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Prophylaxis, therapy and prevention of viral respiratory infections

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Viral respiratory infections are the most common diseases seen in humankind and affect mostly children. Viruses have been shown to cause up to 90% of pneumonias during the first year of life,[1–3] and this percentage decreases to approximately 50% by school age.[1,5] Respiratory syncytial virus (RSV) is the major viral respiratory pathogen that causes lower respiratory tract infection (LRI) (bronchiolitis and pneumonia) in infants and young children worldwide and presents a large burden on healthcare resources.[4] Parainfluenza, and influenza viruses, many types of adenovirus, rhinovirus, enterovirus, and also coronavirus, herpes simplex type I, and other viruses have also been detected in children suffering from respiratory infections (RI).[1,5–9] High-risk groups for severe disease, especially from RSV, include age less than 3 months, preterm infants, and infants with underlying cardio-pulmonary disease and/or immunodeficiencies.[10]

INFLUENZA VIRUS

Antiviral prophylaxis against RI needs to be extremely safe, inexpensive, and widely available for long-term use in children. So far, these criteria have been successfully fulfilled in preventing influenza infections. Influenza viruses are the most important cause of acute illness when considering all age groups. A recent summary of disease burden ranked acute LRI as the most important cause of disability-adjusted life years lost by the world's population.[11] The impact of LRI is greatest in children younger than 5 years of age. The disease burden imposed by influenza justifies the indication for prophylaxis for children. Preventing influenza in children could yield another important benefit, because they are the most important spreaders of influenza in the community and most frequent introducers into the household.[12] The importance of school-aged children in dissemination of influenza was conclusively demonstrated by the Japanese program for influenza immunisation during the 1970s and 1980s.[13] During this period influenza vaccine coverage in schoolchildren reached approximately 80%, and it was estimated that 37,000 to 49,000 deaths among elderly were prevented annually. The main disadvantage of any influenza vaccine however, is the necessity of delivering the vaccine each year during a short interval between the time that vaccine is produced and distributed and the time that influenza virus activity begins.[13] Results from studies with new intranasal influenza vaccines in children are pending[14]. However, the available influenza vaccine is recommended in children older than six months with chronic underlying diseases such as pulmonary, cardiovascular, renal, metabolic, and also immunosuppression, hemoglobinopathies, and children on long term aspirin therapy.[15]

Vaccine efficacy in preventing transmission is usually 60–70% in the elderly, the protection rate is lower, and efficacy in preventing mortality is usually 70–80%.

Prophylaxis and/or treatment using amantadine or rimantadine is available for patients infected by influenza A virus. However, in vitro resistance to amantadine and rimantadine has been documented, and their use has been associated with intra-family transmission of resistant influenza A strains.[16] The neuraminidase inhibitors have gained interest in preventing and treating influenza because they are active against both influenza A and B and also the emergence of resistance is uncommon. These agents became available in the 1999–2000 influenza season, and clinical benefit is documented only if

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they are administered within 48 hours from the onset of symptoms.[17] Treatment with these agents is recommended in healthy adults, patients with asthma and COPD, healthy children, and children with asthma. Prevention is recommended within families, in community setting, during nursing home outbreaks, and as adjunct to late vaccination.

RSV

The best approach to controlling RSV is to prevent its spread. RSV is transmitted via large droplet aerosol by close contact (within three feet distance) or by contaminated fomites. RSV can survive up to 45 minutes on clothes and for six hours on hard surfaces such as toys, tabletops, and stethescopes.[18] Previously healthy children who develop RSV infection may shed the virus for seven to ten days and immunocompromised patients can shed the virus for weeks. Families of at-risk infants and children should be taught the importance of repeated hand washing, warned against exposing their infants to passive smoke, crowds and large day-care centres during RSV season, and they should limit contact with individuals with obvious signs of upper respiratory tract infections.[4,18,19]

Effective RSV prophylaxis in either the active (vaccine) or passive (immune globulin, monoclonal antibodies) form has been evaluated over the past four decades.[20,21] A safe and effective RSV vaccine has thus far not been developed. In vaccine trials conducted in the 1960s, healthy infants who received a formalin-inactivacted vaccine developed enhanced respiratory disease with a fifteen-fold increase in RSV LRI hospitalisation rate, including several fatal outcomes, after they became naturally infected with RSV in the following respiratory season. This tragic experience has delayed the development of RSV vaccines for use in high-risk preterm infants and young children. It is not anticipated that such a vaccine will be available for many years.[22–24]

In the absence of a safe and effective RSV vaccine, passive immune prophylaxis using a humanised monoclonal RSV antibody has been developed. Palivizumab (Synagis) is an RSV F-protein-specific humanised monoclonal (IgG) antibody with neutralising activity, preventing the virus from fusing with and entering the respiratory epithelial cell.[25] This compound has high specific activity against RSV *in vitro* and can be formulated at high concentrations, permitting administration of small volumes by intramuscular injection. Since it is not derived from human plasma, prophylaxis with palivizumab removes the small but potential risk of transmission of blood-borne pathogens.

During the winter of 1996–1997 the IMpact-RSV trial, a multicentre, multicountry, randomised, double-blind, placebo-controlled trial of palivizumab was conducted to facilitate the licensure of Synagis in the USA and Europe (which occurred in 1998 and 1999, respectively).[26] Study subjects included children younger than two years with bronchopulmonary disease (BPD) or chronic lung disease (CLD) who required therapy for their BPD/CLD within six months of study entry, or children with premature gestation ($\leqslant$35 weeks of gestation) without CLD who were $\leqslant$6 months of age at study entry. Subjects received five monthly IM injections of palivizumab at a dose of 15 mg/kg or placebo. RSV-related hospitalisations were reduced by 55%, which is both clinically and statistically significant ($P < 0.001$). Significant reductions were also observed in favour of palivizumab recipients for total RSV-related hospital days per 100 children ($P < 0.001$), total RSV-related hospital days with requirement for increased supplemental oxygen ($P < 0.001$), total RSV-related hospital days with LRI score $\geqslant$3 ($P < 0.001$), and incidence of intensive care unit admission ($P = 0.026$).

Additional studies performed between 1998 and 2001 have resulted in the acquisition of additional safety and efficacy data in paediatric patients.[27–29] In these trials, palivizumab safety has been reaffirmed. No new or unanticipated adverse events have occurred.

While no placebo groups were used in these studies, there are excellent data from a large Spanish epidemiology study (IRIS) which demonstrated a mean hospitalisation rate of 13% in preterm infants $\leqslant$32 weeks gestational age who were not treated with palivizumab. In contrast, the outcome studies show a mean hospitalisation rate of around 2% in patients receiving palivizumab prophylaxis.

Severe RSV LRI is also common in preterm infants without CLD. Such infants have underdeveloped lungs and have received sub optimal amounts of IgG transplacentally from their mothers. The Spanish epidemiology study (IRIS) demonstrated a 10–13% hospitalisation rate from RSV LRI in this group of infants.[28]

RSV can progress to severe lower respiratory tract disease, with apnoea (particularly in premature or very young term infants), pulmonary failure and sometimes death.[29] A key element of support, both at home and in hospital, is the maintenance of good hydration. Aspiration can occur in ill infants and careful feeding is essential. The decision to hospitalise an infant depends on such factors as: parental adequacy in caring for a sick infant, young age (<3 months), history of prematurity, the presence of chronic cardiac and/or pulmonary disease, the

inability to take adequate fluids by mouth, extreme lethargy or irritability, a toxic appearance, and a high respiratory rate (>70 breaths/minute).[30–33] Oxygen saturations of <95% or increasing carbon dioxide levels are useful laboratory adjuncts in deciding whether to hospitalise an infant and to assess the risk for pulmonary failure.

Table 1 lists general classes of treatment. These have been used in studies in infants with RSV LRI in hospitals and emergency settings. Except for the use of oxygen and hydration, none of the therapies below have proven to be consistently useful in treating RSV LRI. Bronchodilators may be tried on a case-by-case basis and should be discontinued if the child does not respond to treatment. The use of steroids is currently not recommended, nor has cromolyn proven to be of any use in the treatment of acute bronchiolitis. Ribavirin is the only licensed antiviral treatment for RSV (in the USA and Europe), but is reserved for only the sickest patients and its efficacy and safety remain controversial. The occurrence of bacterial infection (except for otitis media) is low (2–10%), and therefore, children with RSV should be carefully assessed before antibiotic use is prescribed.[34] Table 2 lists the specific indications for antibiotics.

Table 1
Therapeutic approaches

Symptom	Therapy
Hypoxemia	Oxygen
Hydration	Thin small feeds, IV
Bronchodilators	Beta and alpha agonists
Anti-inflammatory	Cromolyn, Steroids
Antiviral	Ribavirin
Secondary infection	Antibiotics
Prevention of nosocomial infection	Infection control measures

Table 2
Indications for antibiotic use

Acute otitis media
Lobar pneumonia
Evidence of sepsis
Immunocompromised child

OTHER VIRUSES

Parainfluenza viruses, many types of adenovirus, rhinovirus, enterovirus, coronavirus, and other viruses also affect children and could be responsible for LRI. High-risk groups for severe disease include the very young infant (less than 3 months of age), preterm infants, and infants with underlying cardio-pulmonary disease and/or immunodeficiencies.

Human parainfluenza virus (HPIV) groups or subgroups can occur several times during the year. HPIV-1 for instance, occurs in biennial epidemics during the fall. HPIV-2 has been reported to occur biennial with HPIV-1, alternate years with HPIV-1, and more recently in yearly outbreaks.[1,35] Croup is the most frequent LRI caused by both groups, but all of the respiratory syndromes have been described. HPIV-3 is unique in its propensity to infect young infants,[36] while HPIV-4 has been isolated from small numbers of mainly children, but also from adults.[37]

Adenoviral infection does not seem to have as much seasonal variation. However, less often outbreaks may occur in the fall. The majority of LRI and pneumonia caused by this virus occur in preschool-age children.[38]

Rhinoviruses can be recovered year round, but they are recovered more often during the spring, summer, and fall.[39]

Anecdotal use of immunoglobulin (IGIV) to treat adenovirus disease in immunocompromised children has been reported with both positive and negative results.[40] Also, IGIV has been coupled with ribavirin anecdotally for the treatment of RSV, HPIV, and influenza B pneumonia in immunocompromised patients.[41] Ganciclovir was found to have some inhibitory effect on adenovirus, both *in vitro* and *in vivo,* but it has not been studied systematically.[42] Controversy continues about the usefulness of vitamin C for prophylaxis against URI. However, there are some trials suggesting that vitamin C may protect against LRI or pneumonia in children.[43] Also, recent evidence exist to support the role of vitamin A in reducing morbidity and mortality in acute measles infections, including pneumonia and croup.[44]

In conclusion, effective antiviral prophylaxis in either the active (vaccine) or passive (monoclonal antibodies) form for these viruses are not available, with palivizumab (Synagis) being the only approved agent to be used as prophylaxis against RSV infection. A positive treatment approach is good hydration and oxygen supplementation. While the best approach for prevention of viral spread and subsequent illness, is education of families and hospital staff in the importance of infection control (hand washing, avoiding passive smoke and crowds, hospital cohorting of infants suffering from LRI, respiratory infection control measures).

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