One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates (Review)


This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2009, Issue 1

http://www.thecochranelibrary.com
One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates (Review)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
ABSTRACT

Background

Gentamicin is widely used in the treatment of suspected or proven neonatal sepsis. Animal studies and systematic reviews from trials in older children and adults suggest that a one dose per day regimen is superior to a multiple doses per day regimen. Pharmacokinetic studies and retrospective audits in neonatal population also favour once a day administration of gentamicin. However, there is no consensus regarding the dose interval regimen in the neonatal population.

Objectives

To compare the efficacy and safety of one dose per day compared to multiple doses per day of gentamicin in suspected or proven sepsis in neonates.

Search strategy

Eligible studies were identified by searching MEDLINE (March 2005), EMBASE 1980 - 2004, Oxford Database of Perinatal Trials, Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2005) and CINAHL (December 1982 - March 2005). Abstracts of the Society for Pediatric Research were hand searched from 1980 to 2004 inclusive. No language restrictions were applied.

Selection criteria

All randomised or quasi randomised controlled trials comparing one dose per day (‘once a day’) compared to multiple doses per day (‘multiple doses a day’) of gentamicin to newborn infants < 28 days of life.

Data collection and analysis

Methodological quality of eligible studies was assessed according to allocation concealment, blinding of intervention, blinding of outcome assessment and completeness of follow up. Data were sought regarding effects on clinical efficacy, pharmacokinetic efficacy,
ototoxicity and nephrotoxicity of the two regimens. When appropriate, meta-analysis was conducted to provide a pooled estimate of effect. For categorical data, the typical relative risk (RR), typical risk difference (RD) and number needed to treat (NNT) with 95% confidence intervals (CI) were calculated. Continuous data were analysed using weighted mean difference (WMD).

Main results

Twenty four studies were initially identified. Thirteen were excluded and eleven studies (N = 574) included. All studies compared the effectiveness and safety of ‘once a day’ versus ‘multiple doses a day’ regimen of gentamicin in newborn infants. Only one study enrolled infants less than 32 weeks gestation. All except one trial used intravenous infusion. One trial used gentamicin as a bolus dose over one minute. Two trials used intramuscular gentamicin in some of their study infants.

For the primary outcome of ‘clearance of sepsis’, all infants in both ‘once a day’ as well as ‘multiple doses a day’ regimen showed adequate clearance of sepsis [Typical RD 0.00 (95% CI -0.19, 0.19); 3 trials; N = 36]. For the other primary outcome measures relating to gentamicin pharmacokinetics, ‘once a day dosing’ of gentamicin was superior. ‘Once a day’ gentamicin regimen is associated with less failures to attain peak level of at least 5 µg/ml [Typical RR 0.22 (95% CI 0.11, 0.47); Typical RD -0.13 (95% CI -0.19, -0.08); 9 trials; N = 422]; less failures to achieve trough levels of ≤ 2 µg/ml [Typical RR 0.38 (95% CI 0.27, 0.55); Typical RD -0.22 (95% CI -0.29, -0.15); 11 trials N = 503]; higher peak levels [WMD 2.58 (95% CI 2.26, 2.89); 10 trials; N = 440] and lower trough levels [WMD -0.57 (95% CI -0.69, -0.44); 10 trials; N = 440] compared to ‘multiple doses a day’ regimen.

Ototoxicity and nephrotoxicity were not noted with either of the treatment regimens.

Significant heterogeneity was noted for some of the outcomes measured. Hence the results need to be interpreted with caution. Possible reasons for heterogeneity are different gestational ages of study infants and the timing of collection of blood samples in relation to a particular dose and the day of therapy on which the samples were collected.

Authors’ conclusions

There is insufficient evidence from the currently available RCTs to conclude whether ‘once a day’ or ‘multiple doses a day’ regimen of gentamicin is superior in treating proven neonatal sepsis. However data suggests that pharmacokinetic properties of ‘once a day’ gentamicin regimen are superior to ‘multiple doses a day’ regimen in that it achieves higher peak levels while avoiding toxic trough levels. There is no change in nephrotoxicity or auditory toxicity. Based on this assessment of pharmacokinetics, ‘once a day regimen’ may be superior in treating neonatal sepsis in neonates more than 32 weeks gestation.

Plain Language Summary

One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Gentamicin is a commonly used antibiotic that is very effective in treating bacterial infections in newborn babies. However, gentamicin may cause adverse effects on hearing and kidney function. Whether giving gentamicin as one dose per day or in multiple divided doses per day is best for newborn babies is not clear. This review found no change in the clinical outcome of infants with bacterial infections between the two types of treatment regimens. However, safer and potentially more effective levels of the drug were maintained using a one dose per day treatment schedule.
BACKGROUND

Gentamicin, an aminoglycoside antibiotic, is widely used in the treatment of suspected or proven bacterial sepsis in newborn infants. It is rapidly bactericidal. Combined with beta-lactam antibiotics, it provides synergistic activity against the most commonly encountered pathogens in the neonatal period (Chattopadhyay 2002). The potential ototoxicity and nephrotoxicity of gentamicin requires close monitoring of blood levels. High trough concentrations are associated with toxicity (Swan 1997) and lower peak levels are associated with lesser efficacy (Kovarik 1989; Chambers 2001). The bacterial killing is concentration dependent; the higher the concentration, the greater the rate at which bacteria are killed. The generally accepted peak concentrations are 4-10 µg/ml. Even higher peaks (e.g. 25 µg per ml) do not increase toxicity (Chambers 2001). Trough concentrations should be less than 1 - 2 µg/ml (Chambers 2001). Increasing the interval between doses has the potential to maintain maximal antibacterial activity, while minimizing side effects.

Several concepts support the benefit of a treatment regimen that administers one dose per day (‘once a day’ dose) of gentamicin (Miron 2001).

1. Gentamicin exhibits a concentration-dependent bactericidal effect in which a positive linear relationship exists between the peak minimum inhibitory concentration (MIC) ratio and bactericidal response.

2. Gentamicin exhibits the post-antibiotic effect (PAE). The PAE is a period during which the antibiotic continues to suppress bacterial growth despite serum concentrations below the MIC (Chambers 2001; Kahlmeter 1984). A prolonged PAE requires high peak concentrations and is associated with a better clinical response. Because once a day dose produces higher peak drug concentrations, it results in a prolonged PAE.

3. One of the first steps in the uptake of aminoglycosides into sites of toxicity is their binding to the brush borders of renal cells and to the cochlea and vestibular membranes. Uptake by these tissues is more efficient with low sustained concentrations compared to high intermittent levels. Animal models suggest that uptake of gentamicin in the renal cortex and perilymph is a saturable process that is relatively unaffected by drug concentration; transient high peak levels do not lead to excessive drug accumulation (Beaubien 1991; Giuliano 1986; Verpooten 1989). ‘Once a day’ dosing of aminoglycosides has consistently been shown to be less toxic than more frequent dosing in animals (Craig 1995).

4. Adaptive resistance is thought to occur after continuous exposure of bacteria to antibiotic concentrations that are less than the MIC (Lacy 1998). ‘Once a day’ dosing may help to avoid the development of resistance by achieving a higher bacterial kill initially, thereby decreasing the length of time viable bacteria are in contact with the drug.

5. Neonates, especially preterm and sick infants, have low glomerular filtration rate (Aperia 1981; Gallini 2000; Sonntag 1996; Vanpee 1993) which leads to slower clearance of drugs like gentamicin. ‘Once a day’ dosing, by providing more time for clearance, may avoid the toxic effects of gentamicin due to slower clearance.

6. Pharmacokinetics of drugs in neonates are unique and greatly influenced by gestational age and birth weight, postnatal age, post conceptional age and renal function. It may be ideal to use customised dosing for infants based on the gentamicin pharmacokinetics in each infant. However, this involves frequent measurement of serum gentamicin levels and rewriting of the medication orders with the potential for prescription errors. The majority of the use of gentamicin in the neonatal population is for the treatment of infants with risk factors for sepsis pending culture results for a short period of 48 - 72 hours. Once the negative culture results are obtained, the antibiotic is ceased. If the ‘once a day’ regimen attains adequate peak levels while avoiding toxic trough levels, then frequent measurement of serum gentamicin levels may not be necessary in these short (72 hour) rule out sepsis courses. This would significantly reduce the hospital cost associated with gentamicin therapy (Hitt 1997; Nicolau 1996; Thureen 1999).

Meta analyses of studies in adults have consistently shown that once daily dosing of aminoglycosides including gentamicin is as effective as multiple daily dosing, with similar or lesser risk of nephrotoxicity and ototoxicity (Ali 1997; Bailey 1997; Barza 1996; Hatala 1997; Munckhof 1996).

A systematic review of similar studies in children and infants concluded that a ‘once a day’ regimen is more efficacious and has no higher toxicity compared with multiple daily dosing (Miron 2001). A meta-analysis was not done.

A meta analysis (Contopoulos 2004) of extended interval aminoglycoside dosing (the dose is higher and administered less frequently than in traditional dosing regime) in children reported that an extended dose aminoglycoside regimen provides similar or potentially improved efficacy and safety, compared to multiple doses a day regimen. A total of 24 studies in paediatric populations up to 20 years of age, including six studies in neonatal populations, were included in their review. Five neonatal studies used gentamicin and one study used amikacin.

A recently published audit in neonates in one hospital showed that a ‘multiple doses a day’ regimen resulted in sub therapeutic levels and the new practice of extended dosage schedules achieved safe and adequate levels (Bajaj 2004). It has also been suggested that a...
dose interval of > 24 hours is less likely to produce toxic trough levels in the newborns less than 30 weeks gestation (Langlass 1999).

Despite this information, the appropriate dose and dose interval for gentamicin in neonates is still a matter of debate. Caution has been expressed against the use of 'once a day' dose of gentamicin in neonatal infections (Chambers 2001). This approach has yet to become standard practice in most pediatric hospitals (Knoderer 2003). A random survey of acute care hospitals in the USA in 1993 found that extended interval aminoglycoside dosing was not practiced in neonates, whereas, in 1998, 11.3% of the hospitals were using extended interval dosing (Chuck 2000).

In this review, we compared 'one dose per day' versus 'multiple doses per day' of gentamicin in neonates with suspected or proven sepsis.

**OBJECTIVES**

To compare the efficacy and safety of one dose per day ('once a day') gentamicin compared to multiple doses per day ('multiple doses a day') of gentamicin in suspected or proven sepsis in neonates.

Subgroup analysis was performed according to:
(a) Gestation: < 32 weeks and ≥ 32 weeks
(b) Suspected or proven sepsis
(c) Intramuscular or intravenous administration
(d) Use of loading dose

**METHODS**

Criteria for considering studies for this review

**Types of studies**
Randomised and quasi-randomised controlled trials.

**Types of participants**
Newborn infants (≤ 28 days after birth) with suspected or proven sepsis commenced on gentamicin. Suspected sepsis was defined as any condition in the neonate which led to the decision to commence antibiotics. Proven sepsis was defined as clinical condition necessitating use of antibiotics and presence of positive blood, other body fluid or tissue cultures.

**Types of interventions**

One dose per day ('once a day') compared to multiple doses per day ('multiple doses a day') of gentamicin.
- Studies comparing extended dose regimens such as dosing once in 36 - 48 hours versus 'once a day' dosing were not included.
- Studies comparing regimens with or without loading dosage were not included. If a trial used a loading dose of gentamicin in both groups, it was included.
- Since gentamicin is almost always used along with a second antibiotic, studies which used the same second antibiotic in both groups were included.
- If a study used a different second antibiotic along with gentamicin in the study and control groups, it was excluded.
- Studies using gentamicin either intramuscularly or intravenously were included provided both study and control groups were administered gentamicin by the same route.
- A difference of up to 25% while calculating the total daily dose was allowed between 'once a day' and 'multiple doses a day' regimens.

**Types of outcome measures**

Primary
(1) Clinical efficacy: Clearance of proven sepsis defined as negative blood or other body fluid cultures without the need for changing antibiotic.
(2) Pharmacokinetic efficacy:
   (a) Failure to reach adequate peak levels of at least 5 µg/ml. Peak level was defined as the level measured 0.5 to one hour after administration of any dose of gentamicin on any day during the study period.
   (b) Failure to avoid toxic trough levels of > 2 µg/ml. The trough level was defined as the level measured within one hour prior to the administration of gentamicin on any day during the study period (except the initial dose).
Secondary
(1) Otoxicity:
   Auditory: Defined as abnormality in pure tone audiometry or brain-stem evoked auditory response or otoacoustic emission or any other validated hearing test.
   Vestibular: Defined as abnormality in electronystagmography or any other validated vestibular function test.
   Examination could be performed at the end of the study period or before discharge with or without baseline testing.
(2) Nephrotoxicity:
   (a) Primary: Any increase in serum creatinine levels or decrease in creatinine clearance, with thresholds as defined in each study.
   (b) Secondary: Urinary excretion of proteins (retinal binding protein, beta 2 micro globulin, Clara cell protein, micro albumin, N-Acetyl-Beta-D-glucosaminidase, alkaline phosphatase, alanine aminopeptidase, or gamma-glutamyl transferase) or phospholipids.
   Examination could be performed at the end of the study period or before discharge with or without baseline testing.
(3) Treatment failure: Persistent positive blood/body fluid or tissue...
cultures which lead to any modification of the assigned antibiotic dosing or addition of new antibiotic.

(4) Actual peak levels (mean and SD) attained (µg/ml): Peak levels were defined as levels measured at 0.5 - 1 hour after a dose of gentamicin.

(5) Actual trough levels (mean and SD) attained (µg/ml): Trough levels were defined as levels measured within one hour of giving any dose of gentamicin (except the initial dose).

**Search methods for identification of studies**

The standard search strategy of the Cochrane Neonatal Review Group was used. This included electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2005), Oxford Database of Perinatal Trials, MEDLINE (1966 - March 2005), EMBASE (1980 - December 2004) and CINAHL (1982 - March 2005) and previous reviews including cross-references. Abstracts of Paediatric Academic Societies meetings published in Pediatric Research (1995 -2004) were hand searched. MEDLINE and EMBASE were searched for relevant articles using the following MeSH terms or text words: (Gentamicin/OR aminoglycoside) AND (sepsis/OR septicemia OR sepsis) AND (infant, newborn/OR infant, low birth weight/OR infant, very low birth weight/OR infant, premature/OR Infant, Prematurity, Diseases) OR (neonate: OR prematur*: OR newborn) AND (clinical trial OR Randomised Controlled Trials). Reference lists of published narrative and systematic reviews were also reviewed. No language restrictions were applied. The authors of all studies were contacted to clarify reported data or provide additional data and information including details of methodology. They were sent a standardised table and asked to provide missing data not included in their article if it was available. Chotigeat 2001; Hagan 2002; Kosalaraksa 2004; Krishnan 1997; Miron 2003; Romero 1998; Skopnik 1992 and Thureen 1999 provided additional information, clarified existing data and also clarified methodology of studies. Agarwal 2002; Hayani 1997 and Solomon 1999 were contacted initially by e-mail and subsequently by post four weeks later, but did not respond.

**Data collection and analysis**

Two review authors (SR and MA) assessed eligibility of studies for inclusion independently. The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. Quality of the trials included was evaluated in terms of allocation concealment, adequate randomization, blinding of parents or caregivers and assessors to intervention, and completeness of follow up (intention to treat) in all randomised individuals. This was defined as yes, no or can't tell for each category. Differences in the inclusion of trials according to their quality were resolved after consultation with the third review author (RH). Heterogeneity in the results of the trials were examined using the I squared statistic.

A data collection form was used to aid extraction of relevant information and data from each included study. Two review authors (SR and MA) extracted the data separately, compared data, and resolved differences by consensus. Any disagreement between SR and MA was resolved by consultation with the third reviewer (RH).

The standard methods of the Neonatal Review Group were used to synthesize the data. Effects were expressed as relative risk (RR), risk difference (RD) and 95% confidence intervals (CI) for categorical data, and weighted mean difference (WMD) and 95% CI for continuous data. The fixed effect model was used for meta-analysis. Change scores of auditory and vestibular tests and tests for nephrotoxicity were planned to be meta-analysed separately from the final value scores. For significant differences the number needed to treat (NNT) based on 1/RD was calculated.

**RESULTS**

**Description of studies**

See: Characteristics of included studies; Characteristics of excluded studies.

Twenty four studies were identified as potentially eligible. Thirteen were excluded and 11 studies were included for the review.

**Excluded studies**

Alsaedi 2003; Davies 1998; Hansen 2003; Kaspers 1998; Lanao 2004; Lundergan 1999; Skopnik 1995 and Stickland 2001 were excluded because they were not randomized or quasi randomized controlled trials. English 2004 was excluded because loading dose of 8 mg/kg was used in ‘once a day’ gentamicin regimen, whereas no loading dose was used in multiple doses a day regimen.

Mercado 2004 and Rastogi 2002 were excluded because they compared ‘once a day’ to ‘once in 48 hours’ regimen of gentamicin. Isemann 1996 and Semchuk 1995 were excluded because regimen of loading dose was compared to the regimen of no loading dose of gentamicin.

The details are listed in the table, ‘Characteristics of Excluded Studies’.

**Included studies**

Eleven studies were included in this review. All of them were single centre studies. All of the included studies were undertaken since the early 1990s by investigators attached to perinatal centres in North America, India, Thailand, Germany, Spain and Australia. A total of 574 neonates were enrolled in the 11 included trials. Krishnan 1997; Miron 2003 and Solomon 1999 enrolled infants ≥ 32 weeks gestation. Chotigeat 2001; Hagan 2002; Hayani 1997; Kosalaraksa 2004 and Thureen 1999 enrolled infants ≥ 34 weeks.
gestation. Agarwal 2002 enrolled infants ≥ 2500 g birth weight. All except three of the neonates enrolled were ≥ 37 weeks gestation in their study. Skopnik 1992 enrolled only full term neonates. Romero 1998 enrolled infants ≥ 1200 g birth weight and is the only study to enroll preterm infants less than 32 weeks gestational age.

All the studies used intravenous infusion of gentamicin except Krishnan 1997, where gentamicin was given as a bolus over one minute. Hagan 2002 and Hayani 1997 used gentamicin both intravenously and intramuscularly. Of the 574 infants enrolled in the trial, only 39 infants had proven sepsis (Hayani 1997; 1; Hagan 2002; 5; Kosalaraksa 2004; 2; Miron 2003; 2; Romero 1998; 29). The rest were treated for suspected sepsis. All studies used gentamicin in the dose of 4-5 mg/kg/day either as a single dose or as multiple divided doses. The main outcomes assessed were peak and trough levels of gentamicin and renal function. Three studies assessed hearing prior to discharge (Agarwal 2002; Hagan 2002; and Thureen 1999) and one study assessed hearing at one to two months of age (Miron 2003). One study assessed the cost of therapy (Thureen 1999). The details are described in the table, 'Characteristics of included studies'.

Risk of bias in included studies

The quality of the trials was assessed using the criteria of the Cochrane Neonatal Review Group. Assessment was based on allocation concealment, blinding of intervention, blinding of outcome assessment and completeness of follow up.

Allocation concealment:
Allocation concealment was accomplished in Agarwal 2002; Chotigacet 2001; Hagan 2002; Kosalaraksa 2004; Krishnan 1997; Romero 1998 and Skopnik 1992 using computer generated numbers in sealed envelopes. It was not clear if allocation was concealed in Solomon 1999 and Hayani 1997. Allocation was not concealed in Miron 2003 and Thureen 1999. Miron 2003 was a quasi random study with 'once a day' gentamicin being administered in period one (January to March 1998) and multiple doses a day gentamicin being administered in period two (April to June 1998). Thureen 1999 was also a quasi random study (assignment to a particular study group was dependent on the intensive care site, with monthly rotation of dosing regimens).

Blinding of intervention:
Blinding of intervention was not done in any of the studies.

Blinding of outcome assessment:

Completeness of follow up:

Details of the methodological quality of studies are included under the table 'Characteristics of Included Studies'.

Effects of interventions

Eleven studies fulfilled our selection criteria and were included in this review (Agarwal 2002; Chotigacet 2001; Hagan 2002; Hayani 1997; Kosalaraksa 2004; Krishnan 1997; Miron 2003; Romero 1998; Skopnik 1992; Solomon 1999; Thureen 1999). These studies included a total of 574 infants. There was no disagreement regarding inclusion/exclusion of studies, quality assessment or data extraction. Available data were pooled and analysed as listed below.

Primary outcome measures

(1) Clinical efficacy:
Clearance of proven sepsis (01.01):

Clearance of proven sepsis was defined as negative blood or other body fluid cultures without the need for changing antibiotic. In Romero 1998 study, both ‘once a day’ and ‘multiple doses a day’ regimens achieved clearance of sepsis in all the 29 neonates with proven sepsis. There were two gram positive bacterial infections in the Kosalaraksa 2004 trial. They were excluded from analysis by the authors. Only one infant had proven sepsis in the study by Hayani 1997. Its outcome was not reported. Hagan 2002 reported that all five infants with proven bacteriological sepsis in the ‘once a day’ gentamicin group responded by clearance of sepsis. There were no cases of proven sepsis in ‘multiple doses a day’ gentamicin group. Miron 2003 had one infant in each group with proven sepsis. Both infants had clearance of sepsis after institution of antibiotic therapy. Meta-analysis of all the studies did not show significant difference between the two groups [Typical RD 0.00 (95% CI -0.19, 0.19); 3 trials; N = 36].

(2) Pharmacokinetic efficacy:

a. Failure to attain peak levels of at least 5 µg/ml (01.02):
Peak levels of at least 5 µg/ml were considered to be essential to declare that a particular dosing regimen was pharmacologically effective. Agarwal 2002; Chotigacet 2001; Hagan 2002; Hayani 1997; Kosalaraksa 2004; Miron 2003; Romero 1998; Skopnik 1992 and Thureen 1999 reported this outcome. Only Miron 2003 reported a statistically significant difference that favoured ‘once a day’ gentamicin compared to ‘multiple doses a day’ gentamicin. However, meta-analysis of all the studies showed a statistically significant difference indicating that ‘once a day’ regimen is associated with less failures than ‘multiple doses a day’ regimen [Typical RR 0.22 (95% CI 0.11, 0.47); Typical RD -0.13 (95% CI -0.19, -0.08); NNT = 8; 9 trials; N = 422].
b. Failure to achieve trough levels of ≤ 2 µg/ml (01.03):

Trough levels of ≤ 2 µg/ml were considered to be essential to declare that a particular dosing regimen was pharmacologically safe. All studies reported this outcome measure. Kosalaraksa 2004; Krishnan 1997; Miron 2003 and Thureen 1999 reported statistically significant difference favouring ‘once a day’ gentamicin compared to multiple doses a day gentamicin. Meta analysis of all the studies showed a statistically significant difference indicating that ‘once a day’ gentamicin group is associated with less failures than ‘multiple doses a day’ regimen [Typical RR 0.38 (95% CI 0.27, 0.55); Typical RD -0.22 (95% CI -0.29, -0.15); NNT = 4; 11 trials N = 503].

Secondary

(1) Ototoxicity (01.04):

Auditory: Defined as changes in pure tone audiometry or brainstem evoked auditory responses or otoacoustic emissions or any other validated hearing tests.

Vestibular: Defined as changes in electronystagmography or any other validated vestibular function test.

Four studies (Agarwal 2002; Hagan 2002; Romero 1998; Thureen 1999) assessed auditory toxicity. Thureen 1999 replied that all infants in both the ‘once a day’ and ‘multiple doses a day’ gentamicin group passed hearing screening tests. Hagan 2002 used otoacoustic emission tests both prior to the first dose and after the third dose of gentamicin and did not find evidence of ototoxicity in either group. Agarwal 2002 performed hearing screening tests prior to discharge. None of their study infants failed hearing tests. Romero 1998 reported two cases of ototoxicity out of 13 in ‘once a day’ compared to one out of eleven in ‘multiple doses a day’ regimen. Chotigeat 2001 performed the tests for ototoxicity but did not report the results. [RD 0.01; (95% CI -0.04, 0.05)]. Vestibular toxicity was not tested by any of the studies.

(2) Nephrotoxicity (01.05):

(a) Primary: Any increase in serum creatinine levels or decrease in creatinine clearance, with thresholds as defined in each study.

(b) Secondary: Urinary excretion of proteins (retinal binding protein, beta 2 micro globulin, Clara cell protein, micro albumin, N-Acetyl-Beta-D-glucosaminidase, alkaline phosphatase, alanine aminopeptidase, or gamma-glutamyl transferase) or phospholipids.


Agarwal 2002 monitored renal functions by measuring 24 hour urine output on days one, two and three of therapy. Serum electrolytes, blood urea nitrogen and serum creatinine were measured on days two and three of the study. Creatinine clearance and FENA were measured on days two and three of therapy. There was no significant differences between the two groups in all the outcomes measured. Chotigeat 2001 measured serum creatinine before the beginning of treatment and on the third day and the last day of therapy. There was no significant difference between the two dosage regimens. Hagan 2002 measured serum creatinine levels before the beginning of study and subsequently on a daily basis till the completion of treatment. There was no significant difference between the two dosage regimens. Hayani 1997 measured serum creatinine and GFR before therapy and on day two or three of therapy. They also measured urinary beta 2 microglobulin levels before and after completion of therapy. There was no significant difference between the two regimens. Kosalaraksa 2004 measured serum creatinine on day zero, three and seven or the last day of therapy. There was no nephrotoxicity in either group. Krishnan 1997 measured serum creatinine and urea nitrogen and serum concentrations, urinary lysozyme excretion, glomerular filtration rate and fractional excretion of sodium at 72 to 96 hours of therapy. The values were not significantly different between the two groups. None of the babies in either group developed nephrotoxicity. Romero 1998 measured N-acetyl-D-glucosaminidase: creatinine ratio as a sensitive indicator of gentamicin induced nephrotoxicity. First morning urine within the first two days and on the seventh day of treatment was analysed. The enzyme levels increased in urine in both groups, but more so in the in the ‘multiple doses a day’ gentamicin group. Their study suggested that ‘once a day’ gentamicin regimen has fewer renal side effects than ‘multiple doses a day’ gentamicin regimen. Skopnik 1992 measured urinary aminopeptidase levels as a marker of nephrotoxicity and found that it was increased in both groups in the same pattern during and after discontinuation of gentamicin therapy. There were no statistically significant differences between the two groups. [RD 0.00; (95% CI -0.03, 0.03)].

(3) Treatment failure(01.06):

Persistent positive blood/body fluid or tissue cultures which lead to addition of new antibiotic. Hagan 2002; Miron 2003 and Romero 1998 reported in total 36 infants with proven sepsis. There were no treatment failures in either the ‘once a day’ or multiple doses a day regimens. [ Typical RD 0.00 (95% CI -0.19, -0.19); 3 trials N = 36].

(4) Actual peak levels (mean and SD) attained (µg/ml) (01.07):

Peak levels were defined as levels measured at 0.5 - 1 hour after a dose of gentamicin. All studies except Solomon 1999 reported this outcome. All studies except Krishnan 1997 reported a statistically significant difference with higher peak levels attained in ‘once a day’ gentamicin regimen. Meta analysis of all the ten studies involving a total of 440 infants showed a statistically significant difference between ‘once a day’ and ‘multiple doses a day’ gentamicin regimen with of higher peak levels attained in ‘once a day regimen’.
The outcome of 574 neonates from 11 RCTs comparing 'once a day' versus 'multiple doses a day' gentamicin have been reported in this review. For the primary outcome of 'clearance of proven sepsis', there was no statistically significant difference between the 'once a day' and 'multiple doses a day' regimens of gentamicin. Both treatment regimes were successful at treating infants with proven sepsis. However, the numbers were too small to come to any definite conclusions. This is expected because only a very small percentage of neonates with suspected sepsis have a culture positive infection (Stoll 1996 A; Stoll 1996 B). For the primary outcomes of 'Failure to attain peak levels of at least 5 µg/ml', and 'Failure to achieve trough levels of ≤ 2 µg/ml', meta-analysis showed a statistically significant difference favouring 'once a day' gentamicin group. 'Once a day' gentamicin was associated with less pharmacokinetic failure rates than 'multiple doses a day' regimen.

For the secondary outcomes of 'actual peak levels' and 'actual trough levels' attained, meta-analysis showed that 'once a day' regimen achieved higher peak levels and lower trough levels compared to 'multiple doses a day regimen'. However significant heterogeneity was noticed for these two outcomes. These results need to be interpreted with caution. Heterogeneity was explored by re-checking of data that was entered and by excluding individual studies one at a time. Individual trials were studied in detail to explore the cause of heterogeneity. Krishnan 1997; Miron 2003 and Solomon 1999 enrolled infants > 32 weeks gestation. Chotigeat 2001; Hagan 2002; Hayani 1997; Kosalaraksa 2004 and Thureen 1999 enrolled infants > 34 weeks gestation. Agarwal 2002 enrolled infants > 2500 g birth weight. Skopnik 1992 enrolled only full term neonates. Romero 1998 enrolled infants > 1200 g birth weight. These differences in gestational age and birth weight might have contributed to heterogeneity. All studies used a similar dose of gentamicin (4-5 mg/kg/day). Timing of collection of the blood samples for trough levels was the same in all the studies (within 30 minutes of administration of the next dose). Samples for peak levels were collected between 30-60 minutes after administration of the dose. The day of therapy on which samples were collected varied between day one to day five. This variation in the day and

---

**DISCUSSION**

...
time of collection of the samples may have led to heterogeneity. Hagan 2002 and Hayani 1997 used gentamicin both intramuscularly and intravenously. However, significant heterogeneity still remained even when these two studies were excluded from the meta-analysis. Results remained the same when data were re-analyzed using a random effects model instead of a fixed effect model.

Romero 1998 reported less nephrotoxicity in ‘once a day’ gentamicin regimen compared to ‘multiple doses a day’ regimen. They measured urinary levels of N-acetyl-beta-d-glucosaminidase as marker of nephrotoxicity. All other seven studies found no difference in the risk of nephrotoxicity between ‘once a day’ and ‘multiple doses a day’ gentamicin regimens. A recent RCT in adults (Olsen 2004) measured urinary alanine aminopeptidase (AAP) and N-acetyl-beta-d-glucosaminidase (NAG) as markers of nephrotoxicity and found that ‘once a day’ tobramycin was less nephrotoxic than ‘multiple doses a day’ regimen.

Only five studies assessed and four studies reported auditory toxicity. No difference was noted between the two groups. Vestibular toxicity was not assessed in any of the studies.

The findings of this review are consistent with the meta analysis in adults and older children in that ‘once a day’ gentamicin achieves better pharmacokinetic profile than ‘multiple doses a day’ gentamicin regimen with no difference in ototoxicity or nephrotoxicity.

‘Once a day’ gentamicin regimen requires less pharmacy preparation time and less nursing administration time. Thureen 1999 evaluated the cost-effectiveness analysis of ‘once a day’ gentamicin among neonates and found that ‘once a day’ gentamicin regimen was more cost effective than ‘multiple doses a day’ regimen. Individualized dosing regimens may be ideal, but are more expensive as they require more frequent measurement of gentamicin levels. Measurement of gentamicin levels is the major contributor to the expense of administering this relatively inexpensive drug (Thureen 1999; Bajaj 2004). As the great majority of infants treated with gentamicin are treated only for a short time (48 - 72 hours) until deep infection is excluded, this would increase the cost and complexity of their care with no clinical benefit.

Five out of seven infants less than 32 week gestation developed toxic trough levels of > 2 µg/ml. This occurred in both ‘once a day’ and ‘multiple doses a day’ regimen. The possible explanation is that very preterm infants have lower glomerular filtration rate and hence clear gentamicin more slowly than the more mature infants. Hence, even the ‘once a day’ regimen may also be toxic. Evidence is accumulating that an extended dosing regimen of once in 36-48 hours may be more suitable for very preterm infants less than 32 weeks gestation (Hansen 2003; Mercado 2004 and Rastogi 2002). More studies would be needed to decide appropriate dosing regimen for this subset of very preterm infants.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

There is insufficient evidence from the currently available RCTs to conclude whether ‘once a day’ or ‘multiple doses a day’ regimen of gentamicin is superior in treating bacteriologically confirmed neonatal sepsis. However, the pharmacokinetic properties of ‘once a day’ gentamicin regimen are superior to ‘multiple doses a day’ gentamicin in that it achieves higher peak levels while avoiding toxic trough levels. There is no change in nephrotoxicity or auditory toxicity. Hence ‘once a day’ regimen may be superior in treating neonatal sepsis in neonates more than 32 weeks gestation. For infants less than 32 week gestation with their decreased glomerular filtration rates, a further extended regimen of once in 36 to 48 hours may be appropriate.

**Implications for research**

More studies comparing the pharmacokinetics of ‘multiple doses per day’, ‘one dose per day’, and ‘more extended dosing regimen of once in 36-48 hours’ need to be done to find out the appropriate dosing regimen for preterm infants less than 32 weeks gestation.

**ACKNOWLEDGEMENTS**

We are thankful to Chotigeat 2001; Hagan 2002; Kosalaraksa 2004; Krishnan 1997; Miron 2003; Romero 1998; Skopnik 1992 and Thureen 1999 for responding to our queries. We are also very thankful to Kathleen Martin, reference librarian at The Canberra Hospital library, Australia for her help in performing the literature search. We are very much thankful to Jane Bell, Research Officer, Australasian Coordinating Network for the Cochrane Neonatal Review Group for her valuable help in the literature search and suggestions in editing the protocol.
References to studies included in this review

Agarwal 2002  (published data only)

Chotigeeat 2001  (published data only)

Hagan 2002  (unpublished data only)

Hayani 1997  (published data only)

Kosalaraksa 2004  (published data only)

Krishnan 1997  (published data only)

Miron 2003  (published data only)

Romero 1998  (published data only)

Skopnik 1992  (published data only)

Solomon 1999  (published data only)

Thureen 1999  (published data only)

References to studies excluded from this review

Alsaedi 2003  (published data only)

Davies 1998  (published data only)

English 2004  (published data only)

Hansen 2003  (published data only)

Isemann 1999  (published data only)

Kaspers 1999  (published data only)

Lanao 2004  (published data only)

Lundergan 1999  (published data only)

Mercado 2004  (published data only)

Rastogi 2002  (published data only)

Semchuk 1995  (published data only)

Skopnik 1995  (published data only)

Stickland 2001  (published data only)

Additional references
One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates (Review)

Ali 1997

Aperia 1981

Bailey 1997

Bajaj 2004

Barza 1999

Beaubien 1991

Chambers 2001

Chattopadhyay 2002

Chuck 2000

Contopoulos 2004

Craig 1995

Gallino 2000

Giuliano 1986

Hatala 1997

Hitt 1997

Kahlmeter 1984

Knudsen 2003

Kovarik 1989

Lacy 1998

Langlass 1999

Miron 2001

Munckhof 1996

Nicolau 1996

Olsen 2004

Sonntag 1996

Stoll 1996 A

Stoll 1996 B

Swan 1997

Vanpee 1993

Verpooten 1989

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agarwal 2002

<table>
<thead>
<tr>
<th>Methods</th>
<th>Concealment of allocation - Yes. Using sealed envelopes.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinding of intervention - No.</td>
</tr>
<tr>
<td></td>
<td>Blinding of outcome assessment - Can’t tell</td>
</tr>
<tr>
<td></td>
<td>Completeness of follow up - Yes.</td>
</tr>
<tr>
<td></td>
<td>Only three infants were excluded after enrolment.</td>
</tr>
</tbody>
</table>

| Participants                      | N = 44. Infants with BW >= 2500 g, age <= 7 days, Apgar scores of >= 5 at 5 minutes, suspected systemic or focal bacterial infection. Exclusion criteria were history of perinatal asphyxia, shock or cardiopulmonary arrest, seizures, anomalies of the kidney or major congenital anomalies incompatible with life and evidence of neuromuscular disorder. 'Once a day' gentamicin: N = 20. 'Multiple doses a day' gentamicin : N = 21. Three infants excluded after enrolment. Mean BW 3302 674 g in 'once a day' vs 3387 526 g in 'Multiple doses a day' gentamicin group. All infants were enrolled within the first 24 h after birth. |

| Interventions                     | 'Once a day’ gentamicin group were given gentamicin at 4 mg/kg/dose once every 24 h. 'Multiple doses a day’ gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h. Gentamicin was infused over a period of 30 minutes with a metered syringe pump using a microbore tubing. All infants were treated concomitantly with ampicillin. |
Outcomes

Blood for peak serum gentamicin was drawn 30 minutes after completion of the gentamicin infusion and for trough concentration, 30 minutes prior to the start of gentamicin infusion. Trough and peak SGCs drawn with the dose at 48 h were considered to reflect steady state. Other outcomes that were measured were urine output, serum creatinine, creatinine clearance and hearing screen test prior to discharge.

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Chotigeat 2001

Methods

Concealment of allocation - Yes. Using sealed envelopes.
Blinding of intervention - No
Blinding of outcome assessment - Yes
Completeness of follow up - Yes

Participants

N = 54. Infants with BW >= 2000 g age < 7 days, gestational age>= 34 weeks, Apgar scores of more than or equal to 4 at 1 minute and 6 at 5 minutes, suspected or proven bacterial infection. Exclusion criteria were allergy to aminoglycoside, congenital anomalies, renal failure and neuromuscular disorder. 'Once a day' gentamicin: N = 27.
'Multiple doses a day' gentamicin : N = 27. Mean gestational age in 'once a day' group was 38.44 ± 2.12 weeks vs 38.37 ± 2.12 weeks in 'multiple doses a day' gentamicin group. Mean BW 2924 ± 597 g in 'once a day' vs 2987 ± 656 g in 'Multiple doses a day' gentamicin group. Postnatal age in 'once a day' group was 0.94 ± 1.22 days vs 1.43 ± 1.25 days.

Interventions

'Once a day' gentamicin group were given gentamicin at 4-5 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2-2.5 mg/kg/dose every 12 h.
Gentamicin was given as a intravenous infusion over 30 minutes.

Outcomes

In 'once a day' gentamicin group blood was drawn for peak serum concentration within in 30 minutes after completion of 3rd dose and the trough blood sample was drawn within 30 minutes prior to the 3rd dose. In 'multiple doses a day' gentamicin group blood was drawn for peak serum concentration within 30 minutes after completion of 5th dose and the trough level blood sample was drawn within 30 minutes prior to the 5th dose. Other outcomes that were measured were serum creatinine level on day 1, day 3, and on the day when gentamicin was discontinued.

Notes

Risk of bias
### Chotigeat 2001 (Continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

### Hagan 2002

**Methods**
- Concealment of allocation - Yes. Using sealed opaque envelope of card with computer generated random sequence numbers.
- Blinding of intervention - No
- Blinding of outcome assessment - Yes. Laboratory personnel and people performing hearing test were blinded to allocation.
- Completeness of follow up - No. 4 infants were excluded because of withdrawal of consent. Gentamicin levels were done in only 65 out of 100 infants.
- Otoacoustic emission test was done in only 59 infants. Serum creatinine levels were measured in 93 out of 100 infants.

**Participants**
- N = 100. Infants of gestational age more than 33 weeks, age < 7 days and presumed sepsis. Exclusion criteria were BW < 2000 g, history of significant asphyxia, congenital malformation and antenatal diagnosis of renal tract abnormalities. 'Once a day' gentamicin: N = 46.
- 'Multiple doses a day' gentamicin : N = 50. Median gestational age in 'once a day' group was 38 (36-40) weeks vs 39 (35-40) weeks in 'multiple doses a day' gentamicin group. Median; BW in 'once a day gentamicin' group was 3400 (2614, 3720) g vs 3130 (2560, 3750) g in 'Multiple doses a day' gentamicin group. Postnatal age in 'once a day' group was 0 (0,1) in 'once day gentamicin' vs 1(1, 2) days.

**Interventions**
- 'Once a day' gentamicin group were given gentamicin at 5 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2.5 mg/kg/dose every 18 h. Gentamicin was given either intravenously or intramuscularly.

**Outcomes**
- In 'once a day' gentamicin group blood was drawn for peak serum concentration within 30 minutes after completion of 3rd dose and the trough blood sample was drawn within 30 minutes prior to the 3rd dose. In 'multiple doses a day' gentamicin group blood was drawn for peak serum concentration within 30 minutes after completion of 3rd dose and the trough level blood sample was drawn within 30 minutes prior to the 3rd dose. Other outcomes that were measured were daily serum creatinine estimation and otoacoustic emission tests 12 h before the first dose and after the third dose of gentamicin.

### Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates (Review)
### Hayani 1997

| Methods | Concealment of allocation - Can’t tell  
  |         | Blinding of intervention - No  
  |         | Blinding of outcome assessment - Can’t tell  
  |         | Completeness of follow up - No. 5 patient treated intravenously didn’t complete study. 4 infants were discharged home before gentamicin concentration was due for measurement. One infant developed hypotension and shock and was excluded. |

| Participants | N = 31. Infants of gestational age more than or equal to 34 weeks, age <= 24 h with suspected sepsis or focal bacterial infection, BW >=2000 g and Apgar score of 7 or more at 5 minutes. Exclusion criteria were history of cardiopulmonary arrest, shock, seizures, congenital malformation incompatible with life anomalies of kidney or ear, or presence of neuromuscular disorder. 'Once a day’ gentamicin: N = 11. 'Multiple doses a day' gentamicin : N = 15. Overall mean gestational age was 39.1 (35 -41) weeks. Mean BW was 3200 (2100-4500) g. |

| Interventions | 'Once a day’ gentamicin group were given gentamicin at 5 mg/kg/dose once every 24 h. 'Multiple doses a day’ gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h . Gentamicin was given either intravenously or intramuscularly. |

| Outcomes | Serum gentamicin levels were measured on day 3 of life. Peak serum gentamicin levels were obtained 30 minutes after the end of intravenous dose or 60 minutes after an intramuscular dose. Trough levels were obtained 30 minutes before the dose. Other outcomes that were urine output, serum creatinine, serum electrolytes, blood urea nitrogen, urine sodium, urine creatinine, urine Beta 2 microglobulin levels and glomerular filtration rate. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Kosalaraksa 2004

| Methods | Concealment of allocation - Yes. Using computer generated randomised numbers kept in sealed envelopes.  
  |         | Blinding of intervention - No  
  |         | Blinding of outcome assessment - Yes.  
  |         | Completeness of follow up - Yes. Only three out of the 64 study infants did not have blood levels of gentamicin measured. |

| Participants | N = 64. Inclusion criteria were BW >= 2000 g, age <= 7 days Apgar score of > 6 at 5 minutes and suspected sepsis. Exclusion criteria were history of perinatal asphyxia, shock, cardiopulmonary arrest, seizure, neuromuscular disorder or anomalies of kidney or ear. 'Once a day' gentamicin: N = 33. |
Multiple doses a day' gentamicin: N = 31. Mean gestational age in 'once a day' gentamicin group was 38.4 ± 1.8 weeks vs 38.6 ± 2.1 weeks in 'multiple doses a day' group. Mean BW in once a day group was 3044 ± 475 g in 'once a day' group vs 3036 ± 497 g in 'multiple doses a day' group.

Interventions

'Once a day' gentamicin group were given gentamicin at 5 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h. Gentamicin was given as intravenous infusion over 60 minutes.

Outcomes

The peak serum gentamicin level was measured 30 minutes after infusion (after the 3rd dose in 'once a day' group and the 6th dose in the multiple doses group. Trough levels were measured immediately before the 4th dose in 'once a day' group and the 7th dose in the 'multiple doses a day' group. Other outcomes measured were urine output, serum creatinine on day 0, 3 and 7 or on the discontinuation day.

Notes

Risk of bias

 Allocation concealment? Yes A - Adequate

Krishnan 1997

Methods

Concealment of allocation - Yes. Using sealed envelopes.
Blinding of intervention - No
Blinding of outcome assessment - Yes.
Completeness of follow up - Yes.

Participants

N = 18. Inclusion criteria were neonates requiring gentamicin therapy as per unit protocol, 32 -36 weeks gestation, < 96 h of age and serum creatinine < 1 mg/dl. 'Once a day' gentamicin: N = 9.
Multiple doses a day' gentamicin : N = 9. Mean gestational age was 34.1 ± 1.5 weeks in 'once a day' gentamicin group and 34.0 ± 1.9 weeks in 'multiple doses a day' group. Mean BW in once a day group was 1940 ± 510 g and 1739 ± 527 g in 'multiple doses a day' group.

Interventions

'Once a day' gentamicin group were given gentamicin at 4 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h. Gentamicin was given as one minutes bolus intravenously followed by normal saline flush of 0.5 ml.

Outcomes

Peak levels were collected one hour after the first dose and the dose given at 48 h. Trough levels were collected just prior to the dose of gentamicin due at 48 h after the start of the therapy. Other outcomes measured were serum creatinine.

Notes

Risk of bias
### Krishnan 1997 (Continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

### Miron 2003

<table>
<thead>
<tr>
<th>Methods</th>
<th>Concealment of allocation - No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinding of intervention - No</td>
</tr>
<tr>
<td></td>
<td>Blinding of outcome assessment - Yes</td>
</tr>
<tr>
<td></td>
<td>Completeness of follow up - Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>N = 35. Inclusion criteria were BW &gt;= 1500 g, age &lt;= 24 h, gestational age 32-37 weeks and suspected sepsis. Exclusion criteria were shock, impaired renal function and known kidney, ear or heart malformations and metabolic disease. 'Once a day' gentamicin: N = 17. 'Multiple doses a day' gentamicin : N = 18.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
<th>'Once a day' gentamicin group were given gentamicin at 5 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>The serum gentamicin levels were measured at 72 to 96 h of therapy. The peak serum gentamicin level was measured 30 minutes after infusion. Trough levels were measured 30 minutes before the next dose. Other outcomes that were measured were serum and urine creatinine and sodium concentrations, urinary lysozyme excretion, glomerular filtration rate and fractional excretion of sodium at 72 to 96 h of therapy. Pure tone audiometric evaluation was performed at one to two months of age. Brainstem evoked response audiometry was performed if there was suspicion on pure tone audiometry.</th>
</tr>
</thead>
</table>

| Notes         | Additional information and methodology were clarified by the authors.            |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

### Romero 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>Concealment of allocation - Yes. Using sealed envelopes.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinding of intervention - No</td>
</tr>
<tr>
<td></td>
<td>Blinding of outcome assessment - Yes.</td>
</tr>
<tr>
<td></td>
<td>Completeness of follow up - No. Only 65 out of 80 infants completed the study.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>N = 80. Inclusion criteria were BW &gt;= 1200 g, with suspected sepsis. Exclusion criteria were known renal impairment (serum creatinine &gt; 1.2 mg/dl), severe neonatal asphyxia and unavailability of blood samples. 'Once a day' gentamicin: N = 33.</th>
</tr>
</thead>
</table>
'Multiple doses a day' gentamicin: N = 32. Mean gestational age in 'once a day' gentamicin group was 35.5 ± 3.4 weeks vs 36.2 ± 2.9 weeks in 'multiple doses a day' group. Mean BW in once a day group was 2407 ± 757 g vs 2525 ± 730 g in 'multiple doses a day' group.

Interventions

'Once a day' gentamicin group were given gentamicin at 5 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h. Gentamicin was given as intravenous infusion over 60 minutes. All patients received ampicillin concomitantly.

Outcomes

The peak serum gentamicin level was measured 60 minutes after completion of the infusion on the 4th day of treatment. Trough levels were measured immediately before the administration of the dose on 4th day of treatment. Other outcomes that were measured were urinary N acetyl-D glucose-aminidase:creatinine ratio within the first 2 days and on the 7th day of treatment, serum creatinine on the 4th day of treatment.

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Skopnik 1992

Methods

Concealment of allocation - Yes. Computer assisted allocation.
Blinding of intervention - No
Blinding of outcome assessment - No
Completeness of follow-up - Yes

Participants

N=20. Inclusion criteria were neonates with pneumonia, meconium aspiration, suspected bacterial sepsis, and premature rupture of membranes > 36 h before delivery. Exclusion criteria were gestational age < 37 weeks, BW < 2500 g. Apgar score of <= 4 at one minute and <=6 at 5 minutes, serum creatinine > 85 micromol/l and those requiring diuretics during the course of treatment and those who were exposed to aminoglycosides prenatally. 'Once a day' gentamicin: N = 10.
'Multiple doses a day' gentamicin : N = 10. Mean gestational age in 'once a day' gentamicin group was 39.5 ± 1.4 weeks vs 40.3 ± 0.8 weeks in 'multiple doses a day' group. Mean BW in once a day group was 3300 ± 600 g in 'once a day' group vs 3800 ± 600 g in 'multiple doses a day' group.

Interventions

'Once a day' gentamicin group were given gentamicin at 4 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2 mg/kg/dose every 12 h. Gentamicin was given as intravenous infusion over 30 minutes. All patients were treated with ampicillin concomitantly.

Outcomes

The pharmacokinetic profile of gentamicin was determined on the fourth day of treatment. Peak levels, trough levels and area under the concentration time curves, urinary excretion of alanine aminopeptidase as a marker of nephrotoxicity.
Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Solomon 1999

Methods

Concealment of allocation- Can’t tell
Blinding of intervention- No
Blinding of outcome assessment- Can’t tell
Completeness of follow-up- Yes

Participants

N = 73. Inclusion criteria were gestational age >= 32 weeks, with suspected or confirmed sepsis, 48 term and 25 preterm infants were included. 'Once a day' gentamicin: N = 37. 'Multiple doses a day' gentamicin: N = 36. Among preterm infants, the mean gestational age in 'once a day' gentamicin group was 34.2 ± 1.1 weeks vs 33.0 ± 0.7 weeks in 'multiple doses a day' group. Mean BW in once a day group was 1919 ± 255 g vs 1830 ± 184 g in 'multiple doses a day' group. Among term infants, the mean gestational age in 'once a day' group was 39.2 ± 1.4 weeks vs 39 ± 1.3 weeks in 'multiple doses a day' group. Mean BW in once a day group was 2935 ± 552 g vs 2968 ± 613 g in 'multiple doses a day' group.

Interventions

'Once a day' gentamicin group were given gentamicin at 4 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h. Gentamicin was given as intravenous infusion over 30 minutes followed by normal saline flush.

Outcomes

The peak serum gentamicin level was measured 60 minutes after completion of the infusion of the 2nd dose of gentamicin. Trough levels were measured 30 minutes before the administration of the 2nd dose of gentamicin.

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
Thureen 1999

Methods
Concealment of allocation - No
Blinding of intervention - No
Blinding of outcome assessment - No
Completeness of follow-up - Yes

Participants
N = 55. Inclusion criteria were gestational age >= 34 weeks, postnatal age < 7 days, Apgar scores of > 4 at 1 minute and > 6 at 5 minutes respectively, urine output > 0.5 ml/kg/hour in the first 24 h of life or > 1 ml/kg/h in the second 24 h of life and absence of inotropic support. 'Once a day' gentamicin: N = 27. 'Multiple doses a day' gentamicin : N = 28. Mean gestational age in 'once a day' gentamicin group was 37.8 ± 2.1 weeks vs 36.9 ± 2.6 weeks in 'multiple doses a day' group. Mean BW in 'once a day' group was 2831 ± 613 g vs 2795 ± 714 g in 'multiple doses a day' group.

Interventions
'Once a day' gentamicin group were given gentamicin at 4 mg/kg/dose once every 24 h. 'Multiple doses a day' gentamicin group were given gentamicin at 2.5 mg/kg/dose every 12 h. Gentamicin was given as intravenous infusion over 30 minutes. All patients received ampicillin concomitantly.

Outcomes
The peak serum gentamicin level was measured 30 minutes after completion of the infusion on day three of therapy (fifth dose of 'multiple doses a day' and third dose of 'once a day' gentamicin group). Trough levels were measured immediately before the administration of the dose on day three of therapy (fifth dose of 'multiple doses a day' and third dose of 'once a day' gentamicin group). Other outcomes that were measured were cost of therapy.

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

vs = versus

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alsaedi 2003</td>
<td>Not an RCT. The controls were historical. Multiple doses a day regimen was practiced between November 1999 to October 2000 and once a day gentamicin regimen was used between November 2000 to October 2002. Information from the first period was gathered from retrospective chart reviews.</td>
</tr>
<tr>
<td>Davies 1998</td>
<td>Not an RCT. It was a retrospective study of neonates born in the last half of 1995 who received gentamicin.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>English 2004</td>
<td>RCT</td>
</tr>
<tr>
<td>Hansen 2003</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Isemann 1996</td>
<td>RCT</td>
</tr>
<tr>
<td>Kapers 1998</td>
<td>Not RCT</td>
</tr>
<tr>
<td>Lanao 2004</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Lundergan 1999</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Mercado 2004</td>
<td>RCT</td>
</tr>
<tr>
<td>Rastogi 2002</td>
<td>RCT</td>
</tr>
<tr>
<td>Semchuk 1995</td>
<td>RCT</td>
</tr>
<tr>
<td>Skopnik 1995</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Stickland 2001</td>
<td>Not an RCT</td>
</tr>
</tbody>
</table>
## DATA AND ANALYSES

**Comparison 1.** All studies comparing ‘once a day’ versus ‘multiple doses a day’ regimen

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Clearance of proven sepsis</td>
<td>3</td>
<td>37</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>2 Failure to achieve peak levels of at least 5 microgram/ml</td>
<td>9</td>
<td>422</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.22 [0.11, 0.47]</td>
</tr>
<tr>
<td>3 Failure to achieve trough levels of &lt;= 2 microgram/ml</td>
<td>11</td>
<td>503</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.38 [0.27, 0.55]</td>
</tr>
<tr>
<td>4 Ototoxicity</td>
<td>5</td>
<td>214</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5 Nephrotoxicity</td>
<td>8</td>
<td>348</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>6 Treatment failure</td>
<td>3</td>
<td>37</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>7 Actual peak levels (µg/ml)</td>
<td>10</td>
<td>440</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>2.58 [2.26, 2.89]</td>
</tr>
<tr>
<td>8 Actual trough levels (µg/ml)</td>
<td>10</td>
<td>440</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.57 [-0.69, -0.44]</td>
</tr>
</tbody>
</table>

**Analysis 1.1.** Comparison 1 All studies comparing ‘once a day’ versus ‘multiple doses a day’ regimen, Outcome 1 Clearance of proven sepsis.

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing ‘once a day’ versus ‘multiple doses a day’ regimen

Outcome: 1 Clearance of proven sepsis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td>0.0 %</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Hagan 2002</td>
<td>5/5</td>
<td>1/1</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Miron 2003</td>
<td>1/1</td>
<td>1/1</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Romero 1998</td>
<td>14/14</td>
<td>15/15</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20</strong></td>
<td><strong>17</strong></td>
<td><strong>0.0 %</strong></td>
<td><strong>0.0 [ 0.0, 0.0 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 20 (Once a day), 17 (Multiple doses a day)

Heterogeneity: Chi² = 0.0, df = 0 (P=0.00001); I² =0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)
Analysis 1.2. Comparison 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen, Outcome 2 Failure to achieve peak levels of at least 5 microgram/ml.

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen

Outcome: 2 Failure to achieve peak levels of at least 5 microgram/ml

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal 2002</td>
<td>0/20</td>
<td>1/21</td>
<td>4.0 % 0.35 [ 0.02, 8.10 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chotigeat 2001</td>
<td>0/27</td>
<td>7/27</td>
<td>20.6 % 0.07 [ 0.00, 1.11 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hagan 2002</td>
<td>1/32</td>
<td>4/33</td>
<td>10.8 % 0.26 [ 0.03, 2.18 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hayani 1997</td>
<td>0/11</td>
<td>2/15</td>
<td>5.9 % 0.27 [ 0.01, 5.06 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kosarasaksa 2004</td>
<td>2/31</td>
<td>1/30</td>
<td>2.8 % 1.94 [ 0.19, 20.24 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miron 2003</td>
<td>2/17</td>
<td>11/18</td>
<td>29.4 % 0.19 [ 0.05, 0.74 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romero 1998</td>
<td>0/33</td>
<td>7/32</td>
<td>2.10 % 0.06 [ 0.00, 1.09 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skopnik 1992</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0 % 0.0 [ 0.0, 0.0 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thureen 1999</td>
<td>1/27</td>
<td>2/28</td>
<td>5.4 % 0.52 [ 0.05, 5.39 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>208</strong></td>
<td><strong>214</strong></td>
<td><strong>100.0 % 0.22 [ 0.11, 0.47 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (Once a day), 35 (Multiple doses a day)
Heterogeneity: Chi² = 5.35, df = 7 (P = 0.62); I² =0.0%
Test for overall effect: Z = 4.01 (P = 0.000061)
## Analysis 1.3. Comparison 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen, Outcome 3 Failure to achieve trough levels of <= 2 microgram/ml.

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen

Outcome: 3 Failure to achieve trough levels of <= 2 microgram/ml

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal 2002</td>
<td>0/20</td>
<td>4/21</td>
<td>4.9%</td>
<td>0.12</td>
<td>0.12 [ 0.01, 2.03 ]</td>
</tr>
<tr>
<td>Chatigeat 2001</td>
<td>0/27</td>
<td>2/27</td>
<td>2.8%</td>
<td>0.20</td>
<td>0.20 [ 0.01, 3.98 ]</td>
</tr>
<tr>
<td>Hagan 2002</td>
<td>7/32</td>
<td>4/33</td>
<td>4.4%</td>
<td>1.80</td>
<td>1.80 [ 0.58, 5.58 ]</td>
</tr>
<tr>
<td>Hayani 1997</td>
<td>1/11</td>
<td>6/15</td>
<td>5.7%</td>
<td>0.23</td>
<td>0.23 [ 0.03, 1.63 ]</td>
</tr>
<tr>
<td>Kasalarsaka 2004</td>
<td>6/21</td>
<td>20/30</td>
<td>18.5%</td>
<td>0.43</td>
<td>0.43 [ 0.21, 0.88 ]</td>
</tr>
<tr>
<td>Krishnan 1997</td>
<td>0/9</td>
<td>9/9</td>
<td>10.7%</td>
<td>0.05</td>
<td>0.05 [ 0.00, 0.79 ]</td>
</tr>
<tr>
<td>Miron 2003</td>
<td>3/17</td>
<td>10/18</td>
<td>10.9%</td>
<td>0.32</td>
<td>0.32 [ 0.11, 0.96 ]</td>
</tr>
<tr>
<td>Romero 1998</td>
<td>8/33</td>
<td>13/32</td>
<td>14.8%</td>
<td>0.60</td>
<td>0.60 [ 0.29, 1.24 ]</td>
</tr>
<tr>
<td>Skopnik 1992</td>
<td>0/10</td>
<td>0/10</td>
<td>0.0%</td>
<td>0.00</td>
<td>0.00 [ 0.00, 0.00 ]</td>
</tr>
<tr>
<td>Solomon 1999</td>
<td>6/37</td>
<td>10/36</td>
<td>11.4%</td>
<td>0.58</td>
<td>0.58 [ 0.24, 1.44 ]</td>
</tr>
<tr>
<td>Thureen 1999</td>
<td>0/27</td>
<td>14/28</td>
<td>16.0%</td>
<td>0.04</td>
<td>0.04 [ 0.00, 0.57 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>244</strong></td>
<td><strong>259</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.38</strong></td>
<td><strong>0.38 [ 0.27, 0.55 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 31 (Once a day), 92 (Multiple doses a day)
Heterogeneity: Chi² = 15.67, df = 9 (P = 0.07); I² = 43%
Test for overall effect: Z = 5.32 (P < 0.00001)
Analysis 1.4. Comparison 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen, 
Outcome 4 Ototoxicity.

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen

Outcome: 4 Ototoxicity

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Agarwal 2002</td>
<td>0/20</td>
<td>0/21</td>
<td></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Hagan 2002</td>
<td>0/26</td>
<td>0/33</td>
<td></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Miron 2003</td>
<td>0/17</td>
<td>0/18</td>
<td></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Romero 1998</td>
<td>2/13</td>
<td>1/11</td>
<td></td>
<td>100.0 %</td>
<td>1.69 [ 0.18, 16.25 ]</td>
</tr>
<tr>
<td>Thureen 1999</td>
<td>0/27</td>
<td>0/28</td>
<td></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>103</strong></td>
<td><strong>111</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.69 [ 0.18, 16.25 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 2 (Once a day), 1 (Multiple doses a day)

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.46 (P = 0.65)
Analysis 1.5. Comparison 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen, Outcome 5 Nephrotoxicity.

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen

Outcome: 5 Nephrotoxicity

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal 2002</td>
<td>0/20</td>
<td>0/21</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Chotigeat 2001</td>
<td>0/27</td>
<td>0/27</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Hagan 2002</td>
<td>0/46</td>
<td>0/47</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Hayani 1997</td>
<td>0/11</td>
<td>0/15</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Kosalaraksa 2004</td>
<td>0/33</td>
<td>0/31</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Krishnan 1997</td>
<td>0/9</td>
<td>0/9</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Miron 2003</td>
<td>0/16</td>
<td>0/16</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Skopnik 1992</td>
<td>0/10</td>
<td>0/10</td>
<td>*</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>172</strong></td>
<td><strong>176</strong></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 0 (Once a day), 0 (Multiple doses a day)

Heterogeneity: $\chi^2 = 0.0, df = 0 (P=0.00001); I^2 =0.0$

Test for overall effect: $Z = 0.0 (P < 0.00001)$
**Analysis 1.6. Comparison 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen, Outcome 6 Treatment failure.**

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen

Outcome: 6 Treatment failure

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hagan 2002</td>
<td>0/5</td>
<td>0/1</td>
<td></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Miron 2003</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Romero 1998</td>
<td>0/14</td>
<td>0/15</td>
<td></td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20</strong></td>
<td><strong>17</strong></td>
<td></td>
<td><strong>0.0 %</strong></td>
<td><strong>0.0 [ 0.0, 0.0 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 0 (Once a day), 0 (Multiple doses a day)

Heterogeneity: Chi\(^2\) = 0.0, df = 0 (P<0.00001); I\(^2\) =0.0%

Test for overall effect: Z = 0.0 (P < 0.00001)

---

**Analysis 1.7. Comparison 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen, Outcome 7 Actual peak levels (µg/ml).**

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen

Outcome: 7 Actual peak levels (µg/ml)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Mean Difference N/Fixed,95% CI</th>
<th>Weight</th>
<th>Mean Difference N/Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal 2002</td>
<td>20</td>
<td>21</td>
<td></td>
<td>15.2 %</td>
<td>2.10 [ 1.29, 2.91 ]</td>
</tr>
<tr>
<td>Chatigeat 2001</td>
<td>27</td>
<td>27</td>
<td></td>
<td>13.9 %</td>
<td>2.98 [ 2.14, 3.82 ]</td>
</tr>
<tr>
<td>Hagan 2002</td>
<td>32</td>
<td>33</td>
<td></td>
<td>4.1 %</td>
<td>4.30 [ 2.74, 5.86 ]</td>
</tr>
<tr>
<td>Hayani 1997</td>
<td>11</td>
<td>15</td>
<td></td>
<td>5.0 %</td>
<td>4.10 [ 2.70, 5.50 ]</td>
</tr>
<tr>
<td>Kasalaraka 2004</td>
<td>31</td>
<td>30</td>
<td></td>
<td>6.1 %</td>
<td>2.30 [ 1.02, 3.58 ]</td>
</tr>
<tr>
<td>Krishnan 1997</td>
<td>9</td>
<td>9</td>
<td></td>
<td>42.2 %</td>
<td>1.11 [-0.43, 2.65 ]</td>
</tr>
<tr>
<td>Miron 2003</td>
<td>17</td>
<td>18</td>
<td></td>
<td>1.8 %</td>
<td>4.00 [ 1.64, 6.36 ]</td>
</tr>
<tr>
<td>Romero 1998</td>
<td>33</td>
<td>32</td>
<td></td>
<td>15.4 %</td>
<td>3.10 [ 2.30, 3.90 ]</td>
</tr>
</tbody>
</table>

(Continued...)
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skopnik 1992</td>
<td>10</td>
<td>8.3 (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thureen 1999</td>
<td>27</td>
<td>7.9 (1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>217</strong></td>
<td><strong>223</strong></td>
<td></td>
<td></td>
<td><strong>2.58 [ 2.26, 2.89]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 34.21, df = 9 (P = 0.00008); I² = 74%
Test for overall effect: Z = 16.04 (P < 0.00001)

Analysis 1.8. Comparison 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen, Outcome 8 Actual trough levels (µg/ml).

Review: One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates

Comparison: 1 All studies comparing 'once a day' versus 'multiple doses a day' regimen

Outcome: 8 Actual trough levels (µg/ml).

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Once a day</th>
<th>Multiple doses a day</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal 2002</td>
<td>20</td>
<td>0.9 (0.3)</td>
<td></td>
<td></td>
<td>-0.70 [ -0.99, -0.41 ]</td>
</tr>
<tr>
<td>Chatigeat 2001</td>
<td>27</td>
<td>0.9 (0.35)</td>
<td></td>
<td></td>
<td>-0.54 [ -0.77, -0.31 ]</td>
</tr>
<tr>
<td>Hagan 2002</td>
<td>32</td>
<td>1.8 (1.4)</td>
<td></td>
<td></td>
<td>4.5 % 0.40 [ -0.17, 0.97 ]</td>
</tr>
<tr>
<td>Hayani 1997</td>
<td>11</td>
<td>1.7 (0)</td>
<td></td>
<td></td>
<td>0.0 % 0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Kosalaraksa 2004</td>
<td>31</td>
<td>1.6 (1.1)</td>
<td></td>
<td></td>
<td>4.4 % -1.00 [ -1.58, -0.42 ]</td>
</tr>
<tr>
<td>Krishnan 1997</td>
<td>9</td>
<td>1.96 (0.6)</td>
<td></td>
<td></td>
<td>4.1 % -0.80 [ -1.40, -0.20 ]</td>
</tr>
<tr>
<td>Miron 2003</td>
<td>17</td>
<td>1.55 (0.55)</td>
<td></td>
<td></td>
<td>6.1 % -0.85 [ -1.34, -0.36 ]</td>
</tr>
<tr>
<td>Romero 1998</td>
<td>33</td>
<td>1.4 (0.7)</td>
<td></td>
<td></td>
<td>8.3 % -0.80 [ -1.22, -0.38 ]</td>
</tr>
<tr>
<td>Skopnik 1992</td>
<td>10</td>
<td>0.8 (0.2)</td>
<td></td>
<td></td>
<td>19.2 % -0.20 [ -0.48, 0.08 ]</td>
</tr>
<tr>
<td>Thureen 1999</td>
<td>27</td>
<td>1 (0.5)</td>
<td></td>
<td></td>
<td>7.3 % -1.00 [ -1.45, -0.55 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>217</strong></td>
<td><strong>223</strong></td>
<td></td>
<td></td>
<td><strong>-0.57 [ -0.69, -0.44 ]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 27.26, df = 8 (P = 0.00064); I² = 71%
Test for overall effect: Z = 9.15 (P < 0.00001)
WHAT'S NEW

Last assessed as up-to-date: 31 August 2005.

16 October 2008  Amended  Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2005
Review first published: Issue 1, 2006

CONTRIBUTIONS OF AUTHORS

Shripada Rao (SR) framed the questions for the protocol, wrote the protocol, performed the literature search, selected relevant studies, assessed the methodological quality of studies, checked the data entered into RevMan by Mohamed Ahmed, corresponded with authors of the studies to get additional information, wrote the review and compiled other references.

Mohamed Ahmed (MA) performed the literature search and selected relevant studies, assessed the methodological quality of the studies, extracted study data and entered the data into RevMan .

Ronald Hagan (RH) revised and edited the drafts of the protocol, provided guidance in selecting outcomes of interest, resolved any differences between SR and MA in selection of relevant studies and revised and edited the discussion and conclusions.

DECLARATIONS OF INTEREST

One of the review authors (RH) is also the author of one of the included studies (Hagan 2002).

SOURCES OF SUPPORT

Internal sources

- Princess Margaret Hospital for Children, Perth, Australia.
- The Canberra Hospital, Australia.
- Royal North Shore Hospital, NSW, Australia.

External sources

- No sources of support supplied
INDEX TERMS

Medical Subject Headings (MeSH)
Anti-Bacterial Agents [*administration & dosage; adverse effects]; Drug Administration Schedule; Ear Diseases [chemically induced]; Gentamicins [*administration & dosage; adverse effects]; Infant, Newborn; Kidney Diseases [chemically induced]; Randomized Controlled Trials as Topic; Sepsis [*drug therapy]

MeSH check words
Humans