Review Article

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Palivizumab prophylaxis to prevent respiratory syncytial virus infection in high-risk infants in Hong Kong

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Abstract

Respiratory syncytial virus (RSV) is a seasonal infectious disease, with epidemics occurring during the winter and spring seasons in Hong Kong. RSV infection poses significant morbidity and mortality with significant disease burden in paediatric population, especially in those with risk factors for severe infection. Based on most updated international guidelines, palivizumab prophylaxis for RSV infection should be considered in high risk infants aged 12 months or below, including premature infants born at 34 weeks' gestation or earlier, depending on their gestational age, chronological age, and other associated risk factors; infants with chronic lung disease requiring home oxygen therapy or/and medical treatment, congenital neuromuscular diseases or airway abnormalities, haemodynamically significant congenital heart disease, or severe immunodeficiency upon subspecialist consultation. Among high risk infants, the subgroup of premature infants born before 28 weeks of gestation with chronic lung disease requiring home oxygen therapy and below 12 months of age would be most beneficial with palivizumab prophylaxis and therefore the first group of infants to focus and target on, especially when the financial implication is of concern. It is recommended that high risk infants should receive at least 2 monthly doses (up to 5 doses at maximum) of palivizumab during the RSV season in Hong Kong.

Keywords: Children, Hong Kong, Palivizumab prophylaxis, Respiratory syncytial virus, RSV

Background

Respiratory syncytial virus (RSV), a RNA virus of the family *Paramyxoviridae,* is a seasonal infectious disease, with epidemics occurring during the winter and spring seasons in Hong Kong. RSV can cause both upper and lower respiratory tract infection and is one of the most common infectious diseases of childhood, with up to half of all infants infected by 1 year of age.[1] Some children infected with RSV may develop severe disease requiring hospitalisation owing to life-threatening complications such as bronchiolitis and pneumonia. Children who are at high risk of severe RSV infection include premature infants, children with chronic lung disease (CLD) due to abnormal development of the lungs or cystic fibrosis, children who were born with certain types of congenital heart diseases (CHD) and children who have limited resistance to disease due to immunodeficiency.[2] Many of these high-risk infants may need to be hospitalised and some may require admission to an intensive care unit.[3] Furthermore, RSV bronchiolitis may be result in long-term complications, for instance, recurrent wheeze, reactive airway disease, and impaired lung function. RSV reinfection is also common. RSV causes the hospitalisation of approximately 57500 children younger than 5 years annually and is estimated to account for 1 of every 334 hospitalisations in this age group each year.[4]

Apart from supportive care, such as mechanical ventilator support, intravenous fluids and oxygen, ribavirin is the only treatment available for severe RSV bronchiolitis.[5] This is an antiviral medication licensed for inhaled administration for severe RSV bronchiolitis in infants. However, the evidence supporting that ribavirin produces clinically relevant benefit in RSV bronchiolitis is lacking.[5] On the other hand, the development of a vaccine preventing RSV infection has been unsuccessful so far. It is therefore important to consider alternative preventive strategies to prevent RSV infection.

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Palivizumab is the only licensed medication available for prevention of RSV lower respiratory tract disease in children. It is a humanised murine monoclonal anti-F glycoprotein immunoglobulin with neutralising and fusion inhibitory activity against RSV,[6] and is indicated for preventing severe RSV-associated lower respiratory tract disease in high risk children.[5] Common side effects of palivizumab include injection site reactions, nervousness and fever; while diarrhoea, vomiting, constipation, haemorrhage, rhinitis, respiratory problems, pain, drowsiness, asthenia, hyperkinesia, leucopenia and rash are less commonly seen.[5] The recommended dose of palivizumab is 15 mg/kg body weight, injected intramuscularly during RSV season anticipated in the community. The first dose should be preferably given before the start of the RSV season; while subsequent doses administered monthly throughout the RSV season.

In view of the significant clinical disease burden of RSV infection in children and the availability of the palivizumab immunoprophylaxis, we reviewed from published guidelines the recommendation for the indications on the use of palivizumab to prevent RSV infection in infants.

Efficacy of palivizumab immunoprophylaxis

Palivizumab is the only licensed medication available for prevention of RSV lower respiratory tract disease in children. The efficacy of palivizumab has been evaluated in 2 multicentre, randomised placebo-controlled trials, with the primary end point of reduction in RSV-associated hospitalisation. The RSV-Impact trial evaluated children 24 months of age or younger with chronic lung disease requiring continuing medical therapy (supplemental oxygen, bronchodilator, diuretic or corticosteroid therapy within the previous 6 months) and children born prematurely at gestation of 35 weeks or less who were 6 months of age or younger at the start of the RSV season in the United States, United Kingdom and Canada.[7] The primary outcome of RSV-associated admission were compared between the intervention group receiving 5 doses of palivizumab and the placebo group. Prophylaxis resulted in a 55% overall decrease in the rate of RSV-related hospitalisation (4.8% and 10.6% in palivizumab group versus placebo group, respectively [P=0.001]). RSV-related death was found in 2 patients in the placebo group versus none in the palivizumab group. A second study of infants and children with haemodynamically significant congenital heart disease demonstrated a 45% decrease in the rate of RSV-associated hospitalisation (5.3% and 9.7% in palivizumab group versus placebo group, respectively [P=0.003]).[8] RSV -associated hospitalisation rates were found to be reduced by 39% to 82%, relative to control groups among various high-risk groups of infants.[7,8]

Cost considerations

Palivizumab immunoprophylaxis is an effective but expensive intervention to prevent RSV infection, with the primary benefit of reduction in the rate of RSV associated hospitalisation. No prospective, randomised clinical trial has demonstrated a significant decrease in the rate of RSV associated mortality or post-RSV recurrent wheezing among infants.[9] Optimal cost benefit from immunoprophylaxis is achieved during the peak season of RSV circulation and infection, during which most RSV-associated hospitalisations occur. On the other hand, it has been found that it is not cost-effective for early initiation or continuation of monthly palivizumab immunoprophylaxis during months in which RSV is not circulating widely.[10] Economic analyses have failed to demonstrate overall savings in health care dollars because of the high cost if all infants who are at risk receive prophylaxis.[1, 11-16] Wang et al conducted a cost-effectiveness analysis on the use of palivizumab in various high-risk subgroups of children, based on the probabilistic decision-analytical model[1,17] The analysis of what led to the discrepant ICERs showed that the assumed mortality rate for RSV infection was the most important driver. The rates of hospital and paediatric intensive care unit (PICU) admissions and sequelae of RSV also had measurable effects. Prophylaxis with palivizumab did not represent good value based on the UK ICER threshold of £30,000/QALY (UK conventional willingness-to-pay threshold) when used unselectively in pre-term infants and children without CLD/CHD or children with CLD or CHD. However, subgroup analysis showed that prophylaxis with palivizumab may be cost-effective for some subgroups. The cost-effective subgroups for children who had no CLD/CHD have to contain at least two other risk factors apart from gestational age and age, including male gender, siblings at school, multiple births, exposure to passive smoke, overcrowding in the family home, parental education, and age <6 weeks at the start of the RSV season. On the other hand, the cost-effective subgroups for children who had CLD/CHD did not necessarily have any other risk factors apart from gestational age and age.

In Hong Kong, based on the data extracted from the Computerized Management System (CMS) in all public hospitals under the Hospital Authority, there were 156

cases of extreme prematurity with low birth weight <1.5 kilograms; 91 of whom also had bronchopulmonary dysplasia. Assuming a cost of HKD7,500 per dose of palivizumab (1000 mg), the cost for the 91 high risk infants with extreme prematurity, low birth weight <1.5 kilograms and BPD would be HKD7,500x5x91 =HKD3,412,500. Due to the inherent limitation of the completeness of the data extracted from the CMS systems, these figures would have likely underestimated the number of high risk cases for severe RSV infection and hence the consequent cost for the palivizumab prophylaxis.

Initiation and termination of Immuno-prophylaxis

Peak RSV activity typically occurs between November and March in the temperate climates such as in North America, whereas RSV seasonality patterns may be different and sometimes occur throughout the year in tropical or equatorial countries. It is difficult to precisely predict the time of onset, peak and end of the season and the severity of the season. Significant variation have been observed in the timing of community outbreaks of RSV disease from year to year even within the same communities, and the median duration of the RSV season has been reported to be around 17 weeks.[18,19] Recent studies have shown that palivizumab trough serum concentrations greater than 30 days after the fifth dose will be well above the protective concentration for most infants, therefore providing more than 20 weeks of protective serum antibody concentration. A total of 5 monthly doses for high risk infants and young children will provide an optimal balance of benefit and cost. High risk children qualified for palivizumab prophylaxis should receive palivizumab administration during the 5 months after the onset of RSV season (maximum of 5 doses), providing coverage during the peak of the season when prophylaxis is most effective. An initiation of immunoprophylaxis in November with 5 monthly doses in total will provide protection into April. If palivizumab prophylaxis is initiated after start of the RSV season, children will not require all 5 doses.

Eligibility criteria for prophylaxis of infants and young children at high risk

Based on the latest American Academy of Pediatrics (AAP) guideline,[20] palivizumab prophylaxis should be considered during RSV season for high risk infants and children including:

(i) Infants born prematurely

Infants born at 28 weeks' gestation or earlier may benefit from prophylaxis during the RSV season during the first 12 months of life, while infants born at 29 to 32 weeks' gestation (31 weeks 6 days) may benefit most from prophylaxis up to 6 months of age. However, once an infant qualifies for initiation of prophylaxis at the start of the RSV season, administration should continue throughout the season and not stop when the infant reaches either 6 or 12 months of age. A maximum of 5 monthly doses are recommended.

For infants born at 32 to less than 35 weeks' gestation, prophylaxis may be considered for infants in this category born less than 3 months before the onset or during the RSV season with at least 1 of the 2 risk factors: (1) the infant attends child care; or (2) one or more siblings or other children younger than 5 years live permanently in the same household. They should receive prophylaxis only until 3 months of age with a maximum of 3 monthly doses. Immunoprophylaxis is not recommended after 90 days of age.

(ii) Infants and children with chronic lung disease

Children aged 24 months or younger with CLD requiring medical therapy (supplemental oxygen, bronchodilator, diuretic or chronic corticosteroid therapy) for CLD within 6 months before the start of the RSV season may benefit from palivizumab prophylaxis. They should receive a maximum of 5 doses of palivizumab.

(iii) Infants with congenital abnormalities of the airway or neuromuscular disease

Infants with either significant congenital abnormalities of the airway or a neuromuscular condition compromising respiratory tract secretions handling may benefit from palivizumab prophylaxis. They should receive a maximum of 5 doses of palivizumab during the first year of life.

(iv) Infants and children with congenital heart disease

Children aged 24 months or younger with haemodynamically significant cyanotic or acyanotic CHD may benefit from palivizumab prophylaxis,[8] especially for: (1) infants who are receiving medication to control congestive heart failure; (2) infants with moderate-to-severe pulmonary hypertension; and (3) infants with cyanotic heart disease.

(v) Immunocompromised children

Children with severe immunodeficiency may benefit from prophylaxis.

Conclusion

RSV infection poses significant morbidity and mortality in paediatric population, especially in those with risk factors for severe infection. Palivizumab prophylaxis should be considered in premature infants born at 34 weeks' gestation or earlier, depending on their gestational age, chronological age, and other associated risk factors. Infants aged 12 months or below who suffer from with chronic lung disease requiring home oxygen therapy or/and medical treatment, congenital neuromuscular diseases or airway abnormalities, haemodynamically significant congenital heart disease, or severe immunodeficiency should also warrant consideration for palivizumab prophylaxis upon subspecialist consultation. Among high risk infants, the subgroup of premature infants born before 28 weeks of gestation with chronic lung disease requiring home oxygen therapy and below 12 months of age would be most beneficial with palivizumab prophylaxis and therefore the first group of infants to focus and target on, especially when the financial implication is of concern. It is recommended that high risk infants should receive at least 2 monthly doses (up to 5 doses at maximum) of palivizumab during the RSV season in Hong Kong.

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