dimercaptosuccinic acid (DMSA) after the age of 4 years (1/189 children) was 0.5% (95% confidence interval (CI) 0 to 2.9) for both sexes combined. It is not clear, however, if their results represent antenatal renal dilatation diagnosed at 20 or 28 weeks gestation; as more than half of such findings subside between 20 and 28 weeks, the resulting calculation of prevalence of abnormalities could vary by a factor of at least 2 if the cases they reported were diagnosed at 20 weeks gestation.

Their results contrast with our findings, here described. Over a five year period, out of 355 children with antenatal pelvic dilatation at 20 weeks gestation, 137 children were found to have an antenatal renal pelvic diameter of 5–15 mm at 28 weeks gestation and were investigated postnatally while receiving antibiotic prophylaxis. Those with a defined multicystic kidney, pelvic dilatation over 15 mm, suggestive of posterior urethral valve, or with multiple congenital anomalies were not included in the study. None of the 137 children developed a urinary tract infection throughout the study period. Postnatal investigations within a few months of birth, including ultrasonographic evidence of an increase in renal pelvic diameter in 50 infants, confirmed the presence of obstructive uropathy in four children, with a prevalence of 2.9% (95% CI 0.7 to 7.4), including one child with posterior urethral valve and three with unilateral pelvi-ureteral junction obstruction. A high prevalence of obstructive uropathies has already been well documented in infants with pelvic dilatation >8 mm at 28 weeks,² well below the 15 mm upper limit suggested by Plant *et al.*¹ Renal scarring by DMSA (in the first few months of life) was found in two children with a prevalence of 1.4% (95% CI 0.1 to 5.3), and vesicoureteric reflux was diagnosed in five children with a prevalence of 3.6% (95% CI 1.1 to 8.5). No DMSA scans were carried out after the 4 years of age in our study. Without dwelling on the controversy surrounding the clinical significance (or lack of it) of vesicoureteric reflux, the relative risk of renal scarring in our series was therefore 2.75 times that in the report of Plant *et al.* (if their infants were scanned at 28 weeks gestation), but this was not statistically significant (95% CI 0.3 to 10.1; $p = 0.2$). However, and more importantly, without postnatal imaging of these children with moderate antenatal renal pelvic dilatation, four cases of obstructive uropathy (2.9% of these children) would not have been detected early nor benefited from antibiotic prophylaxis and prompt evaluation by a paediatric urologist. They may still have probably been diagnosed later, with the occurrence of obstructive symptoms or urinary tract infections, but after some possible damage to the affected kidney(s), which would have been, to some extent, preventable if the diagnosis had been made earlier. If, as in the report of Plant *et al.*, postnatal imaging had not been carried out in this cohort and the DMSA scans were carried out at 4 years of age, a higher number of infants with scarred kidneys on DMSA would be expected, in addition to the two we reported, because of potential renal damage resulting from diagnostic and therapeutic delays in the four infants with obstructive uropathies who would not have been identified in the newborn period.

Although we strongly agree that most children with moderate antenatal pelvic dilatation would not benefit from antibiotic

prophylaxis and postnatal imaging, and with the absence of other published evidence to support such a change in practice at this stage, we cannot yet agree with the recommendations of Plant *et al.* of not offering postnatal evaluation unless the antenatal pelvic dilatation is more than 15 mm, as this would miss about 3% who have an underlying obstructive uropathy. Although we recognise that invasive imaging studies with exposure to radiation, such as cystogram, DMSA, or MAG scintigraphy, may not be required in the majority, we strongly feel that a postnatal ultrasound still remains indicated in all these children, with antibiotic prophylaxis and further imaging reserved for those with persistent or worsening ultrasound findings until a significant uropathy has been ruled out. Such a strategy based on postnatal ultrasound for antenatal pelvis dilatation up to 10 mm (below the limit of 15 mm suggested by Plant *et al.*) is recommended to exclude an underlying uropathy.³

Until better criteria and/or diagnostic tools have been developed, we cannot at this stage endorse the recommendation of Plant *et al.* of avoiding any postnatal investigation in many such infants (at risk) because only a few (with significant problems) may benefit.

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Association of hydrogen peroxide in exhaled breath condensates from infants with respiratory distress syndrome with the development of chronic lung disease

We read with interest the review on exhaled breath measures of inflammation by Harrison *et al.*¹ We agree that there is a need to develop and standardise methods for the collection of exhaled breath markers as part of clinical monitoring of neonates on respiratory support. A major limitation we encountered with collecting exhaled breath condensates using a method we published earlier was that hydrogen peroxide concentrations were not significantly different between condensates from babies and “dummy” controls.² This could be a result of signal dilution of small expired gas volumes from infants by relatively large bias flow, mixture of gases, and airway humidification in the ventilator/continuous positive airway pressure circuits.²

Nevertheless, their article prompted us to analyse whether there were any trends in exhaled hydrogen peroxide concentrations from 44 ventilated infants with respiratory

distress syndrome (median gestation and birth weight of 28 weeks and 1025 g respectively) in relation to the development of chronic lung disease (CLD; oxygen requirement at 36 weeks postmenstrual age). The median hydrogen peroxide concentration in infants who developed CLD was 0.30 μM (interquartile range 0.21–0.46) compared with 0.21 μM (interquartile range 0.16–0.37) in those with resolved respiratory distress syndrome ($p = 0.042$). There was no significant correlation between fractional inspired oxygen and hydrogen peroxide concentrations.

We emphasise that these results are still inconclusive because of deficiencies in our collecting system. Further evaluation is required using more refined methods of collection. In this respect, Hitka *et al.*³ attempted to capture only expired gases from ventilated preterm infants using a double valve outlet system. This looks promising, although validation of the method with various modes of ventilation and settings, and with a larger and more diverse patient group, is necessary before exhaled hydrogen peroxide can be considered for monitoring of ventilated neonates at risk of CLD.

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Reducing the dosing frequency of aminoglycosides can increase errors

We were interested to read the meta-analysis by Nestaas *et al.*[1] which states in its title that less frequent aminoglycoside dosing is safe and effective. About two years ago at this hospital, we reviewed the literature on gentamicin dosing and made the change to a larger but once daily gentamicin dose for term infants who received antibiotics after delivery. In our hospital, we routinely give benzyl penicillin and gentamicin in combination to any newborn term infant with suspected infection. Over the succeeding months, we had a significant rise in the

number of clinical adverse incident reports relating to gentamicin dosing errors. Investigation of these events showed that, with clearly written prescriptions showing benzyl penicillin to be given twice daily and gentamicin once daily, gentamicin was still being given more frequently or at the wrong time resulting in dosing levels exceeding the therapeutic range. This was despite double checking of doses and timings by two clinical staff members and perhaps highlights human fallibility even with standard systems in place. It was clear that the change to two different time regimens for the two antibiotics resulted in significant errors. To overcome this we have reverted to twice daily gentamicin given at the same time as the benzyl penicillin, the frequency of which cannot be reduced. The number of reported errors has since fallen dramatically.

This meta-analysis has focused predominantly on the reduction of serum drug concentrations outside the therapeutic range. Although this is clearly to be avoided in principle, there is little evidence that the increased number of both sub peak and elevated trough concentrations (which would normally be acted on) resulted in any significant adverse events in either group. Peak concentrations are notoriously unreliable, as the samples are often not taken at the correct time intervals, and this leads to a falsely increased number of sub peak threshold values. Most laboratories do not now routinely measure peak levels for this reason. The meta-analysis has not reported any nephrotoxic or ototoxic adverse effects that resulted in short or long term harm. Care should be taken over an assumption that laboratory or other changes such as the one raised creatinine concentration is meaningful. The authors themselves have counselled caution over interpreting the data as confirming that the extended dosing schedule is as effective.

Although this meta-analysis is interesting, it does raise the question as to whether a reduction in the number of measurements outside the defined range is the most important safety issue. We believe that a greater number of errors may occur, as in the clinical example above, if a wider risk assessment is not taken into consideration when considering a change to the dosing interval.

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Reference

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Single daily dose aminoglycosides in the neonatal period appear to be effective: but are they safe?

A recent article by Nestaas *et al*¹ deserves comment. This meta-analysis attempts to evaluate the relative efficacy and toxicity of extended interval dosing (EID) compared with traditional dosing (TD) of aminoglycosides administered to newborn infants. The conclusion of the analysis was that "extended interval dosing of aminoglycosides in neonates is safe and effective, with a reduced risk of serum drug concentrations outside the therapeutic range".

This interpretation of the data presented can be questioned on several grounds. Even with meta-analysis, the number of reported treatment failures (two in the TD group, none in the EID group from a total of 555 patients) was too small to establish a statistically significant difference between the two regimens in relation to efficacy.¹

There were certainly more serum drug concentrations, both peak and trough, that were outside the defined therapeutic range using TD than using EID. However, this difference was only seen in trials that were aiming for a higher (usually 5-12 mg/l) peak serum drug concentration.¹ This observation is a self fulfilling prophecy. With EID, the drug is given at the same maintenance dose rate (mg/kg/day), but with higher single doses and longer dosage intervals than with TD. Basic pharmacokinetic principles indicate that during EID, peak serum drug concentrations will be higher and trough concentrations lower than when smaller drug doses are given at shorter dosage intervals (TD).²

The finding of increased numbers of serum drug concentrations outside the desired therapeutic range seems compelling, but is *per se* not necessarily a strong argument in favour of EID. The efficacy of aminoglycosides should not be based on this observation alone, even though there are theoretical and *in vitro* data to support the concept of "post antibiotic effect".^{1,3} Because treatment failures with TD are extremely rare,¹ the possible benefit in efficacy of EID becomes less important than establishing with confidence that this regimen has similar or less toxicity than TD.

Clinically significant renal impairment in neonates receiving aminoglycosides is extremely rare,^{3,4} and is nearly always transient.⁴

Of greater significance is the potential for ototoxicity, which can occur with excessively high serum drug concentrations.³ In 1979, Finitzo-Hieber *et al*⁵ published a comprehensive evaluation of ototoxicity in newborns receiving TD aminoglycosides (gentamicin or kanamycin). More than 100 infants in each of three groups (gentamicin treated, kanamycin treated, and controls) were followed annually for up to four years. Detailed audiological testing was performed together with measures of vestibular function and psychometric assessment. There were no significant differences between the three groups in any of these measures.

In contrast, only four of the 16 studies included in this meta-analysis provided any data on ototoxicity. Brain stem evoked responses were only measured during, or shortly after, a course of an aminoglycoside (gentamicin or amikacin).^{3,4,6,7} No adequate long term assessment of the incidence of hearing impairment has yet been reported in studies using EID. Until conclusive ototoxicity data are available in infants treated with EID, we will continue to use traditional dose aminoglycoside therapy.

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Book reviews in ADC this month

The following book reviews are published in this month's *Archives of Disease in Childhood*:

- Practical approach to pediatric intensive care
- Ethical dilemma in pediatrics: cases and commentaries
- Evidence paediatrics and child health, 2nd edition
- Antiepileptic drugs: combination therapy and interactions