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Review Article

Respiratory syncytial virus infections: characteristics and treatment

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Abstract

In this review, we describe the history, epidemiology and clinical manifestations of infections attributed to respiratory syncytial virus (RSV) in children. At present, no cure exists for RSV infection but commonly employed palliative treatments include oxygen and inhaled β_2-adrenoceptor agonists, such as salbutamol, to relieve the wheezing and increased bronchiolar smooth muscle constriction. Adrenaline (epinephrine) has been found to be superior to the selective β_2-adrenoceptor agonists. Oral or inhaled corticosteroids should counteract the inflammatory response to RSV infection but their effectiveness is controversial. Inhaled ribavirin is the only licensed antiviral product approved for the treatment of RSV lower respiratory-tract infection in hospitalized children, although its use is now restricted to high-risk infants. Other treatments considered are nasopharyngeal suctioning, surfactant therapy, recombinant human deoxyribonuclease I, heliox (helium:oxygen) and inhaled nitric oxide. Prevention of infection by RSV antibodies is another strategy and, currently, palivizumab is the only safe, effective and convenient preventative treatment for RSV disease in high-risk populations of infants and young children. Its cost-effectiveness, however, has been questioned. Both live attenuated and subunit vaccines against RSV infection have been developed but so far there is no safe and effective vaccine available. Finding effective treatments and prophylactic measures remains a major challenge for the future.

Introduction

Respiratory syncytial virus (RSV) was originally recovered and identified as a novel virus in 1956 after an outbreak of common cold infections from a colony of chimpanzees (Blount et al 1956). A few years later, Channock et al (1957) isolated and characterized a virus from adult family members of children who presented with pneumonia and bronchiolitis, which was serologically identical to the virus that affected the respiratory system of captive chimpanzees. In the ensuing decade, the virus was renamed RSV because of its propensity to induce cell fusion, producing characteristic giant syncytia (large cell-like structures formed by the joining of two or more cells), which form in tissue culture (Figure 1) and within airways and lung parenchyma following infection.

Over the ensuing 20 years, a series of epidemiological studies recognized RSV as the most common cause of the lower respiratory-tract infection during infancy and early childhood worldwide (Channock & Parrott 1965; Glezen 1987; McIntosh 1997). The virus produces considerable morbidity and mortality in affected individuals following upper respiratory-tract infections, pneumonia and bronchiolitis. The burden of the illness is most significant for infants less than 2 years of age and affects health care costs, both at the community level and following hospitalization.

In the USA alone, it is estimated that 100 000–125 000 hospitalizations can be attributed to RSV lower respiratory-tract infections each year (Holberg et al 1991; Meissner 1994; Shay et al 1999, 2001) with costs of $356–585 million per annum (Stang et al 2001).

Epidemiology

RSV is a seasonal virus, with annual outbreaks occurring at regular, predictable intervals during the winter in temperate climates, especially in large urban areas and during the rainy season in tropical climates (Glezen & Denny 1973). In the UK, outbreaks of RSV occur in a distinct seasonal pattern between the months of

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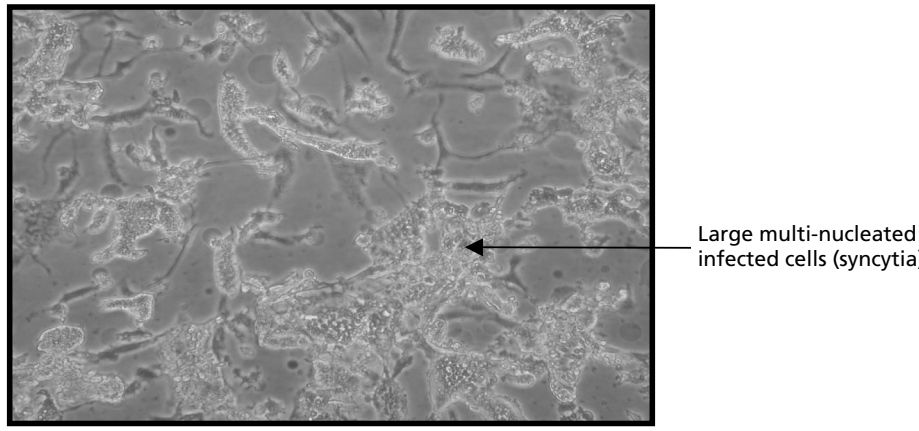

Figure 1 Monkey kidney cells infected in culture with RSV 5 days post infection displaying cytopathic effects (× 10).

November and April, peaking in December, January and February, with outbreaks lasting an average of 22 weeks (Glezen & Denny 1973).

RSV has two heterotypic strains, group A and group B, which both circulate simultaneously during an outbreak (Hall et al 1991). Group A viruses tend to predominate and it has been suggested that they are associated with more severe disease (McConnochie et al 1990; Walsh et al 1997). Both RSV A and B have several subgroups and the major difference between these subgroups is the antigenic properties of the G surface glycoprotein (Levine et al 1987). The F surface glycoprotein remains antigenically conserved between the RSV groups (Johnson & Collins 1988).

RSV is the pathogen most commonly recovered from children, accounting for approximately 90% of the cases of acute bronchiolitis and 50% of all pneumonia cases (Glezen 1987). Within the first year of life, RSV infects 70% of children, with a peak occurrence in the second month (Glezen & Denny 1973).

One-third of those infected develop lower respiratory-tract disease, resulting in 2.5% requiring hospitalization (Holberg et al 1991; Domachowske & Rosenberg 1999), and 0.1% will die (Holberg et al 1991). The frequency of RSV lower respiratory-tract disease decreases gradually during pre-school years, and by the age of three virtually all children have been infected (Glezen & Denny 1973).

Several factors lead to an increased risk of RSV disease. These include prematurity, especially in those with underlying chronic lung disease (Groothuis et al 1988), multiple births, congenital heart diseases (MacDonald et al 1982) and immunodeficiency (Hall et al 1986). Environmental factors, such as household crowding, school-age siblings, day-care attendance, passive exposure to smoke and malnutrition, also further predispose to RSV infection (Henderson et al 1979).

Classification and structure

Human RSV is a member of the *Pneumovirus* subfamily of the family Paramyxouiridae (Collins et al 2001). RSV is a medium-sized enveloped RNA virus (200 nm), consisting of a nucleocapsid N protein within a lipid envelope (Figure 2). The nucleocapsid is a symmetrical helix and the lipid bilayer is derived from the host cell plasma

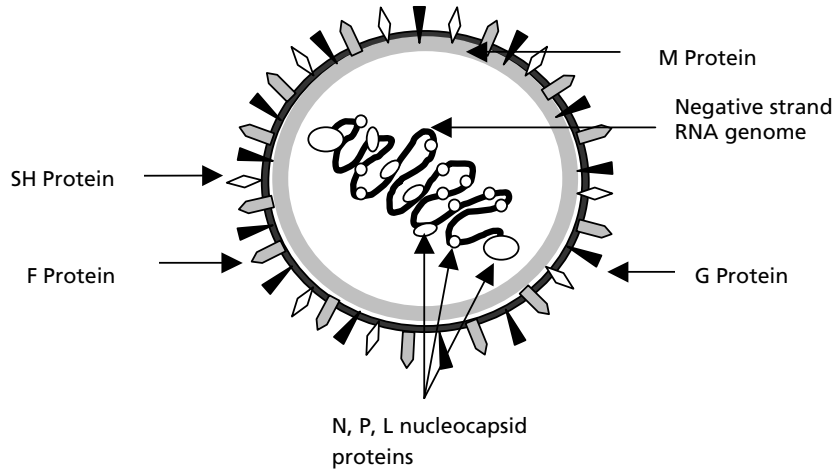

Figure 2 Respiratory syncytial viral structure.

Table 1 RSV-encoded proteins and their characteristics

Protein		Characteristics	
Surface proteins	F	Mediates syncytium formation	
	G	Mediates viral attachment	
	SH	Unknown function	
Nucleocapsid-associated proteins	N	Major nucleocapsid protein	Viral replicase
	P	Phosphoprotein	
	L	RNA polymerase	
Matrix protein	M	May mediate association between nucleocapsid and envelope	
Non-structural proteins	NS1	Unknown function	
	NS2	Unknown function	

membrane and contains virally encoded transmembrane surface glycoproteins (Collins et al 2001).

The RSV genome is composed of single-stranded negative-sense RNA of 15 000 nucleotides and encodes 10 viral proteins (Collins et al 2001). The genome is tightly encapsidated by the nucleocapsid N protein, which, together with the phosphoprotein P and large polymerase subunit L, forms the minimum unit for RNA replication (Table 1). In addition, RSV encodes a non-glycosylated virion matrix protein M, to mediate interaction between the nucleocapsid and envelope during virion morphogenesis.

RSV also consists of two non-structural proteins, NS1 and NS2, whose functions are currently unknown, although NS1 appears to be a negative regulatory factor for RNA synthesis (Collins et al 2001).

Integral to immunity and pathogenesis, RSV encodes three transmembrane surface envelope proteins that are components of the virion: the attachment protein G, the fusion protein F and the small hydrophobic protein SH (Domachowske & Rosenberg 1999). The heavily glycosylated RSV G protein is responsible for viral attachment to cells (Meanwell & Krystal 2000). The RSV F protein has a trimeric-coiled structure and promotes fusion of both viral and cell membranes resulting in the transfer of viral genetic material, and fusion of infected and adjacent cell membranes causing the formation of syncytia in the lung (Domachowske & Rosenberg 1999). Syncytia are the hallmark of the RSV cytopathic effect and are necessary for cell-to-cell viral transmission (Hall 2003). The precise role of the third transmembrane protein SH is currently unknown (Domachowske & Rosenberg 1999).

Pathogenesis

An infant's first encounter with RSV is usually apparent, but the symptoms may range from those of a mild cold to severe bronchiolitis or pneumonia (Loranzo & Wang 2002). RSV gains entry to the host through the mucous membranes in the eye, nose, throat and mouth via the respiratory mucosa (Hall et al 1981). Individuals affected with RSV shed large quantities of virus in their nasopharyngeal secretions and saliva, for up to 3 weeks in infants less than 1 year of age who have lower respiratory-tract infection (Hall et al 1976). RSV is spread by direct exposure to large droplet secretions through coughing and sneezing and by direct contact with contaminated surfaces (Hall & Douglas 1981).

The virus survives in nasopharyngeal secretions of infants and has been shown to remain infectious on counter tops for up to 6 h, on rubber gloves for 2 h, on cloth gowns and paper tissue for up to 1 h and on skin for up to 20 min with significant implications for infection control within care facilities (Hall et al 1980).

The incubation period of RSV disease has been reported as being 2–8 days (Collins et al 2001). During the initial stages of infection, RSV replicates in the nasopharynx, infecting the ciliated epithelial cells that line the nose as well as the large and small airways. The first step in viral replication is attachment of the viral particle to the host cell in the nasal epithelium. The viral RNA enters the host cell along with the viral enzymes that direct production of a new viral RNA and proteins. Multiple new viruses are assembled within the cell, which is ultimately destroyed. The destruction of ciliated epithelial cells lining the airways ultimately causes the symptoms characteristic of the infection. For most individuals, if epithelial-cell destruction is limited, RSV is restricted to the upper respiratory tract producing influenza-like illness or appearing as a persistent cold that is self-limiting. However, in some individuals where large amounts of epithelial cells are destroyed, they release a number of pro-inflammatory mediator substances, including cytokines, which cause increased capillary permeability and elevated secretion production. Chemokines are released, attracting additional pro-inflammatory cells, such as macrophages, neutrophils, eosinophils and natural killer cells, to the site of infection (Van Schaik et al 2000). Increased capillary permeability results in leakage of plasma proteins into interstitial areas, small airways and alveoli. This causes generalized interstitial swelling and appears to inhibit pulmonary surfactant function. The combination of increased secretion production, decreased secretion clearance due to compromised mucociliary elevator function, and ineffective surfactant function results in small airways filling with secretions and debris from destroyed cells. The release of bronchoconstrictor substances may cause small airways to narrow even further, resulting in increased airway resistance, air trapping and wheezing, which are characteristic of severe lower respiratory-tract infections (Van Schaik et al 2000).

Primary RSV infection does not induce substantial immunity and has limited effect on illness associated with the first re-infection, so that immunity after infection is neither complete nor durable (Collins et al 2001). Thus, a susceptible population is always available, which further adds to the burden on the health care system. Growing epidemiologic evidence illustrates that re-infection occurs throughout life involving infants, adults and families, manifesting as upper respiratory-tract illness (Beem 1967; Henderson et al 1979; Hall et al 1991). Re-infection of children with RSV is 76% in the second year of life and the clinical manifestations are difficult to distinguish from influenza. However, the severity of the disease generally

decreases with subsequent re-infections and is significantly reduced by the third infection (Henderson et al 1979).

Therapeutics and prophylaxis

While significant advances in the knowledge of RSV biology, immunology, pathophysiology and epidemiology have been made in the past 40 years, there continues to be controversy over the optimum management of infants with RSV infection. Their treatment is complicated because of the multifactorial nature of this infection. The available therapeutic and prophylaxis modalities are discussed below.

Therapeutics

Attempts to develop effective therapy for RSV infection has been ongoing since the virus was isolated. However, so far no effective treatment beyond palliative measures has been developed.

Oxygen. The use of supplemental oxygen therapy has not been subjected to randomized controlled clinical trials but its use is considered appropriate to overcome hypoxaemia. In general, supplemental oxygen ≥ 93% saturation should be maintained during the acute phase and during recovery (Rakshi & Couriel 1994).

Adrenaline (epineprine). Adrenaline (epineprine) is an adrenergic agonist with α- and β-adrenoceptor activity, which could be beneficial in RSV infection. The β-adrenoceptor activity causes bronchodilatation, easing breathing by opening the small airways, while the α-adrenoceptor activity causes localized vasoconstriction, which relieves the oedema and consequent congestion of the nasopharynx. Adrenaline, given either via injection or via nebulization, has also been used in an attempt to ameliorate the symptoms of RSV infection. Nebulized adrenaline has been reported in some studies to be superior to saline in increasing oxygenation and clinical scores in infants (Abul-ainine & Luyt 2002). In contrast, a randomized study demonstrated no statistically significant differences in short-term improvements between infants treated with nebulized adrenaline or 0.9% saline (Abul-ainine & Luyt 2002). Studies have reported that adrenaline may be most effective if it is nebulized in 3% rather than 0.9% saline (Mandelberg et al 2003). The beneficial effect may be a result of the hypertonic saline decreasing mucosal oedema, mechanically clearing mucus or improving mucociliary function.

Others have reported that adrenaline is superior to salbutamol in the treatment of RSV infection with regard to improvements in oxygenation, clinical severity scores and pulmonary resistance (Sanchez et al 1993; Menon et al 1995; Bertrand et al 2001). In the emergency department, a smaller proportion of infants treated with adrenaline rather than salbutamol were admitted to hospital (Menon et al 1995). The difference between patients' responses to adrenaline and salbutamol may be due to the α-adrenoceptor agonist activity of adrenaline being more effective at decreasing interstitial and mucosal oedema and therefore possibly being more effective at opening the small airways than a β-adrenergic bronchodilator (Barr et al 2000a). Studies by Hartling et al (2004) have determined that there is insufficient evidence to support the use of adrenaline for the treatment of bronchiolitis among inpatients.

Bronchodilators. The bronchodilator β_2-adrenoceptor agonists have been commonly used in the management of bronchiolitis. Bronchodilators are intended to relieve wheezing and air trapping and increased airways resistance caused by constriction of the bronchiolar smooth muscle. The efficacy of bronchodilators compared with placebo have been investigated in many studies, yielding conflicting results, but overall demonstrating little or no improvement in oxygenation, clinical scores or time in hospital. This limited bronchodilator effectiveness may be the result of poor aerosol penetration into the peripheral airways. Amirav et al (2002), using radio-labelled salbutamol, showed that only about 0.6% of the salbutamol leaving the nebulizer actually reached the small airways of infected infants. They suggest that this is very inadequate and that delivery of medication to peripheral airways in the infant lung could be improved by the use of superfine aerosols.

This correlates with the observation by some investigators that bronchodilator therapy seems to be most effective in the early stages of infection, at a time when the small airways are not so obstructed with secretions and cellular debris. This is further supported by a study that determined the practice variation in emergency departments in the treatment of paediatric bronchiolitis and confirmed the findings are consistent with the literature regarding the use of bronchodilators (Plint et al 2004). Studies by Kellner et al (2000) demonstrated that bronchodilators produce modest short-term improvement in clinical scores when bronchiolitis is mild-to-moderately severe but no significant effect on the duration in hospital. This study concluded that the high cost of bronchodilators and the uncertain benefit of their use meant that routine management of first-time wheeze cannot be recommended and further research is necessary (Kellner et al 2000).

Corticosteroids. Corticosteroids have powerful anti-inflammatory activity and are commonly prescribed for treatment of unwanted inflammation in a number of conditions. The pathophysiology of RSV suggests that the anti-inflammatory action of corticosteroids should provide effective therapy for infections. A small selection of studies has shown beneficial effects of corticosteroids in the acute phase of RSV infection. Oral prednisolone given for 7 days resulted in a more rapid decrease in symptom score and a reduction in length of hospital stay, but only in ventilated infants (Van Woensel et al 1997). In addition, in a double-blind randomized study, which included 70 children, an oral dose of dexamethasone to infants with moderate-to-severe bronchiolitis in the emergency room resulted in a lower rate of hospitalization (Schuh et al 2002). Studies have also reported beneficial effects of inhaled budesonide (Reijonen et al 1996; Fox et al 1999).

Overall, however, corticosteroids have not been demonstrated to have clinically significant effects in acute RSV infection, regardless of the method of administration (Roosevelt et al 1996; Klassen et al 1996; De Boeck et al 1997; Richter & Seddon 1998; Bulow et al 1999) or the severity of the infants' RSV illness (Buckingham et al 2002). Indeed, in ventilated infants, intravenous dexamethasone did not result in a significant reduction in the duration of mechanical ventilation, length of stay in the paediatric intensive care unit, hospital stay or the duration of supplementary oxygen administration (Van Woensel et al 2003). Despite all the clinical research to date, the efficacy of steroid use for RSV remains controversial.

Ribavirin

Ribavirin (Virazole), a synthetic guanosine nucleoside analogue (Figure 3), prevents viral multiplication. The mechanism of action of its antiviral properties is to inhibit the synthesis of viral structural proteins, thereby slowing replication. This drug is the only licensed anti-viral preparation approved for the treatment of RSV lower respiratory-tract infection in hospitalized children. Ribavirin is administered in a small-particle aerosol via an oxygen hood for a period of 12–20 h per day. Early double-blind, placebo-controlled studies were extremely encouraging, indicating that ribavirin aerosol resulted in more rapid clinical improvement in previously well infants (Hall 1983; Taber et al 1983; Barry et al 1986; Conrad et al 1987; Rodriguez et al 1987) and in infants requiring mechanical ventilation for severe infections (Smith et al 1991). A systematic review of 12 studies examining the acute efficacy of ribavirin concluded that trials of ribavirin for RSV lacked sufficient power to provide reliable estimates of its effects (Ventre & Randolph 2004).

Furthermore, there are practical difficulties with administration of the agent and concerns about teratogenic effects for attending hospital personnel have led to restriction of the use of ribavirin to high-risk infants requiring mechanical ventilation. Studies evaluating the growing concern surrounding ribavirin and its high cost led to a change in the recommendation for usage from 'should be used' to 'may be considered' for selected infants and young children at high risk for serious RSV disease (Committee on Infectious Disease 1996).

Nasopharyngeal suctioning. Nasopharyngeal suctioning is a technique that involves extending a suction catheter up through the nose, passing a tip to the hypopharynx and then applying suction as the catheter is withdrawn (Black 2003). This has proved to be a remarkably effective palliative measure for the treatment of infants with RSV. During RSV infection, copious secretions are present in the nose, pharynx and lower airways. Approximately 60% of the resistance to breathing is located in the upper airway and, given that infants are primarily nose breathers, clearance of these secretions should have a positive impact on work of breathing and provide symptom relief.

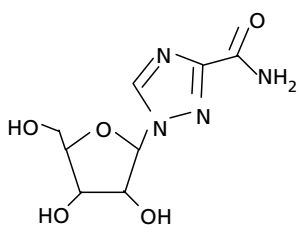

Figure 3 Stucture of ribavirin.

Investigations have determined an improvement in bronchiolitis following nasopharyngeal suctioning in patients with RSV infection (McKinley et al 2001), and in patients requiring oxygen to maintain arterial oxygen saturation ≥ 88%, 31% could be weaned following the first suctioning, and a further 24% could be weaned following the second and third suctioning episode (Zemlicka-Dunn et al 2001). In addition, when nasopharyngeal suctioning was used as both a single intervention and in combination with salbutamol, suctioning was found to be more effective at lowering the bronchiolitis score than the salbutamol treatment (Bennion et al 2001).

The evidence for nasopharyngeal suctioning suggests that it is a remarkably safe and inexpensive intervention and is an effective palliative measure for the treatment of infants with RSV.

Surfactant. Ventilated infants with RSV infection have been reported to show the occurrence of surfactant abnormalities, including lower levels of dipalmitylphosphatidylcholine (Dargaville et al 1996) and phospharidylglycerol (Skeleton et al 1999) in bronchoalveolar lavage fluid with reduced functional activity and surfactant protein A deficiency (Dargaville et al 1996). It has been hypothesized that RSV invades Type II pneumocytes and, thus, could impair surfactant protein A production. Surfactant protein A is a collectin, which binds to RSV and is then phagocytosed (Barr et al 2000b). Surfactant therapy by Tibby et al (2000) prevented the deterioration in lung mechanics and improved ventilation indices. Although the evidence is encouraging, surfactant therapy is expensive and studies are required to determine if it is cost-effective.

Nitric oxide. Inhaled nitric oxide has a number of actions that might be useful in RSV infection. Animal studies have shown that nitric oxide has a bronchodilator effect, mediating the noradrenergic, non-cholinergic neuronal inhibitory response in human airways, and through that mechanism, modulates airway tone and has the ability to cause pulmonary vasodilatation (Broughton & Greenough 2003).

Inhaled nitric oxide has been shown to be of benefit in the treatment of infants suffering severe RSV pneumonia and bronchopulmonary dysplasia. Inhaled nitric oxide, in addition to conventional mechanical ventilation, improved both oxygenation and respiratory system resistance (Leclere et al 1994) and inhaled nitric oxide used with high frequency ventilation improved oxygenation more than the high frequency ventilation alone (Hoehn et al 1998). In addition, the treatment of 12 ventilated infants with severe RSV infection compared respiratory system resistance measurements after 1 h of inhaled nitric

oxide at concentrations of 20, 40 and 60 parts per million versus the administration of salbutamol and concluded that inhaled nitric oxide failed to improve lung mechanics (Patel et al 1999). The evidence suggests that inhaled nitric oxide has some benefit in the treatment of severe RSV infection although it is not cost effective.

Recombinant human deoxyribonuclease I. Bronchiolitis is characterized by thick mucous plugs, which result in airway occlusion, air trapping and atelectasis. Lysis of inflammatory cells means that DNA is present in large amounts in the mucous plugs. DNA is a polyanion molecular compound and contributes to increased viscosity and adhesiveness (Broughton & Greenough 2003). Studies have examined the effects of aerosolized recombinant human DNase to break down the DNA in infants with RSV infections. Investigations by Nasr et al (2001) demonstrated significantly improved chest radiograph scores after DNase administration, although respiratory rate, retractions and the length of stay in hospital were not significantly different. However, a case study involving RSV-infected infants on mechanical ventilation showed clinical and radiologic improvement on DNase administration (Merkus et al 2001). This treatment cannot be recommended as being cost effective for infants with RSV infection.

Heliox. Heliox is a mixture of helium and oxygen, which has a lower density than air, thus there is increased flow for a given driving pressure and a lower work of breathing when airflow is turbulent (Gross et al 2000). Several studies have investigated the effect of heliox in RSV-infected infants. Increasing the helium-to-oxygen ratio failed to significantly decrease ventilation or oxygenation in infants ventilated with bronchiolitis (Gross et al 2000). Non-intubated infants with severe bronchiolitis administered heliox (helium:oxygen, 70%:30%) had a significantly improved clinical score (Hollman et al 1998), respiratory rate, heart rate, arterial oxygen saturation and length of time spent in the intensive care unit (Martinon-Torres et al 2002). Further testing is required to determine whether this therapy is cost effective.

Antibiotics. Antibiotics are commonly prescribed in bronchiolitis, although they have no action against viruses. Studies have failed to demonstrate any benefit in hospitalized infants with bronchiolitis. The only role for antibiotics is in complicated bronchiolitis where a secondary bacterial infection, such as with streptococcus or staphylococcus, is suspected (Friis et al 1984). However, studies have demonstrated that infants with RSV infection are at a lower risk from serious bacterial infection than patients without RSV infection (Levine et al 2004).

Prophylaxis

RSV infection is, so far, incurable by medical intervention and infection therefore prevention would be the most effective way to relieve the disease and its economic impact.

RSV immunoglobulin. Currently, two antibodies are prescribed in RSV, including RSV immune globulin (RSV-IGIV; Respigam, MedImmune Inc.) and palivizumab (Synagis, MedImmune Inc.).

RSV-IGIV is a polyclonal preparation containing concentrated neutralizing antibody produced from the sera of adult humans. In a PREVENT study (The PREVENT Study Group 1997) performed during 1994–1995, an infusion of RSV-IGIV, 750 mg every 30 days, was given to prematurely born infants, which resulted in an overall decrease in hospitalization of 41%, a 53% reduction in hospital days and a 60% reduction in hospital days with oxygen. However, in this study 1% of prematurely born infants and 13% of those with bronchopulmonary dysplasia required diuretics at the time of treatment. RSV-IGIV has been shown to be effective against RSV infection but it has several limitations. Firstly, it is a blood-derived product with the possibility of transmission of infectious pathogens. RSV-IGIV is administered under medical surveillance, which is time consuming, and it has a high viscosity, which in combination with the large dosage volumes has the potential to precipitate fluid overload. In the 1997–1998 RSV season, market sales in the USA were $70 million (Kamal-Bahl et al 2002); however, sales have declined to negligible levels as it has been replaced by palivizumab.

Palivizumab is a chimeric humanized IgG monoclonal antibody preparation licensed for RSV prophylaxis and produced by recombinant DNA technology directed to an epitope on the A domain of the F glycoprotein. The F protein is selected as the antibody target to enable both A and B subtype strains to be neutralized (Young 2002). Antibody binding to the F protein has either of two effects. First, it prevents cellular infection by preventing the viral membrane from fusing with the cell membrane of both type A and B clinical RSV isolates on respiratory epithelial cells (Johnson et al 1997). Secondly, it prevents cell-to-cell spread of the virus, which in turn prevents the formation of syncytia in the lung.

In 1998, palivizumab received approval in the USA for the prevention of serious lower respiratory infection by RSV and it is the current market leader in RSV therapy, with annual sales of $849 million in 2003 (Maggon & Barik 2004). Monthly intramuscular injections ($15\,mg\,kg^{-1}$) are administered seasonally and confer passive immunity to those most susceptible to infection and most vulnerable to its serious and potentially fatal effects (Black 2003). The effectiveness of palivizumab was tested in a randomized, double-blind study (The Impact-RSV Study Group 1998) involving thousands of pre-term infants in various demographic groups, with infants receiving five monthly intramuscular injections of palivizumab. The overall rate of hospitalization was 55% lower in the treated groups and respiratory severity scores, hospital days, days of oxygen requirement and the rate of intensive care unit admission were all significantly lower in the treated group. This study suggests that palivizumab administration reduces overall hospitalization rates due to RSV, and that it is well tolerated with few side effects. A post-marketing surveillance in

more than 250 000 high-risk infants over a 4-year period (1998–2002) has confirmed its safety and clinical effectiveness (Romero 2003).

The Committee on Infectious Diseases (2003) recommends the use of palivizumab over RSV-IGIV for a number of reasons. Palivizumab is more convenient, since it can be administered by intramuscular injection rather than by intravenous infusion (as for RSV-IGIV), which interferes with the measles–mumps–rubella vaccine and the lack of complications associated with intravenous administration of human immune globulin products. Palivizumab has also been shown to be 50–100 times more potent than RSV-IGIV and its use is approved in 50 countries (Maggon & Barik 2004).

The American Academy of Paediatrics Committee on Infectious Diseases (1998) guidelines for palivizumab are as follows. The groups recommended for treatment include children less than 2 years old who have required therapy to treat chronic lung disease within 6 months before the next RSV season; infants without chronic lung disease born at less than 28 weeks gestation, up to the age of 12 months; infants born at 29–32 weeks gestation up to the age of 6 months; and infants born at 32–35 weeks gestation who have risk factors such as day-care attendance or school-age siblings, up to the age of 6 months. Currently, palivizumab is not recommended for children with congenital heart disease.

Where there are constraints on health budgets, local decisions should be made balancing the cost of palivizumab against other therapeutic options. Several studies have determined the cost effectiveness of treating patients with palivizumab. The studies have included the assessment of the projected costs in a cohort study (Joffe et al 1999; Lofland et al 2000) comparing the cost related to hospitalization with the cost of prophylaxis with palivizumab (Clark et al 2000).

This is further supported by a study in the UK, which determined that prophylaxis would have resulted in a saving of £195 134 in hospital costs but the prophylaxis would have cost the local health authority £1.1 million (Clark et al 2000). Therefore, the combination of limited efficacy and the high cost of treatment has led to wide variation in its clinical use.

Currently, Numax, an affinity-matured monoclonal antibody, is under development. This claims to be 20 times more active than palivizumab in reducing viral loads in cell cultures in cotton rats (Maggon & Barik 2004).

General hygiene procedures

RSV is a major nosocomial hazard and both patients and care workers are at risk of transferring the virus to uninfected patients unless strict infection-control procedures are implemented. Simple rapid diagnostics are readily available and will enable patients to be placed at the appropriate level of isolation as soon as possible. The primary focus for the prevention of nosocomial RSV transmission is by hand washing and the wide availability of hand washing sites. Gown and gloves should be worn when entering the room of a patient with confirmed or suspected RSV and when handling the patients, their respiratory secretions and objects in the room potentially contaminated with those secretions. A surgical mask and eye protection should be worn when providing care that might generate sprays of respiratory secretions from any patient. Infection-control procedures consume valuable time and resources and it is therefore important that infected patients be identified quickly (Hall 2000). Education of care workers is also critical regarding infection control procedures.

Those in contact with patients should receive formal instruction in the modalities of the spread of RSV disease at the start of each RSV season (Hall 2000). One study has shown that the implementation of such procedures resulted in a reduction in nosocomial infection (McCartney et al 2000).

Vaccines. The morbidity and mortality associated with bronchiolitis, coupled with its frequency and global distribution make RSV a prime target for the development of a vaccine that can be administered early in life. Several major efficacy and safety obstacles have prevented the development of a safe and effective vaccine.

Firstly, there is the possibility that vaccination will potentiate naturally occurring RSV disease, as observed with a formalin-inactivated vaccine in the 1960s, which produced tragic consequences as it induced severe disease in infants who were subsequently infected with RSV from the community (Kim et al 1969). Secondly, newborns and very young infants may not mount a protective immune response because of relative immunological immaturity or because of suppression of their immune response due to circulating maternally derived anti-RSV antibodies. Thirdly, an effective RSV vaccine needs to provide protection against multiple antigenic strains of RSV in the two major groups A and B. Despite these early experiences, a wide variety of approaches to production of an RSV vaccine are being considered, including both live and subunit vaccines, which are rapidly progressing (Maggon & Barik 2004). In the past 20 years of RSV vaccinology, two main types of vaccines have been formulated – live attenuated virus and subunit vaccines.

Live attenuated vaccines. The benefit of live attenuated virus vaccines is that viral replication allows the generation of immunity that may mimic natural infection without causing significant morbidity. Measles, mumps, rubella and oral polio vaccines have demonstrated the effectiveness of this approach. A live attenuated RSV vaccine would have the advantage of being able to be given intranasally and would provide protection against both upper and lower respiratory-tract RSV infections, despite the presence of maternal antibodies.

Several strategies for the development of a live attenuated RSV vaccine have been explored, including the creation of host-range mutants, cold-passaged mutants and temperature-sensitive mutants (Juhasz et al 1999; Whitehead et al 1999; Wright et al 2000). Generally, these

vaccine candidates were unsuitable, being either under or over attenuated.

Subunit vaccines. RSV F and G are the viral glycoproteins that induce neutralizing antibodies and are therefore potential vaccine candidates. Studies have demonstrated safety and immunogenicity in purified F protein vaccines (Groothuis et al 1998; Piedra et al 2003; Munoz et al 2003). In these studies, purified F protein-2 was shown to be safe for RSV-seropositive children with bronchopulmonary dysplasia (Groothuis et al 1998), and in third-trimester pregnant women showed safe and efficient transfer of RSV-neutralizing antibodies to infants (Munoz et al 2003). Studies have also demonstrated safety, tolerance and immunogenicity in young adults using a subunit G vaccine BBG2Na (Power et al 2001, 2003). In addition, an FG chimeric vaccine is also in development (Prince et al 2000).

Conclusion

RSV remains a major cause of morbidity and mortality in early childhood, causing significant economic burden to the health care system at both the community level and following hospitalization. Treatment of RSV should be individualized as RSV infection is a complex disease with many variables that may affect management decisions, such as patients' age and stage of infection. At present, RSV prevention strategies should focus on the interruption of transmission using hand-washing techniques and reducing exposure to potential environmental risk factors.

At present, no cure exists for RSV infection but commonly employed palliative treatments include oxygen, adrenaline, inhaled β_2-adrenoceptor agonists, systemic and inhaled corticosteroids and inhaled ribavirin. Nasopharyngeal suctioning has also been investigated. Currently, palivizumab is the only safe, effective and convenient preventative treatment for RSV disease in high-risk populations of infants and young children. Development of an RSV vaccine for paediatric immunization offers the best hope to reduce the burden of the disease. Nearly half a century of research into RSV infection has failed to yield an effective and safe treatment or the immediate prospects of an RSV vaccine. Finding effective treatments and prophylactic measures remains a major challenge for the future.

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