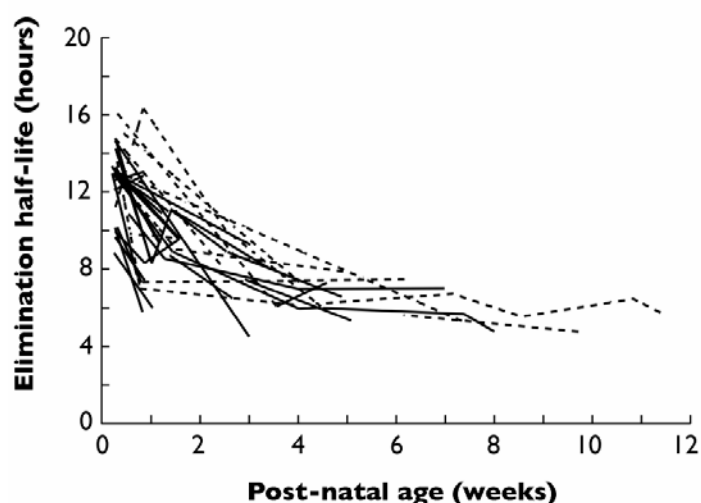


## GENTAMICIN (Commentary)

## Aminoglycoside prescribing regimens

Many policy options exist - one recent study reviewed 22 (Lannigan and Thomson, 2001). One reason for confusion is that, although it is widely accepted that the manufacturer's advice on treatment in the neonatal period is completely out of date, and in urgent need of revision, the regulatory authorities have made no move to get a revision undertaken. Nor has the profession applied pressure either. However, an appropriate policy should not, in theory, be difficult to construct because the apparent volume of distribution ( $V_D$ ) is known to be only a little greater than that of the extracellular space. It decreases in the first three months of life in much the same way as this space does, and then remains relatively stable throughout childhood, only reaching adult levels in adolescence. ( $V_D$  0.5 – 0.8 l/kg at birth, 0.3 – 0.4 l/kg during childhood, and 0.2 – 0.25 l/kg in adult life).

Similarly, because aminoglycosides are not metabolised by the body, and are excreted almost exclusively by glomerular filtration, it is easy to predict drug clearance from the body, because we have long known how this rate (GFR) varies during childhood. While the mean half life varies from 12 hours in the first 2–3 days of life in babies of 24 weeks gestation to 8 hours in babies born at term, this difference is much smaller than the fall that occurs in all babies during the first 2 weeks of life (see fig). Because renal function varies from baby to baby much more than it varies with gestation in babies more than one week old, policies based on a knowledge of postmenstrual age are invoking a false and unattainable precision. Adjusting for the presence of a duct, or its treatment, is also unnecessary for similar reasons. While clearance is low in the first day or two of life when related to body weight, it stabilises within one, or at most two, weeks of birth (see fig) before increasing by six months to a value from which it then halves progressively over the next ten years. It is during this latter period that the relationship to surface area remains more constant than the relationship to body weight – and why, in turn, many measures of renal function are traditionally related to body surface area.



Serial measurements of the half life of gentamicin in 25 babies of 25 to 40 weeks gestation. Dotted lines link measurements undertaken in babies born more than eight weeks early. The half life falls rapidly in the first week of life. By two weeks it is much the same as it is at three months.

For eight years now this *Formulary* has recommended once daily dosing on the basis that it is just as effective, less time consuming and reduces the number of intramuscular injections that older children sometimes face. It is, of course, true that most of the evidence of efficacy for once-a-day treatment initially still comes from trials in adults. However, Andrews *et al.* reviewed eleven studies of once-a-day treatment in neonates in 2000, and there have now been 16 controlled trials of once-a-day aminoglycoside prescribing in neonates (Nestaas *et al.*, 2005) as well as 18 trials in older children (Contopoulos-Iaonnidis *et al.*, 2004). This text continues to recommend a single daily dose when initiating aminoglycoside treatment in early infancy, accepting that this will sometimes cause a transient raised trough level when treatment is started within hours of birth, because clearance is slower in the first day or two of life. High trough levels (> 2 mg/l) are never seen with such a policy in babies more than 10 days old unless there is a renal problem. Monitoring the trough level after the third or fourth dose can, therefore, serve a useful purpose in identifying early renal failure (see below) well before this causes a recognisable rise in plasma creatinine. However, trough levels marginally

above 2 mg/l in the first week of life seldom call for action because they usually come to light just as renal clearance is improving anyway. There is, in any case, very little evidence that high trough levels ever cause cochlear or vestibular damage unless high dose treatment is sustained for over a week.

What is much more serious, and widely under-recognised, is the potential harm done by low peak levels. In this connection the manufacturer's statement (as approved by the UK licensing authority) that a peak level of 4 mg/l is acceptable flies in the face of much evidence suggesting that the level should be twice as high as this. It was also shown almost twenty years ago (Gal *et al.*, 1990) that, unless a loading dose is given, a therapeutic peak blood level is not achieved for 24 hours in infancy if doses are given every 8 – 12 hours (because of the high  $V_D$ ). In the presence of overt sepsis this could be disastrous. It is only because, in the vast majority of babies treated at birth, there never **was** any evidence of infection anyway, or the inadequacy of aminoglycoside treatment was masked by the simultaneous use of a second antibiotic, that the unsatisfactory nature of such a policy was not recognised years ago. Very infrequent dosing could also be hazardous. Several text books currently recommend treatment once every 48 hours in the very preterm baby. While this may give the "optimum" peak and trough levels that people are seeking, such dosing might well be too infrequent to control bacterial replication.

Based on what is known about clearance and the volume of distribution it would seem that a daily dose of 5 mg/kg is appropriate in the first 6 months of life, and a dose of 7.5 mg/kg in babies 6 months to five years old. A dose of 6 mg/kg seems right for children 5–10 years old, and 4.5 mg/kg for children those older than this. The latter is also the dose used in most trials of 'once a day' dosing in adults.

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- Hayami KC, Hatzopoulos FK, Frank AL, *et al.* Pharmacokinetics of once-daily dosing of gentamicin in neonates. *J Pediatr* 1997;**131**:76–80. [RCT]
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- Chotigeat U, Narangosanti A, Ayudhya DP. Gentamicin in neonatal infection: once versus trice daily dosage. *J Med Assoc Thai* 2001;**84**:1109–15. [RCT]
- Uijtendaal EV, Rademaker CMA, Schobben AFEM, *et al.* Once-daily versus multiple-daily gentamicin in infants and children. *Ther Drug Monit* 2001;**23**:506–13. [RCT]
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- Agarwal G, Rastogi A, Pyati S, *et al.* Comparison of once-daily versus twice-daily gentamicin dosing regimens in infants  $\geq$  2500 g. *J Perinatol* 2002;**22**:268–74. [RCT]
- Chong CY, Tan ASL, Ng W, *et al.* Treatment of urinary tract infection with gentamicin once or three times daily. *Acta Paediatr* 2003;**92**:291–6. [RCT]
- Knoderer CA, Everett JA, Buss WF. Clinical issues surrounding once-daily aminoglycoside dosing in children. *Pharmacotherapy* 2003;**23**:44–56.
- Hansen A, Forbes P, Arnold A, *et al.* Once-daily gentamicin dosing for the preterm and term newborn: proposal for a simple regimen that achieves target levels. *J Perinatol* 2003;**23**:635–9. [RCT]
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- Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, *et al.* Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;**114**:e111–8. [SR] (See also **155**:827-8.)
- Nestaas E, Bangstad H-J, Sandvik L, *et al.* Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child* 2005;**90**:F294–300. [SR]

## Monitoring blood levels

Five reasons can be given for suggesting that, unless renal function is poor, aminoglycoside levels only need to be measured after the third dose has been given. First, it takes three half-lives for plasma levels to stabilise after treatment is started. Second, renal clearance, like GFR, often increases rapidly during the first week of life. Third, renal toxicity is uncommon (and reversible), while ototoxicity is only a problem if trough blood levels remain high for a week or more. There are almost no well documented accounts of neonatal use causing ear damage. Fourth, 'precautionary' treatment is frequently stopped after 2–3 days just as soon it becomes clear that there is no convincing evidence of sepsis. Delaying the collection of an antibiotic trough level until after the third dose has been given often makes it possible to dispense with monitoring altogether when treatment is only being given once a day. Fifthly unnecessary blood sampling is not merely pointless – it contributes to iatrogenic anaemia, increasing

the chance that the baby will require an otherwise unnecessary (potentially hazardous) blood transfusion.

Even when monitoring is undertaken, peak levels do not need to be measured as long as an initial loading dose has been given, because there should be no risk of the dose being inadequate. However, trough levels should be used to 'fine tune' treatment in babies in whom renal function is uncertain. It is normally said that trough levels should not exceed 2 mg/l when treatment is given every 8 hours. Certainly there have been very few reports of ototoxicity in children when trough levels are kept as low as this. With once-a-day treatment in adults it is generally recommended that the trough level should ideally not exceed 1 mg/l, because low levels are thought to enhance the drug's potency by allowing 'adaptive resistance' to resolve. However it is only possible to achieve trough levels as low as this in babies if treatment is only given once every 2–3 days. While the effect of giving treatment as infrequently as this is unknown there must be a real, if ill-defined, risk that bacteria will start multiplying again if levels are as low as this for more than a few hours.

Finitzo-Heiber T, McCracken GH, Roeser RJ, *et al.* Ototoxicity in neonates treated with gentamicin and kanamycin: results of a four-year controlled follow up study. *Pediatrics* 1979;**63**:443–50.

McCracken GH. Aminoglycoside toxicity in infants and children. *Am J Med* 1986;**80**:172–8.

### Speed of administration

All aminoglycoside products marketed in north America come with guidance about the need to give any IV dose slowly over 30 minutes (or even longer), but no such advice is issued with any of the products on sale in Europe. Indeed the most commonly used product comes with the advice "Give as a bolus ... over 2–3 minutes. [It] should not be given as a slow infusion". Rapid administration over 2–3 minutes is certainly cheaper, in part because it reduces the work load falling on nursing staff (Robinson and Nahata, 2001). The advice in *BNF for Children* is ambiguous. It says that neonatal doses should be given by "slow intravenous injection or intravenous infusion". What is meant by a "slow injection" is not clear, but it says that any "intravenous infusion" should be given "over 30 minutes". No evidence to support this advice can be found, and the text now accepts "intravenous injection over at least 3 minutes" in children over a month old. While abrupt neuromuscular blockade could, theoretically, occur after abrupt bolus administration, this has never been reported. All the experimental evidence is that damage to vestibular secretory cells and to cochlear hair cells only occurs after exposure lasting several days. Clinical experience also suggests that ototoxicity only occurs after sustained high dose exposure. The damage caused by furosemide is, in contrast, almost immediate.

Wersall J, Lunquist P-G, Björkroth B. Ototoxicity of gentamicin. *J Infect Dis* 1969;**119**:410–6. (See also 427–31.)

Mendelson J, Pornoy J, Dick V, *et al.* Safety of bolus administration of gentamicin. *Antimicrob Agents Chemother* 1976;**9**:633–8.

Bromiker R, Adelman C, Arad I, *et al.* Safety of gentamicin administered by intravenous bolus in the nursery. *Clin Pediatr* 1999;**38**:433–5.

Robinson RF, Nahata MC. Safety of intravenous bolus administration of gentamicin in pediatric patients. *Ann Pharmacother* 2001;**35**:1327–31.

Anon. *BNF for children*. London: BMJ Publishing Group, 2008:330.

### Prescribing in a setting where it is not possible to monitor levels

For babies less than a month old an alternative dosing strategy is the one recommended by English *et al.*, 2004. Any baby with genuine septicaemia is never going to survive unless a bactericidal blood level is achieved with the minimum of delay. However, in many developing countries it is impossible to get blood antibiotic levels measured, and unrealistic to expect staff to cope with a dosage schedule that requires gentamicin to be given every 18, or every 36, hours. English *et al.* suggested that the best strategy is probably to give a first 8 mg/kg loading dose and then a maintenance dose of either 2, 4 or 6 mg/kg once every 24 hours. Peak and trough levels will, however, become subtherapeutic in babies weighing less than 2 kg after 3–4 days if these babies are only given a 2 mg/kg maintenance dose. Modelling suggests that the following minor modification of their scheme abolishes this risk, and also further reduces the risk of high trough developing in heavier babies in the second week of life -

Give an 8 mg/kg loading dose and then a daily dose of		
Age (days)	Birth weight*	
	< 2.0 kg	≥ 2.0 kg
≤ 14 days	3 mg/kg	4 mg/kg
> 14 days	4 mg/kg	6 mg/kg

\* Use above or below 32 weeks instead if gestation is known.

Such a scheme achieves a high early peak bactericidal blood level, but seldom generates a sustained, potentially toxic, trough antibiotic level. Such a regimen deserves to be tested more widely in those neonatal units where it is not realistic to ask for medication to only be given once every 36 hours. The recent WHO recommendation that all babies more than 7 days old should be given 7.5 mg/kg IV or IM once every 24 hours is clearly excessive and could well be toxic if sustained for more than a few days.

Attempts have been made to devise an even simpler dosing system using a pre-filled single-use injection device (the Uniject<sup>®</sup>) that gives all babies the same fixed 10 mg or 13.5 mg dose either once a day or once every other day. The results published to date show that the blood levels are not normally toxic (Darmstadt *et al.*, 2007) but it still remains to be shown that treatment given just once every 48 hours is enough to contain serious Gram-negative neonatal sepsis.

English M, Mohammed S, Ross A, *et al.* A randomised controlled trial of once daily and multi-dose daily gentamicin in young Kenyan infants. *Arch Dis Child* 2004;**89**:665–9. [RCT]

World Health Organisation. Department of Reproductive Health and Research. *Managing Newborn Problems: a guide for doctors, nurses and midwives. Section 3: procedures.* Geneva: WHO; C31–5.

Darmstadt GL, Hossain MM, Jana AK, *et al.* Determination of extended-interval gentamicin dosing for neonatal patients in developing countries. *Pediatr Infect Dis J.* 2007;**26**:501–7.

### Monitoring renal function

Many texts say that plasma creatinine levels should be monitored if gentamicin, or any other aminoglycoside, is to be prescribed in early infancy. Indeed, because gentamicin goes unmetabolised in the body and is only excreted through the renal glomerulus, gentamicin clearance provides a very precise index of the rate of glomerular filtration (GFR). Indeed it is probably almost as reliable as inulin as the perfect inert “marker” for GFR. Creatinine is, in contrast, a flawed marker (Coulthard *et al.*, 1985) partly because chromogens interfere with many of the normal laboratory tests used for its measurement, and also because the plasma level seems far from stable in the first few days of life. Indeed plasma creatinine levels rise significantly in the preterm baby in the first two days of life as a time when renal function is known to be increasing (Maill *et al.*, 2004). In fact, creatinine can only be used to obtain a valid measure of GFR when production and plasma levels are reasonably stable, and that is not the situation in the first few days of life. Here it is better to use the half life of some other inert molecule and, as Koren *et al.* were the first to argue in 1985, a bolus dose of gentamicin is a near-ideal marker of GFR. Clinicians would do well, therefore, to stop using plasma creatinine to influence their prescribing of gentamicin, and start using gentamicin levels to monitor what is really happening to the renal clearance of creatinine in the period immediately after birth.

Rudd PT, Hughes EA Placzek MM, *et al.* Reference ranges for plasma creatinine during the first month of life. *Arch Dis Child* 1983;**58**:991–4.

Coulthard MG, Hey EN, Ruddick V. Creatinine and urea clearances compared to inulin clearances in preterm and mature babies. *Early Hum Dev* 1985;**11**:11–9.

Koren G, James A, Perlman M, *et al.* A simple method for estimation of glomerular filtration rate by gentamicin pharmacokinetics during the routine monitoring of the newborn. *Clin Pharmacol Ther* 1985;**38**:680–5.

Maill LS, Henderson MJ, Turner AJ, *et al.* Plasma creatinine rises dramatically in the first 48 hours of life in preterm infants. *Pediatrics* 2004;**104**:e76.

### Possible ototoxicity

Anyone can become deaf if exposed to high aminoglycoside blood levels for long enough (although most reports have been associated with the use of an unmodified dose for more than a week in a patient in whom kidney failure was blocking renal elimination). There is actually very little objective evidence that aminoglycoside usage in the neonate ever causes deafness unless it is given with a second potentially ototoxic drug such as furosemide, but there is now increasing evidence that one small subpopulation of patients may be at much greater risk than most. These are babies born to mothers carrying a relatively rare mutation (m.1555A>G) of a gene carried on mitochondria and, because of this, there has now been a call for all babies to be screened for this gene before being given an aminoglycoside in early infancy (Bitner-Glindzicz and Rahman 2007). Whether there really is a case for this depends on how often the sort of high-dose but short-course treatment usually given to babies actually *does* cause deafness in such individuals – a question it will not be easy to answer because some people carrying this gene become deaf even though they have never been given an aminoglycoside, and it is not yet clear how soon it is possible to elicit clear signs of deafness after exposure if exposure *is* going to cause damage. A more effective way of addressing some of the current uncertainty would probably be to start by screening all children already receiving care for cystic fibrosis (see below) because vestibular function is even more easily damaged by aminoglycoside treatment than cochlear function and this usually presents with dizziness and vertigo, which later evolves into oscillopsia on head movement and a disabling gait (a problem easily diagnosed in children more than a few years old with the head impulse tests and caloric

testing). In the interim the one thing that clinicians can do is to find out whether the mother or any of her female relatives is deaf and then get the mother tested for this gene if this is the case before the child is even born.

Fischel-Ghodsian N, Prezant TR, Chaltraw WE, *et al.* Mitochondrial gene mutation Is a significant predisposing factor in aminoglycoside ototoxicity. *Am J Otolaryngol* 1997;**18**: 173–8.

Shiyama G, Ishiyama A, Kerber K *et al.* Gentamicin ototoxicity : clinical features and the effect on the human vestibulo-ocular reflex. *Acta Otolaryngol* 2006;**126**:1057–61.

Bitner-Glindzicz M, Rahman S. Ototoxicity caused by aminoglycosides. [Editorial] *BMJ* 2007;**335**:784-5 (See also 952.)

### Evidence of renal toxicity

Nephrotoxicity is routinely listed as a further problem associated with aminoglycoside treatment but there is hardly any published evidence to suggest that this really is a problem. What is clear is that treatment does cause some transient disturbance to tubular function and increases the amount of sodium and calcium lost in the urine. Such affects are, however, transient and resolve quite quickly once treatment is stopped. Nobody has yet published evidence to suggest that the effects are serious enough to be clinically important.

Giapros VI, Andornikou SK, Cholevas VI, *et al.* Renal function and the effect of aminoglycoside therapy during the first ten days of life. *Pediatr Nephrol* 1995;**18**:46–52.

Giapros VI, Cholevas VI, Andornikou SK, *et al.* Acute effects of gentamicin on urinary electrolyte excretion in neonates. *Pediatr Nephrol* 1995;**19**:322–5.

Tugay S, Zelal B, Caglayan C, *et al.* Acute effects of gentamicin on glomerular and tubular functions in preterm neonates. *Pediatr Nephrol* 2006;**21**:1389–92.

### Repeated use in babies with cystic fibrosis

While reports of ototoxicity are rare even in children with cystic fibrosis who often get frequent treatment with an IV or inhaled aminoglycoside, there is some evidence that while tubular damage is usually transient a very small number of children with CF suddenly develop serious renal failure when treated with an aminoglycoside, especially if they have already had repeated courses of treatment, are on diuretics, have become dehydrated and/or are being offered an NSAID such as ibuprofen (q.v.), especially if they already have reduced renal function,. The CF Trust in the UK now recommends that patients with CF should always have their plasma creatinine level assessed at the start of each and every course of aminoglycoside treatment in order to document GFR (glomerular filtration).

Watson AR. Aminoglycosides, toxicity and cystic fibrosis. *J Roy Soc Med* 2007;**100** (Suppl 47):24–8.

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