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) otoxicity 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 indications: 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 audiatory 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.
Aminoglycosides are commonly used among children, infants, and neonates to treat serious Gram-negative infections. 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 bacterial 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. Conventional MDD for adult patients has been abandoned gradually in favor of ODD, and results from meta-analyses of randomized, controlled trials show diminished nephrotoxicity, better or comparable efficacy, and comparable ototoxicity 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 Textbook of Pediatrics*, ODD is mentioned as an alternative for gentamicin and tobramycin. In the *Harriet Lane Handbook*, only MDD regimens are mentioned. In the latest edition of the *British National Formulary*, 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.

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, 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 or were not considered even in recent nonsystematic reviews. 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 sisomycin) and (extended interval aminoglycoside administration, ELAA, 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 parental (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 nephotoxicity outcomes; and 5) comparable efficacy, compared with MDD of the aminoglycoside. We considered clinical and microbiologic failures in children as our primary outcomes as these are the most relevant to the future management of children with serious infections.
RESULTS

Identification of Eligible Studies and Study Characteristics

Twenty-four eligible studies 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 slightly higher aminoglycoside dose was used in the MDD arm; and in 1 case 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 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 systematically 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. The largest study considered 412 patient-episodes and only 7 trials 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 reported the mode of randomization and 3 studies reported enough details of designs that ensured allocation concealment. Two studies were double-blind, 6 studies were open-label, and 16 studies did not report on blinding status.

Efficacy

Efficacy analysis of all trials indicated 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, ie, 1 trial involving critically ill children in the pediatric intensive care unit of a South African university hospital 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. In the other 8 trials, 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, suggesting a statistically significant superiority of ODD. The fixed-effects risk ratio was 0.33.
TABLE 1. Characteristics of Eligible Studies

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Setting</th>
<th>Mean Age (ODD vs MDD)</th>
<th>Aminoglycoside, Total Daily Dose, and MDD Schedule</th>
<th>Other Antibiotics</th>
<th>Outcome Data (Sample Size Analyzed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal et al (2002) ⁴¹</td>
<td>NICU</td>
<td>&lt;7 d</td>
<td>Gentamicin, 4 mg/kg, BID* Gentamicin, 4–5 mg/kg, BID</td>
<td>AMP (all arms)</td>
<td>AO (41) CE (54)</td>
</tr>
<tr>
<td>Chotigeat et al (2001) ⁴²</td>
<td>NICU</td>
<td>&lt;7 d</td>
<td>Gentamicin, 4–5 mg/kg, BID</td>
<td>β-Lactams (all arms)</td>
<td></td>
</tr>
<tr>
<td>Hayani et al (1997) ⁴³</td>
<td>NICU</td>
<td>&lt;24 h</td>
<td>Gentamicin, 5 mg/kg, BID</td>
<td>AMP (all arms)</td>
<td>PEN G (all arms) PN (26), SN (26) AO (40)</td>
</tr>
<tr>
<td>Kolze et al (1999) ⁴⁴</td>
<td>NICU</td>
<td>&lt;5 d</td>
<td>Amikacin, 15 mg/kg, BID</td>
<td>β-Lactams (all arms)</td>
<td>PN (18)</td>
</tr>
<tr>
<td>Krishnan and George (1997) ⁴⁵</td>
<td>NICU</td>
<td>&lt;4 d</td>
<td>Gentamicin, 4 mg/kg, BID*</td>
<td>AMP (all arms)</td>
<td></td>
</tr>
<tr>
<td>Langhendries et al (1993) ³⁷</td>
<td>NICU</td>
<td>&lt;2 d</td>
<td>Amikacin, 15 mg/kg, BID</td>
<td>AMP (all arms)</td>
<td>CE (22), PN (22), SN (22), AO (22)</td>
</tr>
<tr>
<td>Heining et al (1993) ⁴⁶</td>
<td>CF</td>
<td>NS</td>
<td>Tobramycin, 8–10 mg/kg, TID, or netilmicin, 8–10 mg/kg, TID*</td>
<td>CFZ or PIP (all arms)</td>
<td>PN (44), CO (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Master et al (2001) ⁴⁷</td>
<td>CF</td>
<td>14 vs 16 y</td>
<td>Tobramycin, 9 mg/kg, TID</td>
<td>CFZ (TID arm only)</td>
<td>PN (44), SN (44), AO (44)</td>
</tr>
<tr>
<td>Vic et al (1998) ⁴⁸</td>
<td>CF</td>
<td>Range: 5.6–19.3 y</td>
<td>Tobramycin, 15 mg/kg, TID</td>
<td>CFZ (all arms)</td>
<td>CE (22), PEN (22), SN (22), AO (19)</td>
</tr>
<tr>
<td>Ariffin et al (2001) ⁴⁹</td>
<td>Cancer</td>
<td>5.9 vs 6.2 y</td>
<td>Amikacin, 15 mg/kg, TID</td>
<td>CTX (ODD), CFZ (TID)</td>
<td>PN (176), CO (176)</td>
</tr>
<tr>
<td>Calandra et al (1993) ⁵⁰</td>
<td>Cancer</td>
<td>NS</td>
<td>Amikacin, 20 mg/kg, TID*</td>
<td>CTX (ODD), CFZ (TID)</td>
<td>PN (239), AO (49), VO (299)</td>
</tr>
<tr>
<td>Charnas et al (1997) ⁵¹</td>
<td>Cancer</td>
<td>Range: 1–17 y</td>
<td>Amikacin, 20 mg/kg, TID</td>
<td>CTX (ODD), CFZ (TID)</td>
<td>PN (412), AO (213)</td>
</tr>
<tr>
<td>Krivoy et al (1998) ⁵²</td>
<td>Cancer</td>
<td>9.2 vs 5.1 y</td>
<td>Amikacin, 20 mg/kg, BID</td>
<td>PIP (all arms)</td>
<td>CE (23) PN (50)</td>
</tr>
<tr>
<td>Solorzano-Santos et al (1996) ⁵³</td>
<td>NICU</td>
<td>NS</td>
<td>Amikacin, 20 mg/kg, BID</td>
<td>CARB (all arms)</td>
<td></td>
</tr>
<tr>
<td>Carapetis et al (2001) ⁵⁴</td>
<td>UTI</td>
<td>NS</td>
<td>Gentamicin, 7.5, 6, or 4.5 mg/kg,† TID</td>
<td>No</td>
<td>CE (179), ME (119), PN (116), AO (72)</td>
</tr>
<tr>
<td>Chong et al (2003) ⁵⁵</td>
<td>UTI</td>
<td>0.9 vs 0.9 y</td>
<td>Gentamicin, 5 mg/kg, TID*</td>
<td>No</td>
<td>ME (170), PN (172), AO (172)</td>
</tr>
<tr>
<td>Tapaney-Olarn et al (1999) ⁵⁶</td>
<td>UTI</td>
<td>2.0 vs 0.8 y</td>
<td>Gentamicin, 4.5 mg/kg, TID</td>
<td>No</td>
<td>ME (24), PN (24), SN (24)</td>
</tr>
<tr>
<td>Vigano et al (1992) ⁵⁷</td>
<td>UTI</td>
<td>2.0 vs 1.6 y</td>
<td>Netilmicin, 5 mg/kg, TID*</td>
<td>No</td>
<td>ME (144), PN (144), AO (32)</td>
</tr>
<tr>
<td>Bass et al (1998) ⁵⁸</td>
<td>ID</td>
<td>8.9 vs 5.7 years</td>
<td>Gentamicin, 7.5 mg/kg, TID</td>
<td>Yes (NS)</td>
<td>AMP and/or METRO (all arms)</td>
</tr>
<tr>
<td>Elhanan et al (1995) ⁵⁹</td>
<td>ID</td>
<td>6.6 vs 4.7 y</td>
<td>Gentamicin, 4.5 mg/kg, TID</td>
<td>Various (all arms)</td>
<td></td>
</tr>
<tr>
<td>Forsyth et al (1997) ⁶⁰</td>
<td>ID</td>
<td>7.5 vs 7.5 y</td>
<td>Amikacin, 15 mg/kg, BID</td>
<td>β-Lactams (all arms)</td>
<td>CE (52), PN (40), CO (52)</td>
</tr>
<tr>
<td>Uijtendaal et al (2001) ⁶¹</td>
<td>ID</td>
<td>3.7 vs 3.6 y</td>
<td>Gentamicin, 5 mg/kg, TID</td>
<td>β-Lactams (all arms)</td>
<td>CE (74), ME (22), PN (46)</td>
</tr>
<tr>
<td>Were et al (1997) ⁶²</td>
<td>ID</td>
<td>NS</td>
<td>Gentamicin, 6 mg/kg, TID</td>
<td>β-Lactams (all arms)</td>
<td>CE (132), ME (56), PN (132), AO (132)</td>
</tr>
<tr>
<td>Marik et al (1991) ⁶³</td>
<td>PICU</td>
<td>0.4 vs 0.4 y</td>
<td>Amikacin, 20 or 15 mg/kg,‡ BID</td>
<td>AMP, CFX, or CFZ (all arms)</td>
<td></td>
</tr>
</tbody>
</table>

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: cefazidime; PIP: piperacillin; CTX: ceftriaxone; CARB: carbencillin; 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 ²¹ used 5 mg/kg per day gentamicin, Krishnan and George ³⁸ used 5 mg/kg per day gentamicin, Heining et al ²⁷ used 9 to 12 mg/kg per day tobramycin or netilmicin, Calandra et al ³⁶ used 19.5 mg/kg per day amikacin, Chong et al ²³ used 6 mg/kg per day gentamicin, and Vigano et al ²⁷ 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 ²¹,²³,²⁵,³⁵–⁴⁰,⁴²,⁴⁴,⁴⁶,⁴⁷ 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, ²²,³⁶ 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 ²⁶,²⁷,⁴⁵ 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
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.9–16,48 Those meta-analyses showed no difference in clinical efficacy between ODD and MDD9,13,14,16 or even better efficacy with ODD.10–12,15 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 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,9/2% of children exhibited nephrotoxicity in our meta-analysis. The majority of primary renal toxicity events were contributed by 2 trials,22,47 and renal

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**TABLE 2. Efficacy Outcome Data**

<table>
<thead>
<tr>
<th>Outcome (Studies)</th>
<th>Events/Total* (%)</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined clinical or microbiologic failure (n = 13)</td>
<td>23/501 (5)</td>
<td>0.71 (0.45–1.11)</td>
</tr>
<tr>
<td>Per clinical setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU (n = 2)</td>
<td>0/37 (0)</td>
<td>NE</td>
</tr>
<tr>
<td>CF (n = 1)</td>
<td>0/12 (0)</td>
<td>NE</td>
</tr>
<tr>
<td>Cancer (n = 1)</td>
<td>1/13 (8)</td>
<td>NE</td>
</tr>
<tr>
<td>UTI (n = 4)</td>
<td>1/261 (0)</td>
<td>1.43 (0.24–8.43)</td>
</tr>
<tr>
<td>Others (n = 5)</td>
<td>21/178 (12)</td>
<td>0.65 (0.40–1.06)</td>
</tr>
<tr>
<td>Per aminoglycoside type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin (n = 7)</td>
<td>12/301 (4)</td>
<td>1.32 (0.64–2.70)</td>
</tr>
<tr>
<td>Amikacin (n = 4)</td>
<td>10/114 (9)</td>
<td>0.41 (0.22–0.77)</td>
</tr>
<tr>
<td>Tobramycin or netilmicin (n = 2)</td>
<td>1/86 (1)</td>
<td>1.82 (0.17–19.21)</td>
</tr>
<tr>
<td>Clinical failure (n = 10)</td>
<td>22/330 (7)</td>
<td>0.67 (0.42–1.07)</td>
</tr>
<tr>
<td>Microbiologic failure (n = 7)</td>
<td>5/283 (2)</td>
<td>0.51 (0.22–1.18)</td>
</tr>
</tbody>
</table>

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.

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**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).
function deterioration was reversible following 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.

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.

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...
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.9,48 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.28

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 trial37 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 administration, with comparable or even potentially improved efficacy and safety profiles.

**REFERENCES**


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