

PALIVIZUMAB (Commentary)**Cost effective prophylactic use**

Respiratory syncytial virus (RSV) is responsible for significant respiratory morbidity in infancy (La Rosa *et al.*, 2004). Those with chronic respiratory or heart conditions are at particular risk, because even though they are no more likely to acquire the disease, they are significantly more likely to be re-hospitalised if infected. About 10–15% of infants with chronic lung disease may be re-hospitalised with RSV, but less than 5–10% of preterm infants (<35 weeks) without lung disease end up back in hospital (Impact Study Group, 1998).

This group showed that the monoclonal antibody, palivizumab, is effective at reducing the risk of re-hospitalisation, although it is only half as effective in those with chronic lung disease as in those without (a 39% v. 78% reduction). Hospitalisation is easily defined, but is not a precise measure of illness severity and it will, in part, reflect the way health care is organised (Behrendt *et al.*, 1998). There is no evidence that palivizumab affects length of hospital stay: only 0.7% of infants in the original controlled trials were in hospital for more than 14 days. Although admission to an intensive care unit was less in those receiving palivizumab, there was no reduction in the need for mechanical ventilation. Neither the original IMPact study, nor the study in those with heart disease (Feltes *et al.*, 2003) was of sufficient power to show whether prophylaxis significantly reduced the number of babies dying. The product is expensive (a 50 mg vial costs £360), but costs can be reduced a little by using the larger 100 mg vial and arranging to treat more than one child at the same time (Coffman *et al.*, 2001; Wills *et al.*, 2006; Marshall *et al.*, 2008).

The American Academy of Pediatrics (AAP) has long recommended the product's quite liberal use. They still recommend the use of palivizumab for all babies of less than 29 weeks gestation if the winter epidemic is due to start before they are 12 months old, and for all babies of 30–31 weeks gestation if they are less than 6 months old. Those with congenital heart disease or chronic lung disease (BPD) are judged to merit prophylaxis until they are 24 months old. However, the AAP's most recently updated guideline (based on the epidemiological studies of Law *et al.* 2004 and Figueras-Aloy *et al.*, 2008) now only recommends its administration to babies of 32–34 weeks gestation inclusive if they are attending a child care nursery or have at least one sibling less than 5 years old. Even then they now say that these babies only merit prophylaxis if they are less than 90 days old when the usual winter epidemic seems likely to start, and only need to be given 3 doses at most (American Academy of Pediatrics, 2009).

The National Institute of Health Research in the UK recently looked at the cost-effectiveness of offering prophylaxis in line with the advice coming from the company marketing the product (Wang *et al.*, 2008). This Health Technology Assessment (HTA) report had concluded that there was relatively little good data on which to base a reliable cost-benefit analysis (see below), but despite this the Joint Committee on Vaccines and Immunisation (JCVI) in the UK has since come out in support of quite widespread use.

Babies with chronic lung disease: The biggest problem is that the various advisory groups have defined what constitutes “chronic lung disease” very variably. The AAP would offer prophylaxis to all infants less than 24 months old who were receiving “medical therapy (supplemental oxygen, bronchodilator, diuretic or chronic corticosteroid therapy)” 6 months before the start of the RV season. The JCVI would focus treatment on babies who had been oxygen dependent for at least 28 days after birth and who were either

- less than 9 month old at the start of the RSV season and born before 27 weeks gestation or
- less than 6 months old at the start of the RSV season and born before 31 weeks gestation or
- less than 3 months old at the start of the RSV season and born before 36 weeks gestation.

However, the problem with the JCVI approach is that has defined “chronic lung disease” as it relates to the ex-preterm baby in a way that was largely abandoned by neonatologists ten years ago in favour of a definition that looks to see, not at how much oxygen the baby had received in the period immediately after birth, but at whether there was still any objective need for oxygen at 36 weeks gestation at a time when the child would otherwise be nearly ready for discharge home (Davis *et al.*, 2002).

The pragmatic approach currently adopted by the British National Formulary (BNFc) accords more closely with what most neonatologists and respiratory paediatricians in the UK would support – which is that prophylaxis “should be considered for children under 2 years who are using oxygen at home or have been on prolonged oxygen treatment”.

Other preterm babies: The AAP continues to recommend prophylaxis for all babies born before 32 weeks gestation who are less than 12 months old at the start of the RSV season even if they do not have any evidence of “chronic lung disease” (however defined), but the cost-effectiveness of such a policy remains very unclear. The JCVI were not prepared to back such widespread use.

Babies with congenital heart disease: Prophylaxis in those with congenital heart disease certainly almost halved the number of babies requiring hospital admission (5.2 v. 9.7%) in the one, commercially funded, trial involving 1287 children reported by Feltes *et al.*. However only 6 died of RSV, and the

decrease in the number requiring mechanical ventilation (1.3 v. 2.2%) was not statistically significant. Similar benefit was seen in a recent national survey of use in Japan (Saji *et al.*, 2008). Guidelines have suggested that all babies less than a year old with increased pulmonary blood flow, pulmonary venous congestion, or pulmonary hypertension, merit seasonal prophylaxis, as do babies with a cardiomyopathy severe enough to merit treatment. However there is, as yet, no general consensus on any of these issues (Duppenhaler *et al.*, 2001; Yount *et al.*, 2004).

As just one example of this, the current AAP guideline recommends prophylaxis for all babies with cyanotic heart disease until they are 24 months old, whereas the latest JCVI guideline is that it should only be offered to *acyanotic* babies with “haemodynamically significant congenital heart disease” until they are 6 months old. The JCVI guideline does not define “significant”, but the AAP guideline limits it to those receiving treatment to control congestive heart failure. Since it currently costs over £2,000 to provide such seasonal protection for just one baby, and only 2% of the babies in the recent trial ever became ill enough to be offered respiratory support, many cardiologists are at present only providing prophylaxis for their most vulnerable patients. Babies likely to need surgery in the near future may be one such group. Cardiopulmonary bypass procedures cause the palivizumab level to fall by nearly 60%, so such children probably merit an additional postoperative booster dose.

Babies with severe combined immunodeficiency: There is no good evidence on which to base management, but the JCVI has not unreasonably concluded that the 20–30 babies born with this problem in the UK each year should receive prophylaxis until such time as their immune mechanisms are restored.

Cystic fibrosis: The AAP recently concluded that “Limited studies suggest that some patients with cystic fibrosis may be at increased risk of RSV infection. Whether RSV infection exacerbates the chronic lung disease of cystic fibrosis is not known.”

How long to continue prophylaxis: As the AAP guidelines stress there is no point in continuing to provide prophylaxis once the winter epidemic is over, so the recommendation is that children should have a *maximum* of five doses at monthly intervals, and less if prophylaxis is only started late in the year. Clinical trials show that trough serum palivizumab concentrations 30 days after the last of a series of doses are still well above the concentration needed to provide most babies with protection.

The economic case for prophylaxis: The results of the many economic analyses of palivizumab that have been performed are highly variable. This reflects not only the quality of the data, but highlights the discretionary nature of model building and the potential for introducing bias. The only cost-effectiveness analyses to identify cost savings as yet had some form of industry sponsorship or affiliation (c.f. Kamal-Bahl *et al.*, 2002). Clinicians vary in the criteria they use to justify hospital admission. Views also differ as to how long admission remains justified once it is fairly clear that the child’s condition has stabilised and the child is not too breathless to take some fluid by mouth. Others have explored discharge in selected families even when the child is still considered to need oxygen (Tie *et al.*, 2009). Strategies that reduce the need for (and the length of) inpatient care all serve to make prophylaxis with palivizumab less cost-effective. Unless barrier nursing precautions are observed when caring for any child with RSV in hospital, admission puts other children in the ward at significant risk.

Several studies have extrapolated the non-significant differences in mortality, or used observational data, to claim a major economic benefit for palivizumab use [by identifying ‘Life Years Gained’, (Nuijten *et al.*, 2007)] although neither of the controlled trials ever conducted a contemporaneous economic analysis. The relationship between RSV infection and subsequent asthma is clear (Broughton *et al.*, 2005; 2006), but causality has yet to be shown. The IMPact study was large enough for long-term health benefit to be demonstrable if it was there, but the manufacturers have not, to date, shown any indication that they plan to support such an assessment. Indeed, many reviews have now questioned whether prophylaxis is really as justified for most babies of less than 32 weeks gestation as most of the early guidelines had originally suggested (Embleton *et al.*, 2005).

Some clinicians currently share the view expressed by the editors of the recent book on Evidence-based Pediatric Infectious Diseases (Isaacs *et al.*, 2007) who said in their review of this topic that they “do not feel that the evidence supports the use of palivizumab unless cost is not a consideration”. Prophylaxis is, however, relatively easy to justify for the small number of preterm babies who are still oxygen dependent when the seasonal epidemic first appears, since here any serious infection may be life-threatening. Even here, however, protecting the baby from contact with any family member who may be harbouring the virus can probably do as much as palivizumab to reduce the risk of infection, and such precautionary measures (as outlined in the *Formulary* monograph on the influenza vaccine) cost almost nothing.

Comment: The continued substantial and very widespread uncertainty as to when prophylaxis with palivizumab is of genuine value is an indictment of the limited, commercially-driven, way in which its clinical value was evaluated when it first came onto the market 12 years ago. A new and potentially more potent product, motavizumab (Abarca *et al.*, 2009), may well be licensed for use relatively soon now. It is to be hoped that its introduction will be more carefully and objectively evaluated.

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