

Aminoglycoside extended interval dosing in neonates is safe and effective: A meta-analysis

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Abbreviations:

- SDL: Serum drug level
- EID: Extended interval dosing, typically 4-5 mg/kg gentamicin given to neonates at dosage interval 24 hrs or longer
- TD: Traditional dosing, typically 2-3 mg/kg gentamicin given to neonates at dosage interval 8-24 hrs

Keywords: aminoglycosides, meta-analysis, neonates, sepsis

Abstract

Objectives: To review the evidence from controlled clinical trials of neonates given equal daily aminoglycoside dose as extended interval dosing (dosage interval typically 24 hrs in term and 36-48 hrs in immature neonates) compared to traditional dosing (dosage interval typically 8-12 hrs in term and 12-24 hrs in immature neonates).

Design: Systematic review and meta-analysis of controlled trials found in electronic databases, trial registers and references in reviews and selected trials.

Settings: The selected trials were blinded and assessed for methodological quality. Each trial's own predefined criteria for treatment failure, nephrotoxicity, ototoxicity and therapeutic serum drug levels were used.

Subjects: Controlled trials of neonatal aminoglycoside therapy in which equal aminoglycoside daily dose were given at traditional and extended dosage intervals.

Main outcome measures: Serum drug levels outside the therapeutic range. Treatment failure and toxicity.

Results: Sixteen trials involving 823 neonates met the inclusion criteria for the systematic review. Twelve trials involving 698 neonates were included in the meta-analysis of the pharmacokinetics. Compared to traditional dosing, extended interval dosing was associated with a significantly lower risk for both peak (summary risk ratio 0.50, 95% confidence interval 0.26 to 0.94) and trough (0.36, 0.25 to 0.56) serum drug levels outside the therapeutic range. Accurate information on treatment failure was obtained in nine trials involving 555 neonates. One trial reported treatment failure. In this trial two neonates in the traditional dosing group did not respond to therapy within 72 hrs. Nephrotoxicity was investigated in 589 neonates in twelve trials and ototoxicity in 210 neonates in four trials with no significant differences between the two dosing regimens.

Conclusions: Extended interval dosing of aminoglycosides in neonates is safe and effective, with a reduced risk for serum drug levels outside the therapeutic range.

Introduction

Aminoglycosides, usually combined with a betalactam, is widely used for neonatal sepsis. The serum drug level (SDL) should be within the therapeutic range to secure effect and avoid toxicity. An early high peak SDL has in adult patients been associated with an improved clinical outcome in severe infections¹. In extended interval dosing (EID) a higher dose is given less frequently than in traditional dosing (TD). Meta-analysis of trials in adults and children have shown equal or better performance in EID than in TD²⁻⁹. Several trials have addressed the pharmacokinetic performance of EID compared to TD in neonates, often without sufficient statistical power. The dose and dosage interval for neonatal aminoglycoside dosing varies widely among guidelines. We have carried out a systematic review of controlled trials in neonates given aminoglycosides as EID or TD. We compared efficacy and toxicity and performed a meta-analysis of the pharmacokinetics based on each trials own predefined criteria for treatment failure, nephrotoxicity, ototoxicity and therapeutic SDL.

Box 1 Abbreviations used

- SDL: Serum drug level
- EID: Extended interval dosing, typically 4-5 mg/kg gentamicin given to neonates at dosage interval 24 hrs or longer
- TD: Traditional dosing, typically 2-3 mg/kg gentamicin given to neonates at dosage interval 8-24 hrs

Box 2 Search methods

Bibliographic databases (to Oct 04)

- Biosis (Winspurs)
- Cochrane controlled trial register (2004 issue 4)
- Embase (Winspurs)
- Medline (PubMed)

Search terms

- (newborn OR newborns OR neonate OR neonates OR infant OR infants) AND (aminoglycoside OR aminoglycosides OR gentamicin OR tobramycin OR netilmicin OR amikacin OR dibekacin OR isepamicin)

Reference lists

- Selected reports and review articles

Other resources (Oct 04)

- United Kingdom National Research Register of ongoing health research (www.doh.gov.uk/research/nrr.htm)
- Current Science register of controlled trials (www.controlled-trials.com)

Methods

Search strategy

The databases Biosis, Cochrane, Embase and Medline were searched from their inception to October 2004. Trials in any language were considered. References in reviews and the trials found were searched manually. Electronic trial registers were searched for unpublished and ongoing trials. (Box 2 for details.) The manufacturers of aminoglycosides were not contacted for unpublished trials.

Selection

Controlled clinical trials were evaluated for inclusion on the basis of the study design, the target population and the endpoints reported (box 3). In trials with subgroups fulfilling the criteria, these were included if data extraction was possible.

Data extracted

From each trial, the following data were extracted: Inclusion criteria, type of aminoglycoside used, dose and dosage interval, therapeutic range for peak and trough SDL, number of neonates evaluated, prevalence of therapeutic SDL, toxicity and clinical cure rate.

Data abstraction

EN performed the search and blinded the trials. HJB and KOW independently filled in a form for data extraction and assessed the presence of possible systematic errors¹⁰ in each trial. Disagreements were solved by consensus. Data were extracted from final reports, except for one question concerning clinical cure rate. Some authors did not report clinical cure rate completely and were contacted by mail or email for additional information.

Outcome measurements

The primary outcome in the meta-analysis was the SDL inside and outside the therapeutic range. The occurrence of treatment failure and toxicity was registered. For each trial, we used its own predefined criteria for treatment failure, toxicity and therapeutic SDL.

Validity assessment

The presence of systematic errors¹¹ was assessed in each trial (box 4 for details), and all trials were classified according to design.

Quantitative data synthesis

The main results are presented as estimates of summary risk ratios. A risk ratio less than one expresses a lower risk for SDL outside the therapeutic range in the EID group than in the TD group. Each trial was weighted by the inverse variance of the natural logarithm of risk ratio. We considered the finding of heterogeneity at the 0.1 level of significance as proof of the random effects model being more suitable than the fixed effects model¹², and we chose the same level of significance for heterogeneity between subgroups. In the case of no events, 0.5 was added to each cell of the table. We performed a subgroup analysis based on a priori hypothesis that the therapeutic peak SDL range chosen could influence the difference in pharmacokinetic performance between the EID and the TD groups. Two-sided p-values and 95% confidence intervals were used. We performed tests for presence of publication bias (funnel plot asymmetry¹³) and sensitivity analyses¹⁴ for design (randomised vs. other trials) and internal validity (bias vs. no bias). The regression analyses for funnel plot asymmetry were performed by using SPSS 11.0.0 for Windows. All other analyses were performed by using EasyMA¹⁵.

Box 3 Inclusion criteria

Design

- Controlled clinical trials of neonates given the same type of aminoglycoside as EID or TD
- Maximum 20% difference in daily dose between the EID and the TD group
- The EID dosage interval at least 24 hrs
- The EID dosage interval at least 50% longer than the TD dosage interval

Target population

- Neonates aged less than 30 days at start of treatment

Endpoints

- Clinical cure rate, toxicity or prevalence of peak and trough SDL inside and outside the therapeutic range reported in both the EID and the TD group.

Box 4 Assessment of internal validity – extent to which systematic error (bias) is minimized in clinical trials. (Campbell¹¹)

Selection bias – biased allocation to comparison groups

Performance bias – unequal provision of care apart from treatment under evaluation

Detection bias – biased assessment of outcome

Attrition bias – biased occurrence and handling of deviation from protocol and loss of follow up

Box 5 Number of hits in the initial search and trials included from each database

Database	Biosis	Cochrane	Embase	PubMed
No of hits	574	197	4788	5408
Trials included	8	11	13	15

Results

We found 16 trials¹⁶⁻³¹ from which data for 823 neonates could be used. In five trials^{16-19;31} only a subgroup of neonates fulfilled our inclusion criteria. All trials were found in electronic databases.

Trial characteristics

Eleven of the trials^{18-20;22-25;27-30} had a prospective randomised design, four^{16;17;21;31} used a historical control group and one²⁶ had a cohort design. Asphyxia, risk of deafness, kidney malformations and concomitant use of potentially nephrotoxic or ototoxic drugs were exclusion criteria frequently used. Amikacin was studied in two trials^{18;30}. In all other trials gentamicin was used. The daily amikacin dose was 15 mg/kg in both trials. The daily gentamicin dose was 2,5-5 mg/kg. The dosage interval was 12 hrs in the TD group and 24 hrs in the EID group in all but two trials. Gooding¹⁶ used 24 hrs TD dosage interval and 36 hrs EID dosage interval and Mercado¹⁹ compared 24 hrs in the TD group to 48 hrs in the EID group.

Table 1 Design, inclusion criteria and number of neonates included from the relevant trials. (See box 4 for criteria used for evaluation on systematic errors)

Trial	Kind of control group	Year of publication	Gestational age (week)	Birth weight (g)	Drug	Daily dose (EID/TD) (mg/kg /24 hrs)	Dosage interval (EID/TD) (hrs)	Therapeutic peak SDL range (mg/l)	Therapeutic trough SDL range (mg/l)	Systematic error (bias in internal validity)	Number of neonates included
Gooding et al ¹⁶	Historical	2001	<28	*	Gentamicin	2.67/2.5	36/24	5-8	0-1.5	Yes	57
Mercado ¹⁹	Randomised	2004	*	750-1500	Gentamicin	2.5/2.5	48/24	5-12	0-2	No	20
Solomon et al ²⁵	Randomised	1999	32->	*	Gentamicin	4/5	24/12	4-10	0-2	Yes	73
Krishnan et al ²⁹	Randomised	1997	32-36	*	Gentamicin	4/5	24/12	>5	0-2	No	18
Kosalaraksa et al ²⁰	Randomised	2004	*	2000->	Gentamicin	5/5	24/12	4-12	0-2	Yes	64
Hayani et al ²²	Randomised	1997	34->	2000->	Gentamicin	5/5	24/12	5-18	0-1.5	Yes	24
Chotigeat et al ²⁴	Randomised	2001	34->	2000->	Gentamicin	4-5/4-5	24/12	5-18 (EID) 4-12 (TD)	0-1.5 (EID) 0-2 (TD)	Yes	54
Thureen et al ²⁶	Cohort	1999	34->	*	Gentamicin	5/5	24/12	5-10	0-2	Yes	55
Langhendries et al ¹⁸	Randomised	1993	34->	*	Amikacin	15/15	24/12	Not stated	Not stated	Yes	22
Andrews et al ³¹	Historical	2000	36->	*	Gentamicin	5/5	24/12	>6	0-2	Yes	49
Kotze et al ³⁰	Randomised	1999	37-42	*	Amikacin	15/15	24/12	>20	0-10	No	40
Skopnik et al ²³	Randomised	1992	37->	2500->	Gentamicin	4/4	24/12	4-12	0-2	No	20
Lundergan et al ¹⁷	Historical	1999	37->	2500->	Gentamicin	4/5	24/12	5-12	0-2	Yes	121
de Alba et al ²⁸	Randomised	1998	*	1200->	Gentamicin	5/5	24/12	6-12	0-2	No	65
Alsaedi ²¹	Historical	2003	37-42	2500->	Gentamicin	4/5	24/12	5-12	0-2	Yes	100
Agarwal et al ²⁷	Randomised	2002	*	2500->	Gentamicin	4/5	24/12	5-12	0-2	No	41

* Not an inclusion criterion in the trial

Methodological quality assessment

In general, design and methodology were seldom completely reported. Often the process of randomisation and the blinding towards both the caregivers and those determining outcome was not described. Four trials used a historical control group. In two trials^{17;21} the control group consisted of neonates given aminoglycoside treatment within a specified period. One trial³¹ used a group matched for gestational age, while the last trial¹⁶ only described a retrospective audit being conducted. In the cohort trial²⁶ the cohorts were defined from the time treatment was given. Different daily dose and different point of time for assessing SDLs were the bias in internal validity that occurred most often. Possible systematic errors was found in all but six trials^{19;23;27-30}.

Table 2 Pharmacokinetics in trials included in the meta-analysis.

Trial	No of neonates included in the meta-analysis	Prevalence of peak SDL outside therapeutic range outside/total (%)		Prevalence of trough SDL outside therapeutic range outside/total (%)	
		TD-group	EID-group	TD-group	EID-group
Skopnik et al ²³	20	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)	0/10 (0.0%)
Hayani et al ²²	24	2/13 (15.4%)	0/11 (0.0%)	6/13 (46.2%)	1/11 (9.1%)
Kotze et al ³⁰	40	8/20 (40.0%)	0/20 (0.0%)	0/20 (0.0%)	0/20 (0.0%)
Agarwal et al ²⁷	41	2/21 (9.5%)	1/20 (5.0%)	9/21 (33.3%)	0/20 (0.0%)
Andrews et al ³¹	49	21/26 (80.8%)	0/23 (0.0%)	13/26 (50.0%)	0/23 (0.0%)
Chotigeat et al ²⁴	54	1/27 (3.7%)	0/27 (0.0%)	2/27 (7.4%)	1/27 (3.7%)
Thureen et al ²⁶	55	2/28 (7.1%)	2/27 (7.4%)	14/28 (50.0%)	0/27 (0.0%)
Gooding et al ¹⁶	57	29/36 (80.6%)	7/21 (3.3%)	3/36 (8.3%)	2/21 (9.5%)
Kosalaraksa et al ²⁰	64	1/31 (3.2%)	7/33 (21.2%)	21/31 (67.7%)	8/33 (24.2%)
Solomon et al ²⁵	73	9/36 (25.0%)	8/37 (21.6%)	10/36 (27.8%)	6/37 (16.2%)
Alsaedi et al ²¹	100	7/50 (14.0%)	3/50 (6.0%)	13/50 (26.0%)	3/50 (6.0%)
Lundergan et al ¹⁷	121	9/57 (15.8%)	0/64 (0.0%)	17/57 (29.8%)	0/64 (0.0%)
Total	698	91/355 (25.6%)	28/343 (8.2%)	108/355 (30.4%)	21/343 (6.1%)

Quantitative data synthesis

SDLs inside and outside the therapeutic range were described sufficiently for inclusion in the meta-analysis in twelve of 16 trials^{16;17;20-27;30;31}. We used SDLs assessed at the most equal point of time in the two groups, preferably 48-72 hrs after start of treatment. Eleven trials^{16;17;20-27;31} used gentamicin and one³⁰ used amikacin.

When combining all trials, 91 of 355 (25.6%) peak SDLs in neonates given TD and 28 of 343 (8.2%) in neonates given EID were outside the therapeutic range. The summary risk ratio for peak SDL outside the therapeutic range was 0.50 (95% confidence interval 0.26 to 0.94, $p=0.033$). 108 of 355 (30.4%) trough SDLs in the TD group and 21 of 343 (6.1%) in the EID group were outside the therapeutic range. The summary risk ratio was 0.36 (95% confidence interval 0.25 to 0.56, $p<0.001$). No clear evidence of publication bias¹³ was found for neither peak nor trough risk ratio ($p>0.10$).

The therapeutic peak range

Adequate peak SDL, for gentamicin and tobramycin above 5 mg/l and for amikacin above 20 mg/l, has in adult patients been associated with an improved clinical outcome in severe infections¹. In the four trials^{20;23-25} accepting lower peak SDL in the TD group, the summary peak risk ratio showed no statistically significant difference between the two dosing regimens. The summary risk ratio was 1.12 (95% confidence interval 0.56 to 2.24, $p=0.76$).

In the trials aiming at a higher peak SDL, the summary peak risk ratio was statistically significant in favour of EID. The summary risk ratio was 0.38 (95% confidence interval 0.24 to 0.61, $p<0.001$). The difference in summary risk ratio between these subgroups was statistically significant ($p<0.1$).

Design

There were statistically significant differences in peak risk ratio between randomised and non-randomised trials ($p<0.1$). The summary peak risk ratio in the randomised trials was 0.84 (95% confidence interval 0.45 to 1.58, $p=0.60$). When the trials with low therapeutic peak range^{20;23-25} were excluded, the summary risk ratio was 0.28 (95% confidence interval 0.07 to 1.12, $p=0.072$). The non-randomised trials all had high therapeutic peak range, and the summary risk ratio for these trials was 0.40 (95% confidence 0.24 to 0.66, $p<0.001$). There was no statistically significant difference in summary peak risk ratio between randomised and non-randomised trials when trials with low therapeutic peak range were excluded ($p>0.1$). There were no statistical significant differences in summary trough risk ratios between randomised and non-randomised trials ($p>0.1$). The summary trough risk ratio was statistically significant in favour of EID for the six randomised trials, 0.42 (95% confidence interval 0.26 to 0.66, $p<0.001$).

Bias in internal validity

There were no statistically significant differences in summary peak or trough risk ratio between trials with and without systematic errors ($p>0.1$). In trials without systematic errors the summary peak risk ratio was 0.35 (95% confidence interval 0.08 to 1.51, $p=0.16$). The summary trough risk ratio was 0.24 (95% confidence interval 0.04 to 1.69, $p=0.15$).

Efficacy and toxicity

Only three trials reported clinical efficacy completely. After contacting authors of the other trials asking if there were bacterial infections the aminoglycoside failed to cure, the clinical course was obtained for 555 neonates in nine trials. No deaths were reported. One trial²⁰ reported two treatment failure, both in the TD group. This trial defined clinical response as improvement within 72 hrs of treatment, but clinical improvement was not evaluated in neonates with metabolic disturbances, congenital heart diseases or gram-positive bacterial

infections. Of the two neonates, one was diagnosed with bacterial meningitis and the treatment was changed to cefotaxime. The other neonate, who was treated with cloxacillin and gentamicin, had a nosocomial infection after five days of therapy. Both patients had negative blood and cerebrospinal cultures.

Nephrotoxicity was investigated in 589 neonates in twelve trials^{17-24;27-30}. Skopnik et al²³ found alanine amino peptidase in the urine of all twenty neonates and Kotze et al³⁰ found at least one elevated creatinine level in 30 of 40 neonates. Of these, 13 of 20 were given TD and 17 of 20 were given EID.

Information concerning ototoxicity were obtainable in four trials^{17;18;27;30} and 210 neonates. Lundergan et al¹⁷ found one event in the EID group.

Discussion

The aim of this meta-analysis was to compare the effect of extended interval dosing and traditional dosing of aminoglycosides. To exclude other possible causes for differences found in pharmacokinetics, efficacy or toxicity, only trials with similar daily dose in the two groups were included. Many trials were excluded on the basis of this criterion. Although this meta-analysis was based also on non-randomized trials, we used the QUOROM statement checklist. Our findings suggest that extended interval dosing of aminoglycoside in neonates is safe and effective and decreases the risk for serum drug levels outside the therapeutic range.

Pharmacokinetics

The summary risk ratios for therapeutic SDLs were statistically significant in favour of the EID for both peak and trough serum drug levels. The summary peak risk ratio was more in favour the EID in trials aiming at peak SDLs associated with an improved clinical outcome in severe infections¹ than in trials with lower therapeutic peak range. This supports the use of EID. When discarding peak SDLs in trials with lower therapeutic peak range, the summary peak and trough risk ratio were within the same range in randomised trials and in trials without systematic errors as in all trials. The serum drug level should be assessed in extended interval dosing, as eight percent of the peak and six percent of the trough serum drug levels were outside the therapeutic range.

Efficacy and toxicity

In EID the risk for breakthrough infections has been of great concern. However, meta-analyses of trials in adults and children have shown equal or better performance in EID than in TD^{2-7;7-9}. This could be explained by several in vitro findings. Aminoglycosides show post antibiotic effect and post antibiotic leukocyte enhancement³². The bacterial killing is concentration dependent and is largest at first exposure³³. Higher and more infrequent peak SDL might prevent the development of post exposure adaptive resistance³⁴. As shown here, EID will decrease the sub-therapeutic peak SDLs, which is a predictor for poor clinical outcome¹. As only two out of 555 neonates did not respond to the aminoglycoside therapy both ways of dosing might be regarded effective. These results should however be interpreted with care, as morbidity and mortality often were not reported completely, and the presence of persisting positive blood cultures were seldom extractable from the trials.

Given the heterogeneity in the definitions and prevalence of nephrotoxicity, it was not possible to compare the different trials. The finding of only one event of ototoxicity in the 210 neonates tested is consisted with other trials often failing to identify neonatal aminoglycoside treatment as a major cause for deafness^{35;36}.

Future trials

Could these findings apply to neonates in all clinical situations? Some of the prospective randomised trials excluded many of the patients often found in neonatal intensive care units, while studies comparing EID to TD in a control group more often had wide inclusion criteria. As treatment failure is rare, large-scale studies would be needed to study difference in clinical cure rate between the EID and the TD.

Figure Legends

Figure 1

Trials grouped by the peak therapeutic range. Trials accepting lower peak SDL (gentamicin/tobramycin < 5 mg/l, amikacin < 20 mg/l) vs. trials with higher therapeutic peak range.

Figure 2

Randomised trials and results when adding non-randomised trials – peak

Figure 3

Randomised trials and results when adding non-randomised trials – trough

Figure 4

Systematic review profile – flow diagram

Contributors: EN initiated the initial design of this study and undertook the literature search. HJB and KOW extracted the data. LS advised on the statistical analyses. All authors contributed to the writing of the final draft of the manuscript. Nestaas is guarantor.

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Competing interests: None

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What is already known on this topic

In extended interval dosing, the aminoglycoside peak serum drug level is higher and the trough serum drug level lower than in traditional dosing.

The neonatal daily dose and dosage interval varies widely among guidelines, and the need for assessing serum drug levels is debated.

What this study adds

In extended interval dosing, therapeutic aminoglycoside serum drug levels are achieved more often than in traditional dosing.

For the peak serum drug level, the difference is more pronounced in trials with therapeutic peak range associated with improved clinical outcome.

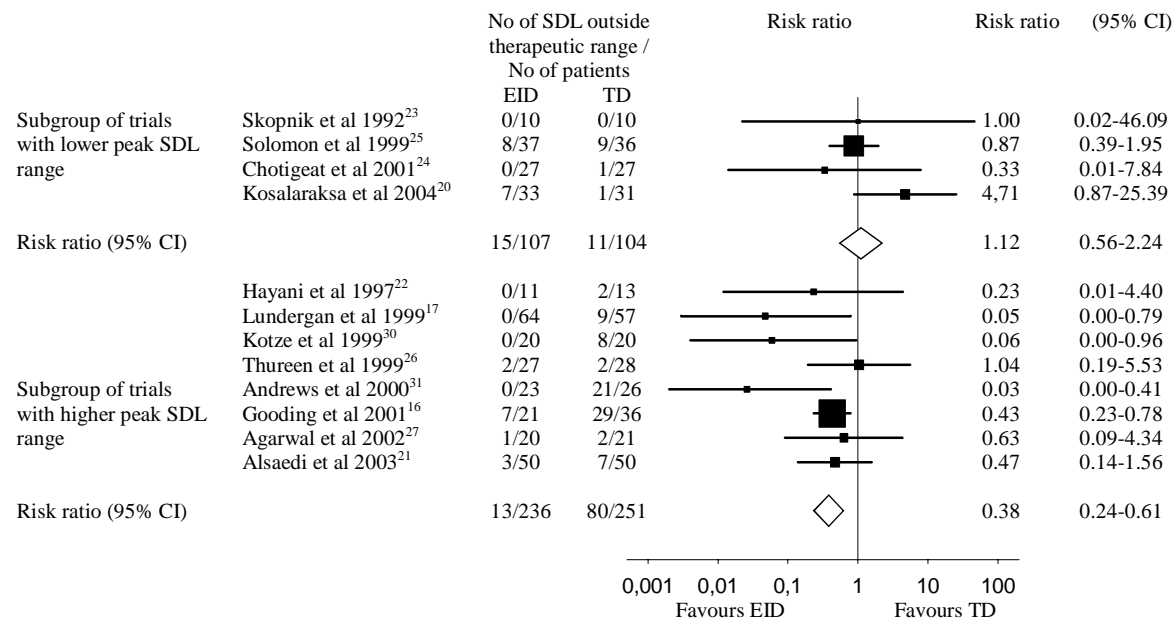
The results of this systematic review indicate that the serum drug level should be assessed in extended interval dosing, as eight percent of the peak and six percent of the trough serum drug levels were outside the therapeutic range.

No significant differences in clinical cure rate or toxicity were found.

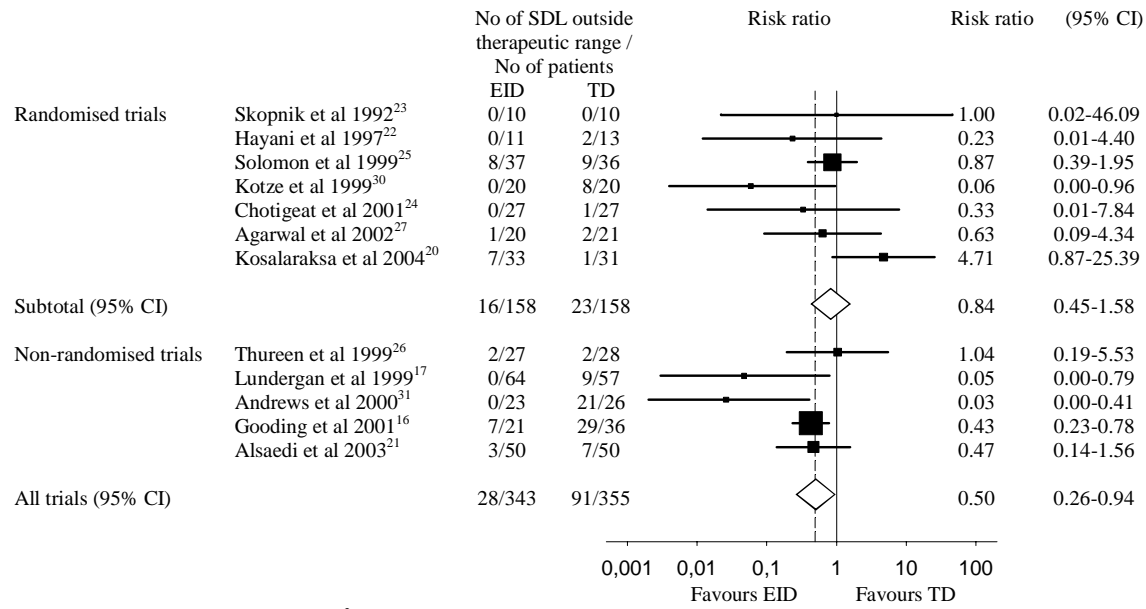
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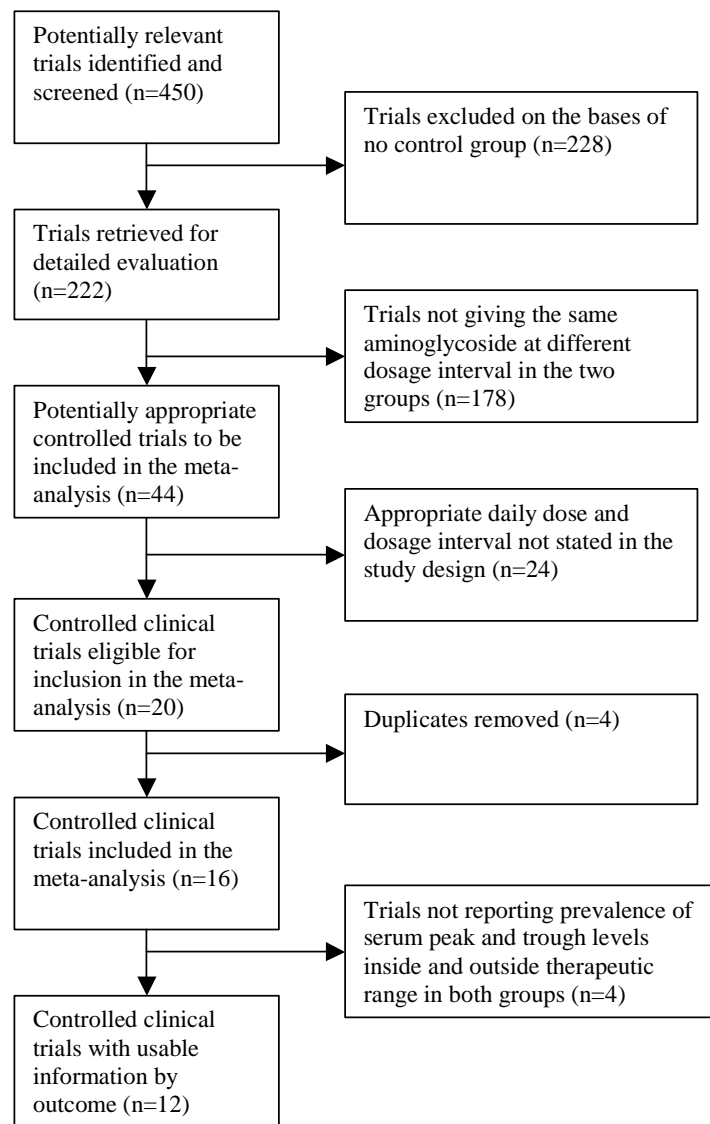


Tests for heterogeneity between subgroups $\chi^2=6.1927$, $df=1$, $p=0.013$



Tests for heterogeneity between trials $\chi^2=19.39$, $df=11$, $p=0.054$

Figure 4 Flow diagram





Aminoglycoside extended interval dosing in neonates is safe and effective: A meta-analysis

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