Palivizumab: an overview

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Respiratory syncytial virus (RSV) affects almost all children in their first 2 years of life and can cause severe or even life-threatening disease in some at-risk infants. Treatment is limited and there is currently no safe or effective vaccine. However, a new monoclonal antibody, palivizumab, reduces RSV hospitalization by 55% in at-risk groups if given prophylactically throughout the RSV season.

Respiratory syncytial virus (RSV) is recognized as the single most important respiratory pathogen in infancy and early childhood (Hall et al, 1975). In most infants, symptoms are mild and similar to those of the common cold but considerable morbidity can occur in high-risk cases (Ottolini and Hemming, 1997). The primary episode of RSV infection does not protect against subsequent infections, and RSV continues to play a significant role in lower respiratory disease for several years thereafter. Serological surveys indicate that RSV is present in all geographical and climatic regions. In the UK, the virus shows marked seasonality with the highest incidence of infection occurring between October and March every year.

IDENTIFYING AT RISK GROUPS

RSV infection in certain high-risk groups can cause severe or even life-threatening disease.

A number of underlying medical problems have been linked with severe RSV disease in the first year of life (*Table 1*), as well as environmental risk factors such as hospitalization during the RSV season, low socioeconomic status, crowding and passive smoking. The fatality rate in infants with heart or lung disease who are hospitalized with RSV infection is 3–4% (Navas et al, 1992).

In the USA, RSV disease results in over 90 000 hospital admissions annually, and about 2% of these infants die (Choy, 1998). RSV is thought to account for more than 25% of paediatric hospitalizations for pneumonia and has been confirmed as the cause of 40–50% of paediatric hospitalizations for bronchiolitis (Levy and Graber, 1997).

Both major strains of RSV, groups A and B, generally circulate concurrently in annual epidemics. Studies of isolates in the UK and the USA suggest that group A strains — which are usually responsible for more severe clinical illness — tend to dominate in most outbreaks (Hall et al, 1990; Hendry et al, 1989; Taylor et al, 1989).

A HIGHLY CONTAGIOUS VIRUS

RSV is highly contagious. Its spread among all age groups, in families, day-care facilities and especially paediatric wards, is well documented. A longitudinal family study in Houston found that 69% of children became infected during the first year of life, and 83% during the second year (Glezen et al, 1986).

RSV is transmitted by direct contact with infectious secretions via the hands, fomites or large-droplet aerosols. RSV in patient secretions has been found to survive for up to 7 hours on countertops, on gloves, paper tissues and cloth, and for half an hour on skin (Hall and Douglas, 1981). Transmission may be prevented by standard infection control practices, including conscientious hand-washing and ensuring that adults and children with colds avoid any contact with the infant.

CLINICAL PRESENTATION VARIES WITH AGE

The younger the infant, the greater the likelihood that severe lower respiratory tract disease requiring hospitalization will occur. The peak incidence

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TABLE 1.
Risk factors for severe respiratory syncytial virus (RSV) disease

Prematurity
Lung disease (especially chronic lung disease of prematurity)
Congenital heart disease
Other major congenital anomalies
Compromised immune function

of hospitalization for RSV bronchiolitis or pneumonia occurs in children aged 2–5 months old. Hospitalization rates vary according to geographical and socioeconomic factors but may be as high as 3% in the UK. Severity tends to lessen with age and repeated infections.

Upper respiratory tract infection as a single manifestation of the illness is most common in reinfections, and so affects older age groups. Otitis media frequently complicates both the initial and repeated infections in young children. Reinfection from RSV is extremely common at all ages, with the highest rates reported from day-care centres such as nurseries and playgroups.

CURRENT TREATMENT OF RSV INFECTION

Treatments for established RSV disease are limited. Severe RSV disease of the lower respiratory tract often requires considerable supportive care, including administration of humidified oxygen and ventilation (McIntosh and Chanock, 1990). Non-specific treatment may include nebulized beta-agonists, aminophylline and steroids (Walker et al, 1994), although the recent Cochrane meta-analysis showed quite clearly that bronchodilators, aminophylline and steroids are ineffective in the management of RSV (Brion et al, 1999).

The only drug approved for treatment of RSV infection is the antiviral agent ribavirin (American Academy of Pediatrics, 1993). Ribavirin has shown some efficacy in the treatment of RSV pneumonia and bronchiolitis, modifying the course of severe RSV disease in immunocompetent children (Smith et al, 1991). However, ribavirin has had only limited use. The drug requires prolonged aerosol administration. Each treatment takes several hours and is continued over a period of days. Administration of ribavirin using a nebulizer can result in an accumulation of the drug, causing mechanical ventilator dysfunction and associated increased pulmonary pressures. Aerosolized ribavirin has also been associated with a sudden deterioration of respiratory function, although this has not been shown to be statistically significant (Randolph and Wand, 1996).

LACK OF SAFE, EFFECTIVE RSV VACCINES

Despite over 25 years of research, there is still no vaccine available for RSV prevention. A major obstacle to vaccine development is safety. A formalin-inactivated vaccine, although immunogenic, unexpectedly caused a higher and more severe incidence of lower respiratory tract disease caused by RSV in immunized infants than in infants immunized with a similarly prepared trivalent parainfluenza vaccine (Kim et al, 1969; Kapikian et al, 1969). Several candidate vaccines have been abandoned and others are under development (Murphy et al, 1994). If safety issues are resolved, vaccine efficacy must also be improved.

A number of problems remain to be solved. Immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory tract disease occurs between 2 and 5 months of age. The immaturity of the neonatal immune response along with high titres of maternally acquired RSV antibody may reduce vaccine immunogenicity in the neonatal period. Also, primary RSV infection does not protect well against subsequent RSV disease (Henderson et al, 1979).

PASSIVE IMMUNIZATION: RSV HYPERIMMUNE GLOBULIN

Clinical studies have shown that passively administered RSV hyperimmune globulin (RSV IVIG) helps protect at-risk children from severe lower respiratory tract infection by RSV (Groothuis et al, 1993; PREVENT Study Group, 1997). While this was an important advance in preventing RSV infection, RSV IVIG use has a number of limitations. First, large volumes of RSV IVIG must be infused intravenously over several hours to achieve an effective dose. Second, as the product is derived from pooled human plasma, there is a small risk of transmission of bloodborne pathogens and interference with live vaccines such as the measles, mumps and rubella (MMR) vaccine. RSV IVIG is not currently licensed in the UK or Europe.

A MAJOR NEW PROPHYLACTIC DEVELOPMENT: PALIVIZUMAB

Researchers in the field recognized that better protection against RSV could, in theory, be achieved by improving the specific activity of the passively administered immunoglobulin. As a result, an RSV-specific monoclonal antibody (MAb) has been developed, called palivizumab (Synagis, MedImmune, USA). Palivizumab is produced by recombinant biotechnology and, when given by monthly intramuscular injection, provides a high level of protection against RSV in infants and children considered to be at risk of RSV disease.

Palivizumab is the only treatment available in the UK that helps babies combat RSV before they develop major symptoms and potentially fatal complications of infection. Palivizumab is the first MAb licensed for paediatric use and the first for the prevention of an infectious disease.

MODE OF ACTION

MAbs are an advanced technology which work in a similar way to natural antibodies: identifying and binding to the target 'invading' antigens. Two glycoproteins on the surface of RSV (F and G) were

initially identified as potential targets for anti-RSV antibodies (Johnson et al, 1997). The F (fusion) protein promotes fusion of the virus with the host cell which leads to formation of syncytia (giant cells) characteristic of RSV infection. The G (attachment) protein binds to a specific cellular receptor which mediates host cell attachment. While the two strains of RSV (A and B) show significant antigenic variation in the G protein, antibodies to the F protein show a high degree of cross-reactivity. Palivizumab is therefore directed against the F protein of RSV (Johnson et al, 1997).

Since MAbs are derived from mouse myeloma cells, it was necessary to genetically 'humanize' 95% of the palivizumab molecule (all amino acid sequences other than the antigen-binding site itself) to avoid generating human anti-mouse antibodies in vivo.

PALIVIZUMAB: TREATMENT OUTCOME

Preclinical studies

Preclinical studies have shown that palivizumab can neutralize a broad range of RSV isolates. In the cotton rat model of RSV infection, palivizumab was 20–30 times more potent than an equivalent amount of RSV IGIV and, at a dose of 2.5 mg/kg, reduced viral replication by >99% (Johnson et al, 1997).

Clinical studies

The multicentre IMpact-RSV trial (IMpact-RSV Study Group, 1998) — one of the largest randomized, double-blind placebo controlled trials ever carried out in pre-term infants — showed that palivizumab can reduce the incidence of RSV hospitalizations by 55% in infants born at 35 weeks of gestation or less.

The study population (n = 1502) included children under 2 years of age with bronchopulmonary dysplasia (BPD) (requiring a mixture of different ongoing treatments) and children who had been born prematurely (<35 weeks gestation) and who were less than 6 months of age at study entry (IMpact-RSV Study Group, 1998).

The study was conducted at 139 centres in the USA, Canada and the UK. Of the 1502 children recruited, 500 received placebo and 1002 received palivizumab 15 mg/kg. Treatments were given as monthly intramuscular injections for 5 months through the 1996–97 RSV season. Subjects were monitored for 150 days (30 days from last injection), and 93% of infants had all five injections.

The study's primary endpoint was the incidence of RSV-confirmed hospitalization, and this showed a 55% reduction in the patients given palivizumab prophylaxis compared to placebo (P< 0.001). Significant reductions in hospitalizations were also observed when data were analysed by subgroup according to gestational age at birth, weight and the presence or absence of BPD (*Table 2*). However, the reduction in hospitalization was less pronounced in infants with BPD (39%).

Adverse events

The IMpact-RSV study showed that palivizumab was well tolerated with a safety profile similar to placebo. In the palivizumab and placebo groups the proportion of patients reporting adverse events was 11% and 10% respectively. Most adverse events were mild to moderate, and were not felt to be attributable to the drug. Adverse events potentially related to the drug (reported in <0.5% of patients receiving palivizumab) included fever, nervousness, injection site reaction, rash, diarrhoea, upper respiratory infection and aspartate aminotransferase increase. There was no evidence of the development of significant anti-palivizumab antibodies, but further surveillance will monitor this (American Academy of Pediatrics, 1998).

COST DATA ANALYSIS

The NHS price for palivizumab is £424 for a 50 mg vial and £706 for a 100 mg vial. Cost-effectiveness is difficult to quantify, but the

TABLE 2.
Number (%) of hospitalizations analysed by subgroup

	Placebo	Palivizumab	% reduction in hospitalizations (95% confidence interval)	Significance*
All infants (n=1502)	53/500 (10.6%)	48/1002 (4.8%)	55% (38,72)	P<0.001
Infants with BPD (n=762)	34/266 (12.8%)	39/496 (7.9%)	39% (20,58)	P<0.05
Infants without BPD (n=740)	19/234 (8.1%)	9/506 (1.8%)	78% (66,90)	P<0.001
Infants ≤ 32 weeks (n=1111)	11.0%	5.8%	47%	P<0.01
Preterm infants born at 32–35 weeks† (n=373)	9.8%	2.0%	80%	P<0.001
Infants >5kg	10.7%	5.2%	51%	P<0.05
Infants ≤ 5kg	10.5%	4.5%	57%	P=0.001

BPD = Bronchopulmonary dysplasia. *Fishers exact test. †Rates for preterm infants (n=335) born at 32–35 weeks of gestation, but without BPD, were 10% and 1.8% for placebo and palivizumab patients respectively.

immediate and long-term costs associated with RSV infection can be significant. Evidence from the USA suggests that prophylactic use of palivizumab in appropriate infants can reduce costs of health-care interventions (Marchetti et al, 1999). (It should not be forgotten that many infants who are eligible to receive palivizumab may have already spent several weeks in intensive care.) The only UK study addressing this showed that there may be a cost-benefit for RSV prophylaxis in ex-premature babies on home oxygen or those with more severe chronic lung disease who are not on home oxygen (Thomas et al, 1999).

The UK Drug Information Pharmacist Group (UKDIPG, 1999) recently concluded from the results of the IMpact-RSV trial that, although the cost of palivizumab was high, the price may be warranted. This was a result of reduction in other costly health-care interventions, both at the time of acute infection and with respect to long-term implications. The significant reduction in ICU admission rate in the IMpact-RSV trial was particularly noted in the UKDIPG bulletin.

The UKDIPG review also highlighted the fact that, in the IMpact-RSV study, the rate of hospitalization as a result of RSV infection was lower than might be expected in normal, non-study conditions. The UKDIPG concluded that the IMpact-RSV trial may have underestimated the benefits of treatment.

ADMINISTRATION OF PALIVIZUMAB

Palivizumab is supplied as a sterile lyophilized powder for reconstitution with sterile water, and is available in two vial sizes: 50 mg and 100 mg. Reconstituted palivizumab is administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of damage to the sciatic nerve and injection volumes over 1 ml should be given as divided doses.

WHO SHOULD ADMINISTER PALIVIZUMAB INTRAMUSCULARLY?

Hospital-based neonatologists and paediatricians are most likely to assess at-risk babies in the UK and the initial injection of palivizumab is likely to be given in hospital. Primary care-givers may give subsequent injections during the RSV season.

Infants identified as being at risk of RSV may, subject to careful consideration, require palivizumab treatment for the two RSV seasons during which they are deemed at highest risk.

PALIVIZUMAB LICENSED INDICATION

Palivizumab is indicated for the prevention of serious lower respiratory tract disease requiring hospitalization caused by RSV in children who are born at 35 weeks of gestation or less and were less than 6 months of age at the onset of the RSV season, or in children who are less than 2 years of age and had required treatment for BPD within the last 6 months.

WHICH INFANTS SHOULD RECEIVE PALIVIZUMAB?

When considering the use of palivizumab in clinical practice, it is important that local RSV infection patterns are taken into account to guide treatment decisions. In addition to identification of groups at highest risk of RSV, factors for consideration includes local incidence of RSV, local RSV hospitalization rate and average local length of hospital stay. In order to offer protection to all those infants identified as being at risk, systems are required to ensure that those discharged from care outside the RSV season are recalled for treatment before the next season starts. Treatment effect should be subject to ongoing audit.

The following groups should be priority considerations for palivizumab prophylaxis:

Infants <2 years of age with BPD

Infants <2 years of age with BPD who required medical therapy (e.g. supplementary oxygen, steroids, bronchodilators or diuretics) in the 6 months before the RSV season should be a priority for palivizumab prophylaxis. Within this group, babies who remain oxygen-dependent beyond 36 weeks (especially if at home) are at particular risk of serious RSV infection.

Premature babies born at <35 weeks gestation

Premature babies born at <35 weeks gestation who are less than 6 months of age at the onset of the RSV season could be a priority for palivizumab prophylaxis. Within this group most suitable babies will be <32 weeks gestation although there may be occasions when a baby between 32 and 35 weeks is suitable for prophylaxis. Additional risk factors which put the child at greater risk of serious RSV infection may also be considered.

SEASONAL TREATMENT

Following administration of palivizumab, adequate serum levels for effective immunoprophylaxis are achieved within 3 days, and maintained for 30 days. The first dose of palivizumab should be administered before the start of the RSV season, and further doses given thereafter for the duration of the RSV season. There are currently no data on the administration of more than five doses of palivizumab in one season.

For at-risk infants born during the RSV season, palivizumab should be administered before discharge into the community and for the rest of the season. At risk infants who have had an RSV infection and are considered to be at continuing risk of subsequent serious RSV infection may be considered for ongoing palivizumab prophylaxis.

INFORMING PARENTS

It is essential that a full course of treatment is completed if adequate prophylactic protection is to be achieved. To do this successfully depends on parental compliance. Verbal and written information should include the following points:

- A description of RSV and the consequences of infection
- Explanation as to why prophylaxis is necessary
- Details of what treatment entails and how/when administered
- Information on frequency/duration of immunoprophylaxis for their child
- Support items and services available. HM

Conflict of interest: none.

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TABLE 3.
Contraindications and precautions in the use of palivizumab

No data available for > 5 injections per season
No data for infants with congenital heart disease
No anaphylactic reactions observed in trials but medication for severe hypersensitivity reactions post-intramuscular palivizumab injection should be available
For infants with moderate/severe acute febrile illness, physician decides if delay necessary. Mild upper respiratory infection not usually reason to defer palivizumab intramuscularly
Intramuscular route requires caution in thrombocytopaenia/coagulation disorders
Give injection within 3 hours after reconstitution (no preservative in single-use vial of palivizumab)

KEY POINTS

- Respiratory syncytial virus (RSV) is the most important respiratory virus in infancy and early childhood.
- Risk factors for severe RSV disease include prematurity, lung disease, congenital heart disease, other major congenital anomalies and compromised immune function.
- Treatment options for severe RSV disease are limited and there is currently no effective vaccine.
- Palivizumab is a new monoclonal antibody, which has been shown to reduce the incidence of RSV-confirmed hospitalizations by up to 55%.
- Palivizumab should be given prophylactically as 5 monthly intramuscular injections throughout the RSV season.
- Cost–benefit analysis of use should be dictated by local RSV rehospitalization rates and subject to audit.