacterial infection, it is prudent to vaccinate patients with the influenza vaccine to diminish the risk of OM in children and pneumonia in adults.[62]

It has also been published that live attenuated influenza vaccine is effective in reducing the incidence of all-cause AOM[86–88] and pneumonia[89] compared to placebo in children. In addition, the intranasal influenza vaccine can reduce OM by 44%.[90] Moreover, studies have shown that a combined influenza/pneumococcal vaccine is efficient in the prevention of OM in children and pneumonia.[91,92] However, the credit of protection was awarded to the influenza vaccine since studies have shown that pneumococcal vaccine has no benefit in the reduction of AOM.[93,94] In addition, the pneumococcal polysaccharide vaccine showed no efficacy in the prevention of pneumonia in adults.[95]

Treatment of viral infection is anticipated to prevent bacterial superinfections. Currently, the only respiratory virus that is pharmacologically treatable is the influenza viruses (Type A and B).[62] Neuraminidase inhibitors can potentially diminish the morbidity related to influenza.[96] Oseltamivir can reduce the incidence of AOM in preschool children,[97] and the reduction rate can be up to 44%.[98] A meta-analysis review showed that oral oseltamivir reduces the rate of hospitalization by 25% and morbidity by 75%.[99] In addition, its use can reduce the use of antibiotics by up to 50%,[100,101] The same concept of protection applies to vaccines that prevent against RSV infections.[62] The vaccine available for RSV is palivizumab (MedImmune, Gaithersburg, MD, USA), a humanized monoclonal antibody that perceives the fusion protein of RSV. The other monoclonal antibody that is under clinical trials is motavizumab (MedImmune), which has a higher affinity for RSV fusion protein than palivizumab and can prevent against medically attended lower respiratory tract infection.[102]

Conclusion

The rate of concurrent serious bacterial infections with viral illness is appreciable. Similar emphasis must be given to the prevention and treatment of viral illnesses, especially in young children. Furthermore, health care providers should emphasize to parents on the importance of clinical follow-up of infants and young children diagnosed with VRTI. Moreover, the introduction of MxA in the diagnosis of viral illnesses in children is promising.

Disclosure

The authors declare no conflicts of interest in this work.

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