

# Extended-Interval Aminoglycoside Administration for Children: A Meta-analysis

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**ABSTRACT.** *Background.* There has been a long-standing debate regarding whether aminoglycosides should be administered on a multiple daily dosing (MDD) or once-daily dosing (ODD) schedule. Several unique characteristics of the aminoglycosides make ODD an attractive and possibly superior alternative to MDD. These include concentration-dependent bactericidal activity; postantibiotic effect, which allows continued efficacy even when serum concentrations fall below expected minimum inhibitory concentrations; decreased risk of adaptive resistance; and diminished accumulation in renal tubules and inner ear.

*Objective.* To assess the relative efficacy and toxicity of ODD, compared with MDD, of aminoglycosides among pediatric patients.

*Study Selection.* Randomized, controlled trials among children, evaluating the relative efficacy and toxicity of ODD versus MDD of aminoglycosides, with similar total daily doses in the compared arms, were selected.

*Data Sources.* PubMed (1966–2003) and Embase (1982–2003) databases, the Cochrane Controlled Trials Registry (2003), and references of eligible studies and pediatric review articles were searched.

*Data Extraction.* Study population characteristics and outcome data were extracted independently in duplicate, and consensus was reached on all items. The following outcome data were considered: (1) clinical or microbiologic failure, as defined in each study; (2) clinical failure; (3) microbiologic failure; (4) primary nephrotoxicity, ie, any rise in serum creatinine or decrease in creatinine clearance with thresholds as defined in each study; (5) secondary nephrotoxicity, ie, urinary excretion of proteins or phospholipids; and (6) ototoxicity based on pure tone audiometry, brainstem auditory evoked responses, or otoacoustic emissions for neonates and infants, vestibular testing, clinical impression, or any other method. All of the efficacy and toxicity outcomes were evaluated at the end of therapy.

*Results.* Identification of eligible studies and study characteristics: 24 eligible studies published between 1991 and 2003 were identified. Aminoglycosides were used in different clinical settings (neonatal intensive care unit: 6 studies; cystic fibrosis: 3 studies; cancer: 5 studies; urinary tract infections: 4 studies; diverse infectious in-

dications: 5 studies; pediatric intensive care unit: 1 study). Aminoglycosides used included amikacin (9 studies), gentamicin (11 studies), tobramycin (2 studies), netilmicin (2 studies), and tobramycin or netilmicin (1 study).

*Efficacy:* There was no significant difference between ODD and MDD in the clinical failure rate, microbiologic failure rate, and combined clinical or microbiologic failure rates, but trends favored ODD consistently. There was no between-study heterogeneity for any outcome. Efficacy analysis of all trials indicating either clinical or microbiologic failures demonstrated pooled failure rates of 4.6% (23 of 501 cases) in the ODD arms and 6.9% (34 of 494 cases) in the MDD arms. The fixed-effects risk ratio was 0.71 (95% confidence interval [CI]: 0.45–1.11). A statistically significant benefit was seen with ODD over MDD in trials using amikacin, whereas no statistical significance was seen in trials using other antibiotics. The pooled clinical failure rates were 6.7% (22 of 330 cases) in the ODD arms and 10.4% (34 of 327 cases) in the MDD arms. The fixed-effects risk ratio was 0.67 (95% CI: 0.42–1.07). The pooled microbiologic failure rates were 1.8% (5 of 283 cases) with ODD and 4.0% (11 of 275 cases) with MDD. The fixed-effects risk ratio was 0.51 (95% CI: 0.22–1.18).

*Nephrotoxicity:* There was no significant difference between ODD and MDD in the primary nephrotoxicity outcomes. Secondary nephrotoxicity outcomes were significantly better with ODD. The pooled primary nephrotoxicity rates were 1.6% (15 of 955 cases) in the ODD arms and 1.6% (15 of 923 cases) in the MDD arms. The fixed-effects risk ratio was 0.97 (95% CI: 0.55–1.69). The pooled secondary nephrotoxicity rates were 4.4% (3 of 69 cases) in the ODD arms and 15.9% (11 of 69 cases) in the MDD arms, suggesting a statistically significant superiority of ODD. The fixed-effects risk ratio was 0.33 (95% CI: 0.12–0.89). Results were consistent across types of clinical settings and aminoglycosides.

*Ototoxicity:* There was no significant difference between ODD and MDD in the primary ototoxicity outcomes. The pooled ototoxicity rates for studies that provided auditory testing results were 2.3% (10 of 436 cases) in the ODD arms and 2.0% (8 of 406 cases) in the MDD arms. The fixed-effects risk ratio was 1.06 (95% CI: 0.51–2.19). In studies that provided clinical vestibular function testing results, no toxicity was documented among 209 patients given ODD and 206 patients given MDD. Studies noting only the clinical impression of hearing impairment also failed to identify any toxicity (ODD: 114 cases; MDD: 114 cases).

*Subgroup and bias analyses:* We detected no statistically significant differences between ODD and MDD in any of the examined subgroups (neonatal intensive care unit, cystic fibrosis, cancer, or urinary tract infection), with respect to combined clinical or microbiologic failure

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outcomes, primary nephrotoxicity outcomes, or ototoxicity (based on auditory testing), when sufficient data were available. Moreover, there was no significant relationship between the effect size (risk ratio) and the trial size for any of the outcomes.

**Data Interpretation.** Clinical failures were uncommon in the pediatric trials, regardless of the regimen used. If anything, fewer clinical failures tended to occur with ODD. Moreover, we observed a trend toward decreased bacteriologic failures.

One meta-analysis of adult data suggested that ODD might reduce nephrotoxicity, whereas other meta-analyses showed nonsignificant trends or no difference in nephrotoxicity outcomes. In our meta-analysis, we were not able to show any reduction in the risk of primary nephrotoxicity outcomes with ODD. However, the event rate was much lower among children, compared with adults, and the secondary nephrotoxicity outcomes favored ODD.

Finally, although the 2 regimens seemed equivalent with respect to ototoxicity, reporting on ototoxicity outcomes was incomplete. Reassuringly, even in the trials that performed auditory testing, the rates of ototoxicity in the MDD arms were very low. These results were consistent with meta-analyses of adult data, which showed no difference in ototoxicity rates between ODD and MDD.

**Conclusions.** Although single trials have been small, the available randomized evidence supports the general adoption of ODD of aminoglycosides in pediatric clinical practice. This approach minimizes cost, simplifies administration, and provides similar or even potentially improved efficacy and safety, compared with MDD of these drugs. *Pediatrics* 2004;114:e111–e118. URL: <http://www.pediatrics.org/cgi/content/full/114/1/e111>; *aminoglycosides, once-daily, children, efficacy, toxicity*.

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ABBREVIATIONS. ODD, once-daily dosing; MDD, multiple daily dosing; CI, confidence interval.

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**A**minoglycosides are commonly used among children, infants, and neonates to treat serious Gram-negative infections.<sup>1,2</sup> There has been a long-standing debate regarding whether these drugs should be administered in multiple doses per day or with extended-interval dosing. Several unique characteristics of the aminoglycosides make once-daily dosing (ODD) an attractive and possibly superior alternative to multiple daily dosing (MDD). These features include concentration-dependent bactericidal activity, postantibiotic effect (which allows continued efficacy even when serum concentrations fall below expected minimal inhibitory concentrations), decreased risk of adaptive resistance, and diminished accumulation in renal tubules and the inner ear.<sup>3–8</sup> Conventional MDD for adult patients has been abandoned gradually in favor of ODD, and results from meta-analyses of randomized, clinical trials show diminished<sup>9</sup> or comparable<sup>10–16</sup> nephrotoxicity, better<sup>10–12,15</sup> or comparable<sup>9,13,14,16</sup> efficacy, and comparable ototoxicity<sup>9–11,15,16</sup> with ODD versus MDD among adults.

Recommendations regarding ODD of aminoglycosides for pediatric patients are not consistent in various pediatric drug reference manuals and major textbooks. In the most recent edition of *Nelson's Text-*

*book of Pediatrics*,<sup>17</sup> ODD is mentioned as an alternative for gentamicin and tobramycin. In the *Harriet Lane Handbook*,<sup>18</sup> only MDD regimens are mentioned. In the latest edition of the *British National Formulary*,<sup>2</sup> ODD is mentioned as being more convenient; however, it is recommended that expert advice be obtained regarding dosages and serum concentrations. Nonsystematic reviews increasingly support ODD.<sup>19</sup> Recent surveys of 500 US hospitals regarding extended-interval aminoglycoside administration demonstrated a 4-fold increase in its use and increased adoption for all age groups. However, the relatively low level of adoption among neonates (11%) and children (23%) suggests that this is not yet a standard practice,<sup>20</sup> and considerable uncertainty remains among clinicians regarding the merits and safety of ODD for children.

A large number of randomized trials have addressed the efficacy of ODD versus MDD of aminoglycosides for children. Many of them were published recently<sup>21–26</sup> or were not considered even in recent nonsystematic reviews.<sup>27–31</sup> The available randomized evidence may offer a rational basis for deciding on aminoglycoside dosing. However, given the sample size limitations, single trials are difficult to interpret. Here we systematically reviewed the available evidence on the comparative clinical and microbiologic efficacy, nephrotoxicity, and ototoxicity of ODD versus MDD aminoglycoside regimens and quantitatively synthesized the available data in a comprehensive meta-analysis.

## METHODS

### Search Strategy

We searched Embase and PubMed (from January 1966 to September 2003) using the following key words: (aminoglycoside, amikacin, gentamicin, tobramycin, netilmicin, isepamicin, kanamycin, or sisomicin) and (extended interval aminoglycoside administration, EIAA, extended interval dosing, extended interval, single daily, single dose, once a day, once daily, once-daily, once, or daily) and (children, child, childhood, pediatric, newborn, neonate, infant, or infantile). We also searched the Cochrane Controlled Trials Registry (last search, September 2003). Reference lists of the eligible articles and pertinent reviews were also scrutinized for potential relevant, randomized, controlled trials.

### Selection Criteria

We included only randomized, controlled trials in which ODD was compared with MDD administration with similar total daily doses of the aminoglycoside. We allowed up to 25% dissimilarity in average daily doses between the compared arms. We considered only trials involving pediatric patients (upper age limit: 20 years) and trials involving both adults and children that provided separate data for the pediatric population. We included only studies with parenteral (intravenous or intramuscular) administration of aminoglycosides.

### Data Extracted and Outcomes

From each study we extracted the following data: author, year of publication, patient age range, clinical setting, aminoglycoside type, total daily dose, dosing intervals in the MDD arm, concurrent use of other antibiotics, definitions of clinical and bacteriologic failure, nephrotoxicity and ototoxicity, number of randomized patients per arm, time point for outcome evaluation, and events per arm for efficacy and toxicity outcomes. We also noted whether information on the mode of randomization, allocation concealment, and blinding was presented.

We considered the following outcomes: 1) clinical or microbiologic failure, as defined in each study (when both were available, clinical failure data were preferred over microbiologic failure data); 2) clinical failure; 3) microbiologic failure; 4) primary neph-

rotoxicity outcome, ie, any increase in serum creatinine levels or decrease in creatinine clearance, with thresholds as defined in each study; 5) secondary nephrotoxicity outcomes, ie, urinary excretion of proteins (retinol-binding protein,  $\beta_2$ -microglobulin, Clara cell protein [P1], microalbumin, *N*-acetyl- $\beta$ -D-glucosaminidase, alkaline phosphatase, alanine aminopeptidase, or  $\gamma$ -glutamyltransferase) or phospholipids; and 6) ototoxicity, based on pure-tone audiometry, brainstem auditory evoked responses, or otoacoustic emissions for neonates and infants, vestibular testing, clinical impressions, or any method. All of the efficacy and toxicity outcomes were evaluated at the end of therapy. When no data were available for the end of therapy, we used data for the time point closest to the end of therapy. All data were extracted independently in duplicate. Discrepancies were resolved by review with a third investigator, and consensus was reached for all items.

### Statistical Analyses

We report pooled estimates of efficacy and toxicity outcomes. Study-specific risk ratios were used as the measure of choice. Between-study heterogeneity in risk ratios was appraised with the *Q* statistic.<sup>32</sup> Between-study heterogeneity means that the differences in the results of various studies are not attributable to chance alone. The *Q* test is based on the  $\chi^2$  distribution, and it provides a measure of the sum of the squared differences between the results observed and the results expected in each study, under the assumption that each study estimates the same treatment effect. In the absence of between-study heterogeneity, risk ratios were synthesized across studies with fixed-effects models.<sup>33</sup> Fixed-effects models were also more appropriate in this meta-analysis, because for most studies and outcomes the number of events was either 0 or very small. For studies with 0 events, risk ratios were entered in the calculations by adding 0.5 to the cells of the  $2 \times 2$  table. Fixed-effects analyses are robust with respect to 0 counts and small numbers. Subgroup analyses were performed according to the type of clinical setting and the type of aminoglycoside. Effect sizes in subgroups were compared by using general variance models. Finally, we examined whether larger trials differed from smaller trials in their results, using the test described by Begg and Mazumdar,<sup>34</sup> which examines the  $\tau$  rank correlation between the natural logarithm of the risk ratio and the weight of a study. Analyses were performed with SPSS 11.0 (SPSS Inc, Chicago, IL), StatXact 3.0 (Cytel Corp, Boston, MA), and Meta-analyst (Joseph Lau, Boston, MA) software. All *P* values were 2-tailed.

## RESULTS

### Identification of Eligible Studies and Study Characteristics

Twenty-four eligible studies<sup>21–31,35–47</sup> published between 1991 and 2003 were identified (Table 1). Aminoglycosides were used in different clinical settings (neonatal intensive care unit: 6 studies; cystic fibrosis: 3 studies; cancer: 5 studies; urinary tract infections: 4 studies; diverse infectious indications: 5 studies; pediatric intensive care unit: 1 study).

Aminoglycosides used in the eligible trials included amikacin (9 studies), gentamicin (11 studies), tobramycin (2 studies), netilmicin (2 studies), and tobramycin or netilmicin (1 study) (Table 1). The dosing varied among studies (amikacin 15–20 mg/kg per day; gentamicin 4–7.5 mg/kg per day; tobramycin 8–15 mg/kg per day; netilmicin 5–10 mg/kg per day). Eighteen trials used exactly the same aminoglycoside dose in the ODD arm and in the MDD arm. However, in 5 cases<sup>21,23,27,28,47</sup> slightly higher aminoglycoside dose was used in the MDD arm; and in 1 case<sup>36</sup> a slightly lower dose was used in the MDD arm. Most of the children included in the meta-analysis received short-term aminoglycosides (up to 10 days' duration), although some children in at least 11 trials<sup>22,24,27,29,36–38,42,44–46</sup> were treated for over 10 days.

In 20 trials additional antibiotics were concurrently administered to patients in both arms. In 4 of them concurrently administered antibiotics were sys-

tematically different in the 2 arms. These trials were excluded from all efficacy analyses.

Almost all trials were performed in single countries (United States: 3 studies; Mexico: 1 study; Europe: 5 studies; Australia: 2 studies; Israel: 2 studies; Africa: 5 studies; Asia: 4 studies). There were only 2 international trials.<sup>36,38</sup> The largest study considered 412 patient-episodes,<sup>38</sup> and only 7 trials<sup>22,23,36–38,45,47</sup> included >100 children (or patient-episodes).

The exact definitions of clinical failure, bacteriologic failure, nephrotoxicity, and ototoxicity in each study are detailed in appendices available upon request, along with the number of events per arm. Of the 24 eligible trials, 6 studies<sup>21,29,31,37,42,45</sup> reported in detail the mode of randomization and 3 studies<sup>22,36,41</sup> reported enough details of designs that ensured allocation concealment. Two studies<sup>25,28</sup> were double-blind, 6 studies<sup>22,30,36–39</sup> were stated to be open-label, and 16 studies did not report on blinding status.

### Efficacy

Efficacy analysis of all trials<sup>23,24,26,30,31,37,39,40,43–47</sup> indicating either clinical or microbiologic failures demonstrated pooled failure rates of 4.6% (23 of 501 cases) in the ODD arms and 6.9% (34 of 494 cases) in the MDD arms (Table 2). The fixed-effects risk ratio was 0.71 (95% confidence interval [CI]: 0.45–1.11; *P* = .13) (Fig 1), and there was no significant between-study heterogeneity. There was a suggestion of a significant benefit with ODD versus MDD in trials using amikacin, whereas this was not observed for trials using other antibiotics (Table 2).

The pooled clinical failure rates were 6.7% (22 of 330 cases) in the ODD arms and 10.4% (34 of 327 cases) in the MDD arms (Table 2). The fixed-effects risk ratio was 0.67 (95% CI: 0.42–1.07; *P* = .09). There was no between-study heterogeneity. The majority of clinical failures occurred in 2 trials,<sup>31,45</sup> ie, 1 trial involving critically ill children in the pediatric intensive care unit of a South African university hospital<sup>45</sup> and 1 trial involving children 1 month to 8 years of age with suspected or proven severe bacterial infections in a university hospital in Zimbabwe.<sup>31</sup> In the other 8 trials<sup>24,26,37,39,40,43,44,46</sup> with pertinent data, clinical failure rates ranged from 0 to 11% in the ODD arms and from 0 to 10% in the MDD arms and there was no major difference in the compared regimens.

The pooled microbiologic failure rates were 1.8% (5 of 283 cases) with ODD and 4.0% (11 of 275 cases) with MDD (Table 2). The fixed-effects risk ratio was 0.51 (95% CI: 0.22–1.18; *P* = .1). There was no between-study heterogeneity.

### Nephrotoxicity

The pooled primary nephrotoxicity outcome rates were 1.6% (15 of 955 cases) in the ODD arms and 1.6% (15 of 923 cases) in the MDD arms (Table 3). The fixed-effects risk ratio was 0.97 (95% CI: 0.55–1.69; *P* = .90) (Fig 2). The pooled secondary nephrotoxicity outcome rates were 4.4% (3 of 69 cases) in the ODD arms and 15.9% (11 of 69 cases) in the MDD arms (Table 3), suggesting a statistically significant superiority of ODD. The fixed-effects risk ratio was 0.33

**TABLE 1.** Characteristics of Eligible Studies

Author (Year)	Setting	Mean Age (ODD vs MDD)	Aminoglycoside, Total Daily Dose, and MDD Schedule	Other Antibiotics	Outcome Data (Sample Size Analyzed)
Agarwal et al (2002) <sup>21</sup>	NICU	<7 d	Gentamicin, 4 mg/kg, BID*	AMP (all arms)	AO (41)
Chotigeat et al (2001) <sup>24</sup>	NICU	<7 d	Gentamicin, 4–5 mg/kg, BID	β-Lactams (all arms)	CE (54)
Hayani et al (1997) <sup>41</sup>	NICU	<24 h	Gentamicin, 5 mg/kg, BID	AMP (all arms)	PN (26), SN (26)
Kotze et al (1999) <sup>42</sup>	NICU	<5 d	Amikacin, 15 mg/kg, BID	PEN G (all arms)	AO (40)
Krishnan and George (1997) <sup>28</sup>	NICU	<4 d	Gentamicin, 4 mg/kg, BID*	β-Lactams (all arms)	PN (18)
Langhendries et al (1993) <sup>44</sup>	NICU	<2 d	Amikacin, 15 mg/kg, BID	AMP (all arms)	CE (22), PN (22), SN (22), AO (22)
Heininger et al (1993) <sup>27</sup>	CF	NS	Tobramycin, 8–10 mg/kg, TID, or netilmicin, 8–10 mg/kg, TID*	CFZ or PIP (all arms)	PN (44), CO (44)
Master et al (2001) <sup>25</sup>	CF	14 vs 16 y	Tobramycin, 9 mg/kg, TID	CFZ (TID arm only)	PN (44), SN (44), AO (44)
Vic et al (1998) <sup>46</sup>	CF	Range: 5.6–19.3 y	Tobramycin, 15 mg/kg, TID	CFZ (all arms)	CE (22), PN (22), SN (22), AO (19)
Ariffin et al (2001) <sup>22</sup>	Cancer	5.9 vs 6.2 y	Amikacin, 15 mg/kg, TID	CTX (ODD), CFZ (TID)	PN (176), CO (176)
Calandra et al (1993) <sup>36</sup>	Cancer	NS	Amikacin, 20 mg/kg, TID*	CTX (ODD), CFZ (TID)	PN (239), AO (49), VO (239)
Charnas et al (1997) <sup>38</sup>	Cancer	Range: 1–17 y	Amikacin, 20 mg/kg, TID	CTX (ODD), CFZ (TID)	PN (412), AO (213)
Krivoy et al (1998) <sup>43</sup>	Cancer	9.2 vs 5.1 y	Amikacin, 20 mg/kg, BID	PIP (all arms)	CE (23)
Solorzano-Santos et al (1996) <sup>29</sup>	Cancer	NS	Amikacin, 20 mg/kg, TID	CARB (all arms)	PN (50)
Carapetis et al (2001) <sup>37</sup>	UTI	NS	Gentamicin, 7.5, 6, or 4.5 mg/kg,† TID	No	CE (179), ME (119), PN (116), AO (72)
Chong et al (2003) <sup>23</sup>	UTI	0.9 vs 0.9 y	Gentamicin, 5 mg/kg, TID*	No	ME (170), PN (172), AO (172)
Tapaneya-Olarn et al (1999) <sup>30</sup>	UTI	2.0 vs 0.8 y	Gentamicin, 4.5 mg/kg, TID	No	ME (24), PN (24), SN (24)
Vigano et al (1992) <sup>47</sup>	UTI	2.0 vs 1.6 y	Netilmicin, 5 mg/kg, TID*	No	ME (144), PN (144), AO (32)
Bass et al (1998) <sup>35</sup>	ID	8.9 vs 5.7 years	Gentamicin, 7.5 mg/kg, TID	Yes (NS)	PN (48), AO (48)
Elhanan et al (1995) <sup>39</sup>	ID	6.6 vs 4.7 y	Gentamicin, 4.5 mg/kg, TID	AMP and/or METRO (all arms)	CE (50), ME (23), PN (50), AO (50)
Forsyth et al (1997) <sup>40</sup>	ID	7.5 vs 7.5 y	Amikacin, 15 mg/kg, BID	Various (all arms)	CE (49), PN (53), AO (40)
Uijtendaal et al (2001) <sup>26</sup>	ID	3.7 vs 3.6 y	Gentamicin, 5 mg/kg, TID or BID	β-Lactams (all arms)	CE (52), PN (40), CO (52)
Were et al (1997) <sup>31</sup>	ID	NS	Gentamicin, 6 mg/kg, TID	β-Lactams (all arms)	CE (74), ME (22), PN (46)
Marik et al (1991) <sup>45</sup>	PICU	0.4 vs 0.4 y	Amikacin, 20 or 15 mg/kg,‡ BID	AMP, CFX, or CFZ (all arms)	CE (132), ME (56), PN (132), AO (132)

NICU: neonatal intensive care unit; ID: infectious diseases; UTI: urinary tract infection; CF: cystic fibrosis patients with pulmonary exacerbations; PICU: pediatric intensive care unit; BID: dosing two times a day; TID: dosing three times a day; NS: not specified; AMP: ampicillin; PEN G: penicillin G; CFZ: ceftazidime; PIP: piperacillin; CTX: ceftriaxone; CARB: carbenicillin; METRO: metronidazole; CFX: cefotaxime; AO: auditory ototoxicity; CE: clinical efficacy; ME: microbiologic efficacy; PN: primary nephrotoxicity; SN: secondary nephrotoxicity; CO: clinical impression of ototoxicity; VO: vestibular ototoxicity.

\* Total daily dose in the MDD arm was slightly different from the ODD dose given in the table. In the MDD arm, Agarwal et al<sup>21</sup> used 5 mg/kg per day gentamicin, Krishnan and George<sup>28</sup> used 5 mg/kg per day gentamicin, Heininger et al<sup>27</sup> used 9 to 12 mg/kg per day tobramycin or netilmicin, Calandra et al<sup>36</sup> used 19.5 mg/kg per day amikacin, Chong et al<sup>23</sup> used 6 mg/kg per day gentamicin, and Vigano et al<sup>47</sup> used 6 mg/kg per day netilmicin.

† 7.5 mg/kg per day for <5 years, 6 mg/kg per day for 5 to 10 years, and 4.5 mg/kg per day for >10 years.

‡ 20 mg/kg per day for <1 year and 15 mg/kg per day for >1 year. A loading dose was given before the maintenance dose (≤1 year: 25 mg/kg; >1 year: 20 mg/kg).

(95% CI: 0.12–0.89;  $P = .03$ ). Results were consistent across types of clinical settings and aminoglycosides.

### Ototoxicity

The pooled ototoxicity rates for studies that provided auditory testing results<sup>21,23,25,35–40,42,44,46,47</sup> were 2.3% (10 of 436 cases) in the ODD arms and 2.0% (8 of 406 cases) in the MDD arms. The fixed-effects risk ratio was 1.06 (95% CI: 0.51–2.19;  $P = .92$ ) (Table 3). In studies that provided clinical vestibular

function testing results,<sup>22,36</sup> no toxicity was documented among 209 patients given ODD and 206 patients given MDD (Table 3). Studies noting only the clinical impression of hearing impairment<sup>26,27,45</sup> also failed to identify any toxicity (ODD:  $n = 114$ ; MDD:  $n = 114$ ) (Table 3).

### Subgroup and Bias Analyses

We detected no statistically significant differences between ODD and MDD, in any of the examined

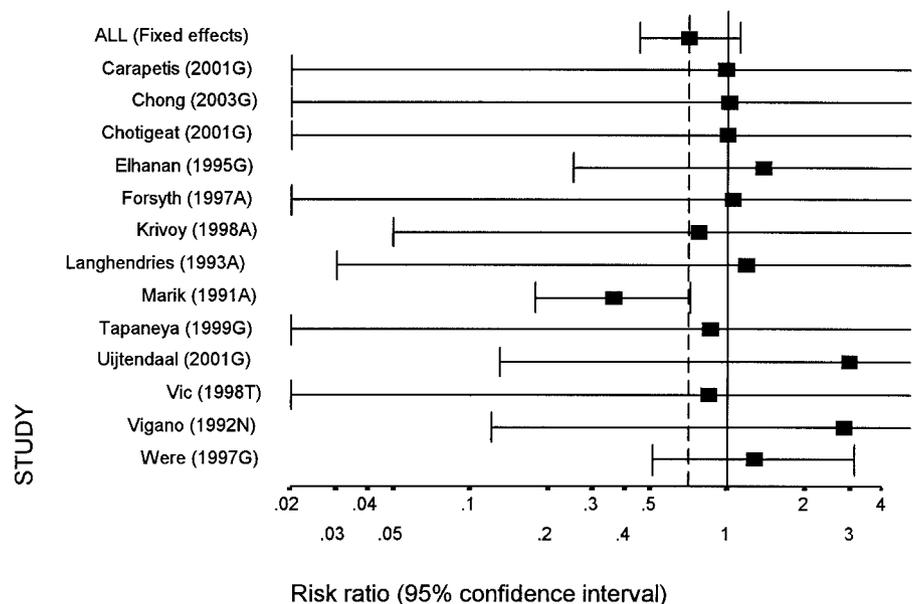
**TABLE 2.** Efficacy Outcome Data

Outcome (Studies)	Events/Total* (%)		Risk Ratio (95% CI)
	ODD	MDD	
Combined clinical or microbiologic failure ( <i>n</i> = 13)	23/501 (5)	34/494 (7)	0.71 (0.45–1.11)
Per clinical setting			
NICU ( <i>n</i> = 2) <sup>24,44</sup>	0/37 (0)	0/39 (0)	NE
CF ( <i>n</i> = 1) <sup>46</sup>	0/12 (0)	0/10 (0)	NE
Cancer ( <i>n</i> = 1) <sup>43</sup>	1/13 (8)	1/10 (10)	NE
UTI ( <i>n</i> = 4) <sup>23,30,37,47</sup>	1/261 (0)	0/256 (0)	1.43 (0.24–8.43)
Others ( <i>n</i> = 5) <sup>26,31,39,40,45</sup>	21/178 (12)	33/179 (18)	0.65 (0.40–1.06)
Per aminoglycoside type			
Gentamicin ( <i>n</i> = 7) <sup>23,24,26,30,31,37,39</sup>	12/301 (4)	9/302 (3)	1.32 (0.64–2.70)
Amikacin ( <i>n</i> = 4) <sup>40,43–45</sup>	10/114 (9)	25/112 (22)	0.41 (0.22–0.77)
Tobramycin or netilmicin ( <i>n</i> = 2) <sup>46,47</sup>	1/86 (1)	0/80 (0)	1.82 (0.17–19.21)
Clinical failure ( <i>n</i> = 10) <sup>24,26,31,37,39,40,43–46</sup>	22/330 (7)	34/327 (10)	0.67 (0.42–1.07)
Microbiologic failure ( <i>n</i> = 7) <sup>23,30,31,37,39,45,47</sup>	5/283 (2)	11/275 (4)	0.51 (0.22–1.18)

NICU: neonatal intensive care unit; CF: cystic fibrosis; UTI: urinary tract infections; Others: infectious diseases occurring in diverse settings; NE: not estimable (zero counts or very small numbers).

\* Total refers to patients or episodes.

**Fig 1.** Meta-analysis of combined clinical or microbiologic failures with ODD versus MDD. Each study is indicated by author name, year, type of aminoglycoside (A: amikacin; G: gentamicin; T: tobramycin; N: netilmicin), point estimate, and 95% CI for the risk ratio. Also shown is the pooled fixed-effects risk ratio. The continuous vertical line passes through the risk ratio of 1 (no effect), and the discontinuous vertical line passes through the summary estimate. The upper 95% CI values are not shown for many studies, because they are very high, but they can be inferred from the lower 95% CI values (the upper and lower CI values are symmetric around the point estimate).



subgroups (neonatal intensive care unit, cystic fibrosis, cancer, or urinary tract infection), with respect to combined clinical or microbiologic failure outcomes, primary nephrotoxicity outcomes, or ototoxicity (based on auditory testing) (Table 3), when sufficient data were available. There was no significant relationship between the effect size (risk ratio) and the trial size for any of the outcomes (data not shown).

### DISCUSSION

This meta-analysis indicates that, among children, ODD of aminoglycosides demonstrates a trend for better efficacy and shows similar low rates of nephrotoxicity and ototoxicity, compared with MDD. Secondary nephrotoxicity outcomes were even significantly improved with ODD regimens.

The clinical efficacy results of this meta-analysis are consistent with the results of several meta-analyses that addressed the same question among adults.<sup>9–16,48</sup> Those meta-analyses showed no difference in clinical efficacy between ODD and MDD<sup>9,13,14,16</sup> or even better

efficacy with ODD.<sup>10–12,15</sup> With the exception of severely ill children, clinical failures were uncommon in the trials we analyzed, regardless of the regimen used. Moreover, clinical failures tended to be less frequent with ODD administration. Also, we observed a trend toward fewer bacteriologic failures, which again was consistent with the results of adult meta-analyses that evaluated this outcome.<sup>10,11,14,15,48</sup>

One meta-analysis<sup>9</sup> of adult data suggested that ODD might reduce nephrotoxicity, whereas other meta-analyses<sup>10–15,48</sup> showed nonsignificant trends or no difference in nephrotoxicity outcomes. In our meta-analysis, we were not able to show any reduction in the risk of primary nephrotoxicity outcomes with ODD. However, the event rate was much lower among children, compared with adults. Although the overall rates were 5.5% vs 7.9% in the ODD versus MDD arms in a meta-analysis of adult data,<sup>9</sup> <2% of children exhibited nephrotoxicity in our meta-analysis. The majority of primary renal toxicity events were contributed by 2 trials,<sup>22,47</sup> and renal

**TABLE 3.** Toxicity Outcome Data

Outcome (Studies)	Events/Total* (%)		Risk Ratio (95% CI)
	ODD	MDD	
Primary nephrotoxicity outcome ( <i>n</i> = 20)	15/955† (2)	15/923† (2)	0.97 (0.55–1.69)
Per clinical setting			
NICU ( <i>n</i> = 3) <sup>28,41,44</sup>	0/30 (0)	0/36 (0)	NE
CF ( <i>n</i> = 3) <sup>25,27,46</sup>	0/56 (0)	0/54 (0)	NE
Cancer ( <i>n</i> = 4) <sup>22,29,36,38</sup>	12/442 (3)	11/435 (3)	1.05 (0.49–2.22)
UTI ( <i>n</i> = 4) <sup>23,30,37,47</sup>	3/235 (1)	4/221 (2)	0.76 (0.21–2.81)
Others ( <i>n</i> = 6) <sup>26,31,35,39,40,45</sup>	0/192 (0)	0/177 (0)	NE
Per aminoglycoside type			
Gentamicin ( <i>n</i> = 9) <sup>23,26,28,30,31,35,37,39,41</sup>	1/279 (0)	2/261 (1)	0.80 (0.25–2.58)
Amikacin ( <i>n</i> = 7) <sup>22,29,36,38,40,44,45</sup>	12/546 (2)	11/538 (2)	1.04 (0.51–2.13)
Tobramycin/netilmicin ( <i>n</i> = 4) <sup>25,27,46,47</sup>	2/130 (2)	2/124 (2)	0.95 (0.22–4.07)
Secondary nephrotoxicity outcome ( <i>n</i> = 5)	3/69 (4)	11/69 (16)	0.33 (0.12–0.89)
Per clinical setting			
NICU ( <i>n</i> = 2) <sup>41,44</sup>	0/22 (0)	0/27 (0)	NE
CF ( <i>n</i> = 2) <sup>25,46</sup>	1/35 (3)	6/31 (19)	0.21 (0.04–1.15)
UTI ( <i>n</i> = 1) <sup>30</sup>	2/13 (15)	5/11 (45)	0.34 (0.08–1.41)
Per aminoglycoside type			
Gentamicin ( <i>n</i> = 2) <sup>30,41</sup>	2/24 (8)	5/26 (19)	0.41 (0.11–1.52)
Amikacin ( <i>n</i> = 1) <sup>44</sup>	0/10 (0)	0/12 (0)	NE
Tobramycin/netilmicin ( <i>n</i> = 2) <sup>25,46</sup>	1/35 (3)	6/31 (19)	0.21 (0.04–1.15)
Ototoxicity on auditory testing ( <i>n</i> = 13)	10/436 (2)	8/406 (2)	1.06 (0.51–2.19)
Per clinical setting			
NICU ( <i>n</i> = 3) <sup>21,42,44</sup>	0/50 (0)	0/53 (0)	NE
CF ( <i>n</i> = 2) <sup>25,46</sup>	0/33 (0)	0/30 (0)	NE
Cancer ( <i>n</i> = 2) <sup>36,38</sup>	3/133 (2)	1/129 (1)	2.30 (0.35–15.23)
UTI ( <i>n</i> = 3) <sup>23,37,47</sup>	3/143 (2)	0/133 (0)	2.37 (0.38–14.89)
Others ( <i>n</i> = 3) <sup>35,39,40</sup>	4/77 (5)	7/61 (11)	0.55 (0.18–1.68)
Per aminoglycoside			
Gentamicin ( <i>n</i> = 5) <sup>21,23,35,37,39</sup>	3/200 (1)	2/183 (1)	1.13 (0.32–4.02)
Amikacin ( <i>n</i> = 5) <sup>36,38,40,42,44</sup>	5/183 (3)	6/181 (3)	0.87 (0.32–2.39)
Tobramycin/netilmicin ( <i>n</i> = 3) <sup>25,46,47</sup>	2/53 (4)	0/42 (0)	1.72 (0.25–11.85)
Ototoxicity on vestibular testing ( <i>n</i> = 2) <sup>22,36</sup>	0/209 (0)	0/206 (0)	NE
Ototoxicity on clinical impression ( <i>n</i> = 3) <sup>26,27,45</sup>	0/114 (0)	0/114 (0)	NE
Any ototoxicity ( <i>n</i> = 17) <sup>21–23,25–27,35–40,42,44–47‡</sup>	10/640 (2)	8/606 (1)	1.05 (0.53–2.08)

NICU: neonatal intensive care unit; CF: cystic fibrosis; UTI: urinary tract infections; Others: infectious diseases occurring in diverse setting; NE: not estimable (zero counts or very small numbers).

\* Total refers to patients or episodes.

† In the ODD group, 10 of 15 primary-nephrotoxicity cases were reversible and another was still within the normal range; in the MDD group, 2 of 15 were within the normal range.

‡ For Calandra et al,<sup>36</sup> where data with various definitions were available, we used the data for patients who also underwent pure-tone audiometry.

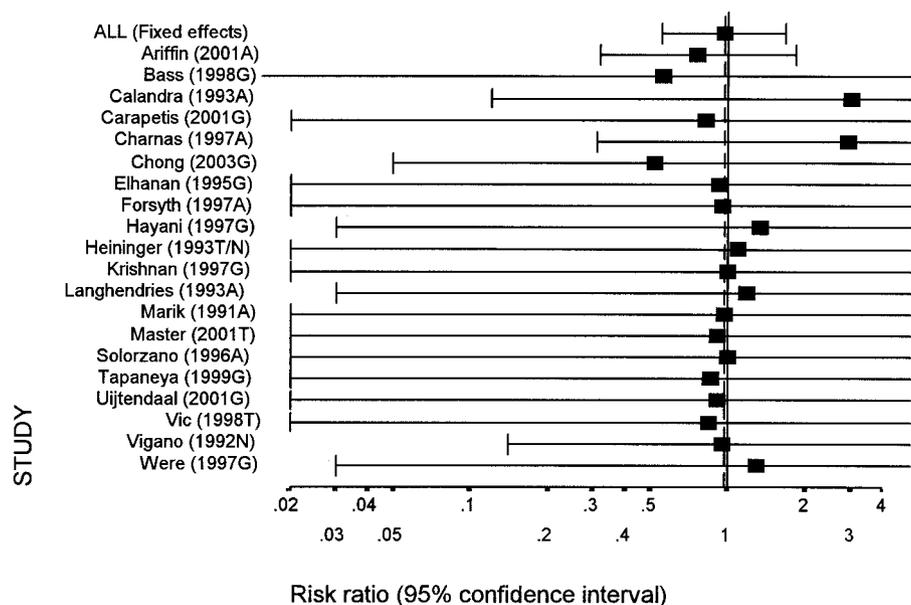
function deterioration was reversible during follow-up monitoring in both studies.

ODD of aminoglycosides offered a significant 70% reduction in relative risk for nephrotoxicity outcomes, as indicated by excretion of enzymes, proteins, or phospholipids. This finding is based on limited data, and outcomes may be too sensitive, not necessarily corresponding to clinically significant impairment of renal function. In the 5 trials that provided both primary and secondary nephrotoxicity data, none of the children who exhibited excretion of proteins, enzymes, or phospholipids developed significant increases in serum creatinine levels or significant decreases in creatinine clearance. Nevertheless, these indices provide complementary, reassuring information regarding the merits of ODD. Much controversy exists regarding the ideal method for measuring and defining renal function impairment attributable to aminoglycoside treatment, especially among neonates. Nephrotoxicity might be recognized only with difficulty, because subtle increases in serum creatinine levels would be superimposed on the physiologic postnatal decreases in serum creatinine levels.<sup>48</sup>

Although the 2 regimens seemed equivalent with respect to ototoxicity, reporting on ototoxicity outcomes was incomplete. Only 13 of the 24 eligible trials incorporated formal audiometric testing; another 4 trials evaluated ototoxicity on the basis of clinical impressions or vestibular testing, which are not sensitive methods for evaluating ear damage. Reassuringly, even in the trials that performed auditory testing, the rates of ototoxicity in the MDD arms were very low. These results were consistent with the findings of meta-analyses of adult data, which showed no difference in ototoxicity rates between ODD and MDD.<sup>10–13,15,16</sup>

Some limitations must be acknowledged. Selective reporting of outcome data was evident in this meta-analysis. Efficacy, nephrotoxicity, and ototoxicity outcome data were not available for all included trials. Moreover, some trials needed to be excluded from our analysis because no clinically meaningful information on the number of patients who experienced clinical or bacteriologic failures or toxicity was provided. The majority of the included trials were small, and some other small trials might have remained unpublished. Small differences in efficacy or

Fig 2. Meta-analysis of primary nephrotoxicity with ODD versus MDD. Each study is indicated by author name, year, type of aminoglycoside (A: amikacin; G: gentamicin; T: tobramycin; N: netilmicin), point estimate, and 95% CI for the risk ratio. Also shown is the pooled fixed-effects risk ratio. The continuous vertical line passes through the risk ratio of 1 (no effect), and the discontinuous vertical line passes through the summary estimate. The upper 95% CI values are not shown for many studies, because they are very high, but they can be inferred from the lower 95% CI values (the upper and lower CI values are symmetric around the point estimate).



toxicity might not have been evident. However, there was no statistically significant heterogeneity for any of the efficacy or toxicity outcomes studied and no clear differences between small and large trials, and the results of this meta-analysis were consistent with existing evidence from adult populations. The lack of detectable heterogeneity in these studies reflects the near-absence of ascertained toxic effects and treatment failures with aminoglycoside use among children in these study populations.

There was 1 pediatric cost-effectiveness analysis of ODD of aminoglycosides among infants >34 weeks of age, in neonatal intensive care units.<sup>9,49</sup> For short courses of aminoglycosides, the ODD regimen proved to be the better strategy, with superior drug performance and reduced hospital costs. Extended-interval administration of aminoglycosides requires less pharmacy preparation time and less nursing administration time. There is also a decreased need for serum gentamicin concentration monitoring for short (<72 hours) courses of aminoglycoside treatment. ODD may be a more suitable option for outpatient management and may also be more convenient for patients in developing countries, where aminoglycosides are administered mainly via the intramuscular route.<sup>28</sup>

Although a comparison of pharmacokinetic data for ODD versus MDD was beyond the scope of our meta-analysis, it is worth noting that 22 of the 23 randomized, controlled trials that had performed pharmacokinetic analyses showed that ODD achieved higher peak and lower trough levels, compared with MDD. Only 1 trial<sup>37</sup> showed high trough levels, above the desired levels, for 4% vs 0.7% of patients in the ODD versus MDD arms. However, the explanation for these high trough levels remained unclear, because the high trough levels were not correlated with high peak concentrations. On the basis of the available randomized evidence, we conclude that ODD should be preferred over MDD, because ODD minimizes costs and simplifies admin-

istration, with comparable or even potentially improved efficacy and safety profiles.

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