- 4 Dundas S, Todd WT, Stewart AJ, *et al*. The central Scotland Escherichia coli O157:H7 outbreak: risk factors for the hemolytic uremic syndrome and death among hospitalized patients. *Clin Infect Dis* 2001;**33**(7):923–31.
- 5 Ikeda K, Ida O, Kimoto K, *et al*. Predictors for the development of haemolytic uraemic syndrome with Escherichia coli O157:H7 infections: with focus on the day of illness. *Epidemiol Infect* 2000;**124**(3):343–9.
- 6 Buteau C, Proulx F, Chaibou M, *et al*. Leukocytosis in children with Escherichia coli O157:H7 enteritis developing the hemolytic-uremic syndrome. *Pediatr Infect Dis J* 2000;**19**(7):642–7.
- 7 Wong CS, Jelacic S, Habeeb RL, *et al*. The risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections. *N Engl J Med* 2000;**342**(26):1930–6.
- 8 Kawamura N, Yamazaki T, Tamai H. Risk factors for the development of Escherichia coli O157:H7 associated with hemolytic uremic syndrome. *Pediatr Int* 1999;**41**(2):218–22.
- 9 Bell BP, Griffin PM, Lozano P, *et al*. Predictors of hemolytic uremic syndrome in children during a large outbreak of Escherichia coli O157:H7 infections. *Pediatrics* 1997;**100**(1):E12.
- 10 Akashi S, Joh K, Tsuji A, *et al*. A severe outbreak of haemorrhagic colitis and haemolytic uraemic syndrome associated with Escherichia coli O157:H7 in Japan. *Eur J Pediatr* 1994;**153**(9):650–5.
- 11 Pavia AT, Nichols CR, Green DP, *et al*. Hemolytic-uremic syndrome during an outbreak of Escherichia coli O157:H7 infections in institutions for mentally retarded persons: clinical and epidemiologic observations. *J Pediatr* 1990;**116**(4):544–51.
- 12 Griffin PM, Tauxe RV. The epidemiology of infections caused by Escherichia coli O157: H7, other enterohemorrhagic Escherichia coli, and the associated hemolytic uremic syndrome. *Epidemiol Rev* 1991;**13**:60–98.
- 13 Morgan D, Newman CP, Hutchinson DN, *et al*. Verotoxin producing Escherichia coli O157 infections associated with the consumption of yoghurt. *Epidemiol Infect* 1993;**111**:181–7.
- 14 Fitzpatrick MM, Shah V, Trompeter RS, *et al*. Long term outcome of childhood haemolytic syndrome. *BMJ* 1991;**303**:489–92.
- 15 Fitzpatrick MM, Shah V, Filler G, *et al*. Neutrophil activation in the haemolytic uraemic syndrome: free and complexed elastase in plasma. *Pediatr Nephrol* 1992;**6**(1):50–3.
- 16 MacConnachie AA, Todd WT. Potential therapeutic agents for the prevention and treatment of haemolytic uraemic syndrome in shiga toxin producing Escherichia coli infection. *Curr Opin Infect Dis* 2004;**17**(5):479–82.

Is a once daily dose of gentamicin safe and effective in the treatment of UTI in infants and children?

Report by

M Shahid, Department of Paediatrics, Portiuncula Hospital, Ballinasloe, County Galway, Ireland; muhdshahid@hotmail.com

R Cooke, Department of Paediatrics, Portiuncula Hospital, Ballinasloe, County Galway, Ireland

doi: 10.1136/adc.2007.121079

An 8-month-old infant is admitted with fever and vomiting. Urinary tract infection (UTI) is diagnosed. You decide to commence IV treatment with gentamicin. In your paediatric ward, gentamicin is routinely administered in three times daily dose (TD) regimens but you look up gentamicin administration in the *BNF for children* and find that it can be given once daily (OD). This prompts debate amongst staff as to whether the same can be done on your ward. Everyone wonders whether there is any supportive evidence for efficacy and safety when OD gentamicin is used in the treatment of UTI.

Structured clinical question

In children aged 1 month to 18 years with UTI [patients], is OD gentamicin [intervention] as compared with TD gentamicin [comparator] as effective in resolving UTI and as safe [outcome]?

Search strategy and outcome

Secondary sources

Cochrane database, DARE, ACP Journal Club and EBM were explored. We could not find any systematic reviews explicitly answering our question.

Primary sources

Medline (Ovid Medline) 1966–February 2007

“Urinary Tract Infection” and “Gentamicin or gentam\$”

Table 3 Use of OD gentamicin in children with UTI

Citation	Study group	Study type (level of evidence)	Outcomes	Key results	Comments (key weaknesses)
Chong <i>et al</i> (2003) ¹¹	210 children (1 month to 9 years) recruited with presumed UTI. 172 were analysable (OD 84, TD 88). Mean age 11 months	Randomised controlled trial (RCT). OD dose at 5 mg/kg/day and TD dose at 6 mg/kg/day (level 1b).	Primary: Microbiological efficacy Secondary: Nephrotoxicity and ototoxicity	Microbiological efficacy OD vs TD (98.7% vs 97.7%, p=0.353) Nephrotoxicity (1.2% vs 2.3%, p=0.627) Ototoxicity (0 vs 0, p=0.506)	No mention how randomisation was done. 1-week follow up for assessment of adverse effects of ototoxicity and nephrotoxicity is questionable.
Carapetis <i>et al</i> (2001) ¹²	184 children (1 month to 12 years) with UTI were recruited. 179 were analysable (OD 90, TD 89)	RCT. Daily doses of gentamicin in both groups were 7.5 mg/kg/day (<5 years old), 6.0 mg/kg/day (5–10 years old) and 4.5 mg/kg/day (>10 years old) (level 1b).	Primary: Clinical efficacy (ie, cure) Secondary: Bacteriological efficacy, nephrotoxicity, ototoxicity	Clinical efficacy (cure): OD 96%, TD 98%. Relative risk (RR) of cure with OD gentamicin was 0.98 (95% CI, 0.93 to 1.03). Median (IQR) time to fever resolution in OD was 27 h (13.5 to 47.5), and in TD was 31.0 h (9.8 to 48) with p=0.61.	Follow-up for assessment of adverse events was incomplete. Author questions the sensitivity of the method used to detect nephrotoxicity.
Tapaneya-Olarn <i>et al</i> (1999) ¹³	49 children (6 months to 12 years) with presumed UTI enrolled in the study. 24 were analysable (OD 13, TD 11).	RCT. Gentamicin dose used was 4.5 mg/kg either OD or TD (level 2b).	Clinical and microbiological efficacy. Nephrotoxicity	Clinical efficacy (indicated by resolution of fever). Most patients in group afebrile by 24 h (mean 8.69 h) as compared with TD group (mean 15.31 h), p=0.067. Laboratory nephrotoxicity measured by urine N-acetyl-D-glucosaminidase (NAG)/creatinine ratio, was detected in 2/13 (15%) of patients in OD group and 5/11 (45%) in TD group with p=0.182.	Small sample size is the major weakness of this study. Also ototoxicity was not accounted as an adverse event.

Limits: human, English language, all child (0 to 18 years), clinical trial

No appropriate primary studies could be found from Cochrane Central, Cinahl or Embase.

32 citations; three were relevant. See table 3.

Commentary

UTIs are the second most common infection in children, after those of the ear and throat.¹ If intravenous antibiotics are required, aminoglycosides or third generation cephalosporins are usually used. *Escherichia coli* is a causative organism in 80–90% of cases² of UTI in children, making it a suitable clinical setting for aminoglycoside use in children. When compared to cephalosporins, aminoglycosides are favoured because of their efficacy, low rate of resistance,³ widespread availability and low cost. Gentamicin is frequently used to treat UTI in children because of experience with its use and its relatively low cost.⁴ In addition, because other aminoglycosides, such as tobramycin, may be more useful in other clinical settings, gentamicin is used in UTI to minimise use of such drugs and, the development of drug resistance. Many clinical trials in adults and neonates^{5–9} have proven that OD gentamicin can be used with equal or better efficacy and similar or decreased ototoxicity and nephrotoxicity as compared with conventional TD dosing. A meta-analysis recently assessed the safety and efficacy of OD dosing of aminoglycosides as compared with multiple dosing in children.¹⁰ This meta-analysis included 24 studies where different aminoglycosides were used in different clinical settings. The authors concluded that although single trials have been small, the available randomised evidence supports the general adoption of OD dosing of aminoglycosides in paediatric clinical practice.

Specifically, the use of OD versus TD dosing of gentamicin in children with UTI is addressed by the three studies^{11–13} selected. The evidence extracted from these studies supports the use of OD gentamicin in the treatment of UTI in children, but certain gaps have been identified. These include the variation in gentamicin dose (OD varied from 4.5 to 7.5 mg/kg/day) and the estimation of ototoxicity and nephrotoxicity. Since it is thought that the prevalence of ototoxicity due to aminoglycoside is low in paediatric patients, large patient samples are needed with near complete follow-up of participants. These aspects were weak in these three studies. In the study conducted by Carapetis *et al*,¹² base-line and follow-up audiology examinations were obtained in 28 (31%) and 39 (43%) patients in the OD group and 16 (18%) and 33 (37%) in

the TD group. Tapaneya-Olarn *et al*¹³ did not measure ototoxicity in their outcome. As regards nephrotoxicity, there is lack of consensus regarding the best way to assess renal damage Carapetis *et al* referred to a method of assessing renal damage through the presence of tubular enzymes in urine but did not use this method in their study.

CLINICAL BOTTOM LINE

- Available evidence supports the efficacy of OD gentamicin in children with UTI. (Grade A)
- There is limited evidence regarding the safety of OD gentamicin. (Grade B)
- Issues of nephrotoxicity and ototoxicity require further clarification by well-structured RCTs with larger samples and complete follow-up of participants.

REFERENCES

- 1 Bonadio W. Evaluation and management of serious bacterial infections in the febrile young infant. *Paediatr Infect Dis J* 1990;**12**:905–12.
- 2 Poole C. Diagnosis and management of urinary tract infection in children. *Nurs Stand* 2002;**16**(38):47–55.
- 3 Lortholary O, Tod M, Cohen Y, *et al*. Aminoglycosides. *Med Clin North Am* 1995;**79**:761–87.
- 4 Hardman JG, Limbird LE, eds. *Goodman and Gilman's the pharmacological basis of therapeutics*. 10th ed. New York: McGraw-Hill, 2001:1231.
- 5 Bates RD, Nahata MC. Once daily administration of aminoglycosides. *Ann Pharmacother* 1994;**28**:757–65.
- 6 Barza M, Ioannidis JPA, Cappelleri JC, *et al*. Single or multiple doses of aminoglycosides: a meta analysis. *BMJ* 1996;**312**:338–45.
- 7 Gilbert DN. Editorial response: meta-analyses are no longer required for determining the efficacy of single daily dosing of aminoglycosides. *Clin Infect Dis* 1997;**24**:816–19.
- 8 Ali MZ, Goetz MB. A meta-analysis on the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997;**24**:796–809.
- 9 Nestas E, Bangstad HJ, Sandvik L, *et al*. Aminoglycosides extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2005;**90**:F294–300.
- 10 Contopoulos-Ioannidis DG, Giotis ND, Baliasta DV, *et al*. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;**114**:111–18.
- 11 Chong C-Y, Tan AS-L, Ng W, *et al*. Treatment of urinary tract infection with gentamicin once or three times daily. *Acta Paediatr* 2003;**92**:291–6.
- 12 Carapetis JR, Jacquier AL, Buttery JP, *et al*. Randomised controlled trial comparing once daily and three times daily gentamicin in children with urinary tract infections. *Paediatr Infect Dis J* 2001;**20**:240–6.
- 13 Tapaneya-Olarn C, Tapaneya-Olarn W, *et al*. Single daily dose of gentamicin in the treatment of pediatric urinary tract infection. *J Med Assoc Thailand* 1999;**82**(1):93–7.