Palivizumab Use in Preterm Neonates

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Abstract
Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis in infants. Palivizumab is an immunoprophylactic agent for RSV prevention in preterm infants and those with neonatal chronic lung disease. This study examines its use across neonatal units in Ireland. A questionnaire was administered to one Consultant Neonatologist or Paediatrician in each of the 20 maternity centres in Ireland about their guidelines for Palivizumab administration. There is variation in administration of Palivizumab with little consistency found between protocols. Ten centres hope in house protocols, 3 centres availed of a home administration programme funded by Abbott Pharmaceuticals and 2 centres used the American Academy of Paediatrics (AAP) guidelines. 2 centres prefer the UK Joint Committee on Vaccination and Immunisation (JCVI) guidelines and 3 centres do not have a set protocol.

Introduction
Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection in infants. The clinical efficacy of bronchiolitis was, first described at least 100 years ago. Morris et al initially isolated RSV from chimpanzees in 1956. Charnock et al virus with bronchiolitis in infants. Children with the highest risk of serious complications from RSV infection include those with prematurity birth, neonatal chronic lung disease (CLD), and congenital heart disease. No effective vaccine against RSV has been developed. Current prevention focuses on infection control and passive immunity through administration of Palivizumab. Palivizumab is a humanised monoclonal antibody. It was approved as immunoprophylaxis for RSV infection in infants with prematurity and/or bronchopulmonary dysplasia / neonatal chronic lung disease by the US Federal Drug Administration in June 1998 following the IMPACT trial. A further analysis of the IMPACT trial demonstrated a 55% reduction in hospitalisation rates for bronchiolitis in premature infants receiving Palivizumab compared to a placebo group. A further trial by Belile et al. showed a 34% reduction in Palivizumab in young children with haemodynamically significant congenital heart disease. Several other studies have confirmed a similar reduction in hospitalisation rates with Palivizumab use.

Palivizumab costs 1105 per 150mg vial. It is administered by intramuscular injection at a dosage of 15mg/kg monthly through the winter RSV season with an average cost of 3000 to 4000 per baby per season. Analysis of the IMPACT trial outcomes reveals that the number of infants with chronic lung disease by the US Federal Drug Administration in June 1998 following the IMpact trial. Antibody to RSV is detected in infants through administration of Palivizumab. Palivizumab is used to prevent one hospital admission between 17 and 20, at an approximate cost of €55000. Several economic analyses of RSV infection in infants with prematurity, and/or bronchopulmonary dysplasia / neonatal chronic lung disease in the United States by the AAP and the JCVI. A study by Cahill et al. at the bronchiolitis management in 2002 reported Palivizumab use by 49% (3103) of paediatricians, the main indications being prematurity and CLD. This study examines the use of Palivizumab in the Republic of Ireland.

Methods
A questionnaire regarding guidelines in place for administration of Palivizumab was distributed via post and email to one Consultant Neonatologist/Paediatrician in twenty maternity centres in the Republic of Ireland. The questionnaire was divided into four sections and was made up of 21 questions.

Results
Eighteen of 20 questionnaires were returned - a response rate of 90%.

Palivizumab Administration
The first dose of Palivizumab is administered in hospital by all centres prior to discharge. There is variation regarding subsequent doses. Five centres administer all subsequent doses in hospital setting or clinic, six centres avail of a home administration programme funded by Abbott Pharmaceuticals and seven centres avail of GP services for the remaining doses. Timing of the administration of the first dose according to the RSV season varies throughout October as shown in Table 1. The second dose of Palivizumab is administered after 4 weeks by sixteen centres while two centres administer the second dose after 3 weeks.

Figure 1: Location for administration of Palivizumab post-discharge from hospital

Recipients of Palivizumab
The AAP recommendations for Palivizumab administration are in use in three centres and two follow the UK JCVI guideline. Individual in house guidelines have been developed by ten centres. Three centres do not follow any specific guidelines in deciding when to prescribe Palivizumab (see Figure 2). In the house protocols can be reviewed according to three criteria, the age of the patient, the presence of neonatal CLD and the presence of congenital heart disease.

There is a wide variety of gestational age (GA) at birth categories deemed suitable for RSV prophylaxis across neonatal centres. The most conservative approach in one centre limits Palivizumab immunoprophylaxis to those infants delivered at < 28 weeks GA. The most liberal approach is in another centre prescribing for all infants delivered below 34 weeks GA. For those centres using > 28 weeks gestation as a threshold for immunoprophylaxis, one centre routinely administers to all infants below 32 weeks GA, another restricts to those < 32 weeks GA who have received medical therapy within 6 months of the start of the RSV season and another to those infants < 32 weeks GA, who have received medical therapy within 6 months of the start of the RSV season.

Discussion
There is variation in eligibility of children with neonatal CLD deemed suitable for immunoprophylaxis across the country. One centre administers Palivizumab to all patients with neonatal CLD, another to all children with CLD less than 2 years of age, another to children with CLD less than 2 years of age who have received medical therapy within 6 months of the start of the RSV season infants and another to infants under 2 years of age living within 6 months of RSV season. Only those under 35 weeks GA at birth and those in intensive care are prescribed Palivizumab in a different neonatal centre. A weight based approach is used in one centre, only prescribing for those with CLD weighing less than 2kg with respect to the definition of neonatal CLD. Half of one centre define CLD less than 2 years of age and in their first “RSV season”. Another centre prescribes Palivizumab for those infants between 29 to 32 weeks GA and less than 6 months at the start of the RSV season. Two centres take birth weight into account in their decision regarding RSV immunoprophylaxis. One prescribes Palivizumab for those infants with a birth weight less than 1.25 kg and under 6 months at the start of the RSV season. The other centre prescribes for those infants with a birth weight less than 1 kg and under 6 months at the start of the RSV season.

Figure 2: Palivizumab guidelines in use in Maternity centres in Ireland

There is variation in eligibility of children with congenital heart disease. No centre restricts to those infants < 1 year of age who have received medical therapy within 6 months of RSV season. Only those < 35 weeks GA at birth and those in intensive care are prescribed Palivizumab in a different neonatal centre. A weight based approach is used in one centre, only prescribing for those with CLD weighing less than 2kg with respect to the definition of neonatal CLD. Half of one centre define CLD less than 2 years of age and in their first “RSV season”. Another centre prescribes Palivizumab for those infants between 29 to 32 weeks GA and less than 6 months at the start of the RSV season. Two centres take birth weight into account in their decision regarding RSV immunoprophylaxis. One prescribes Palivizumab for those infants with a birth weight less than 1.25 kg and under 6 months at the start of the RSV season. The other centre prescribes for those infants with a birth weight less than 1 kg and under 6 months at the start of the RSV season.

Concerns have been expressed that the administration of the second dose after two months may not guarantee protective serum concentrations over the first month especially in the preterm infant. Accordingly, two centres have amended their dosing schedules and administer the second dose after 3 weeks. This is an area which needs further study. No general consensus exists on the definition of neonatal CLD. Given its role in determining the recipients of Palivizumab, this definition should be clarified nationally. The huge variation in acceptable oxygen saturation levels also lends itself to discrepancies in the definition of neonatal CLD. This is also an area that would benefit from standardisation across neonatal units. Prevention remains the cornerstone of bronchiolitis management, infection control measures are a cost effective and often neglected tool. Only three centres have compiled a written RSV infection control policy. The majority of centres acknowledge the role of parent education. Currently published guidelines for parents emphasising hand washing, avoiding crowded places and passive smoking are provided by Abbott Pharmaceuticals. General parent education leaflets from the Health Service Executive could avoid any

Perceived impact on cost effectiveness of Palivizumab
Only 4 of 18 respondents believe that Palivizumab has reduced the number of hospital admissions from RSV yet 11 respondents feel Palivizumab is a cost effective strategy.
The marked variations across the country with respect to selection of infants for RSV immunoprophylaxis, with opinions differing regarding age and weight criteria lends itself to both suboptimal clinical care and potential for suboptimal use of limited pharmacy budgets. Approximately 20% of Consultant respondents regard Palivizumab as having an impact on hospitalisation rates yet 61% believe it is a cost effective agent. A study carried out by the Department of Public Health and Epidemiology in Birmingham 2 concluded that prescription of Palivizumab according to its licensed indications is not a cost effective strategy for preterm infants and children with congenital heart disease. No such cost analysis has been performed in Ireland. With over 650 infants < 32 weeks born in Ireland in 2006 and indeed much larger numbers of infants < 34 weeks, with the birth rate continuing to rise, a conservative estimate of the budgetary implication for RSV immunoprophylaxis in Ireland is at least 1.5 to 2 million euros annually! This is particularly important given current pharmacoeconomic constraints. There is a need to implement a national protocol on RSV immunoprophylaxis. All Consultant Neonatologists and Paediatricians surveyed would welcome its introduction. We recommend commissioning of such a protocol to standardise and optimise this aspect of care for newborns in Ireland.

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