

course, promoting the second. Deterrence and punishment are not rational options, and politicians who seek to inflame public feeling in these distressing cases are being forced to recognise this.

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Preventing respiratory syncytial virus bronchiolitis

Except in very high risk infants there is no cost effective prophylactic agent

Winter in the United Kingdom—wet, cold, miserable, and, yet again, the season for respiratory syncytial virus (RSV) bronchiolitis. About 3% of each year's birth cohort are admitted with bronchiolitis every winter in Europe, Australasia, and North America (20 000 infants in the UK, of whom 600 need ventilation¹). Traditionally certain groups of infants are considered to be at high risk of developing more severe RSV bronchiolitis. These high risk groups include infants born prematurely (insufficient transfer of maternal RSV IgG) and those with chronic lung disease of prematurity, other underlying cardiorespiratory disease, or immunodeficiency. However the great majority of infants admitted are previously normal babies. The treatment of RSV bronchiolitis has had a chequered history, and, despite initial enthusiasm, it is now widely accepted that bronchodilators, steroids, and ribavirin have no overall significant benefit.² This therapeutic nihilism makes paediatricians uneasy, and if we have no treatment, then surely prevention must be the answer.

Pooled hyperimmune RSV intravenous immunoglobulin (RSV IVIG, Respigam) was licensed by the Food and Drug Administration in 1996 after the PREVENT study.³ Monthly prophylaxis over the RSV season with RSV IVIG led to an overall reduction of 41% in admissions for RSV bronchiolitis in high risk groups. However, RSV IVIG required regular intravenous infusions of a high volume and protein load from pooled donors, with the risk of transmission of blood born pathogens. A Cochrane review of RSV IVIG is available.⁴

Palivizumab (Synagis) is a recombinant humanised mouse monoclonal antibody to the RSV F protein. It is a neutralising antibody that prevents RSV fusing with the cell membrane and can be given intramuscularly. The IMPact study was a multicentre randomised double blind placebo controlled trial of palivizumab. Infants born premature (< 36 weeks' gestation) or with chronic lung disease of prematurity were randomised to receive either five monthly injections of placebo (n = 500) or palivizumab (n = 1002) over the RSV season. The primary end point was admission with RSV disease. The study showed a relative reduction in RSV related admissions of 55% (10.6% placebo, 4.8% palivizumab, p = 0.0004).⁵ Adverse events were the same in

both study arms. The study was not powered to detect reductions in mortality. There was no significant reduction in prolonged admission (> 14 days) or the number of days spent on a ventilator between the two groups.

Palivizumab is safe and certainly works, so should we use it? It has been licensed in the US, and the American Academy of Pediatrics suggests that palivizumab should be *considered* for infants either born prematurely or treated for chronic lung disease within six months of the RSV season.⁶ Unfortunately, palivizumab is also very expensive.

The IMPact trial was not designed as a pharmacoeconomic study. When introducing a new preventive therapy clinicians need to consider not only the existing morbidity and mortality of the disease but also the efficacy and cost effectiveness of the prophylactic agent. We have recently summarised the incidence of readmission due to RSV disease noted in observational studies from North America and the UK.⁷ Broadly similar readmission rates for RSV bronchiolitis were noted, of about 6-8 % for infants born < 32 weeks' gestation and 12-17% for infants with chronic lung disease. Even in these high risk groups, mortality from RSV bronchiolitis is now extremely low, 0.13% in the IMPact study.

Several cost effectiveness studies have been performed. In the IMPact study the absolute risk reduction for the whole study group was 5.8%, giving a number needed to treat—that is, to prevent one hospital admission—of 17.2, with an expenditure of £25 500 (95% confidence interval £16 500 to £49 500) to prevent one hospital admission.⁸ This type of analysis has been criticised, mainly because the admission rate among the placebo treated controls in the IMPact study was lower than previously noted. However, the broad agreement of the recent observational studies suggests that the number needed to treat calculations are reasonable, and possibly an underestimate. Other cost effectiveness studies have given similar results.⁹⁻¹²

Although these analyses do not take into consideration the increased incidence in wheezing during childhood after RSV bronchiolitis, it is unlikely that these extra costs will be significant. The only group of infants in whom the cost of admission was similar to the cost of palivizumab was those with severe chronic

lung disease.¹¹ It is in this very small group of infants at the highest risk where more data on the morbidity and mortality of RSV bronchiolitis, and the role of palivizumab, are needed. Either a prospective study or detailed postmarketing surveillance of infants who do and do not receive prophylaxis is required.

In the meantime palivizumab has no role to play in the vast majority of infants admitted with RSV bronchiolitis. Prevention may in future be achieved with the development of a safe, effective vaccine. Bronchiolitis represents an abnormal host immune response to RSV infection.¹³ Further characterisation of this response and its genetic basis could lead to identification and targeting of infants most at risk of developing severe RSV bronchiolitis.

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Severe osteogenesis imperfecta: new therapeutic options?

Aminobisphosphonates offer promise, while bone marrow transplants remain experimental

Research in osteogenesis imperfecta (the brittle bone syndrome) has contributed exciting new chapters in bone biology, but little advance in treatment (International Conference on Osteogenesis Imperfecta, Montreal 1999).¹ Specialised rehabilitation and timely appropriate surgery remain the therapeutic cornerstones. Calcitonin (to reduce bone resorption) and sodium fluoride (to increase formation) are ineffective. Two new approaches using the aminobisphosphonates and stromal cell transplantation now deserve our critical attention.^{2,3}

In osteogenesis imperfecta causal mutations in the genes for type I collagen explain the skeletal fragility, but the clinical range is wide and the relation between genotype and phenotype complex. Thus in type I osteogenesis imperfecta a non-functional allele for type I collagen halves collagen synthesis and causes mild bone disease. In contrast, in severe osteogenesis imperfecta—types II, III, and IV—mutations replace the essential helical glycine with larger amino acids; this wrecks collagen helix formation, produces unstable molecules, and dramatically reduces the amount of normal collagen. These changes may be lethal, as in type II osteogenesis imperfecta. Type III osteogenesis imperfecta is the most severe form in which the child survives. The deformity may be so severe, the fractures so numerous, and the disability so profound, however, that almost any form of treatment deserves consideration.

The young skeleton, abnormal or not, is constantly changing, being formed and resorbed, modelled and remodelled. In theory blocking osteoclastic resorption or encouraging osteoblastic bone formation could produce useful increases in bone tissue even when—as in osteogenesis imperfecta—the primary event is defective osteogenesis.

The first therapeutic option accepts the mutant skeleton as it is but drastically blocks the activity of the osteoclast. Progressive side chain modification has now greatly increased the antiresorptive activity of the bisphosphonates (pyrophosphate analogues with a basic P-C-P structure).⁴ All are poorly absorbed and some are given parenterally. The aminobisphosphonate pamidronate (3-amino-1-hydroxypropylidene-1,1-bisphosphonate, APD), used in Paget's disease and tumour hypercalcaemia, is one example. The main published study describes the effects of intravenous pamidronate at a daily dose of 1.5-3.0 mg/kg body weight for three days every four to six months for 1-5 years in 30 children with severe osteogenesis imperfecta.² All took 800-1000 mg of calcium and not less than 400 IU of vitamin D daily. Biochemically assessed bone turnover rate fell; age corrected bone mineral density (Z score) and metacarpal cortical thickness both increased, and the number of radiologically confirmed fractures also fell. Growth, which was unaffected, could be estimated by the distance between