# Single Daily Dosing of Aminoglycosides in Immunocompromised Adults: A Systematic Review

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**We examined the efficacy and toxicity of single daily dosing (SDD) of aminoglycosides for febrile, immunocompromised adults by systematically reviewing four randomized, controlled trials of SDD vs. standard dosing regimens. We assessed the methodological quality of each study and extracted data pertaining to efficacy and toxicity outcomes. Pooled risk ratios for the efficacy outcomes were bacteriologic cure, 1.00 (95% confidence interval [CI], 0.86–1.16); clinical cure, 0.97 (95% CI, 0.91–1.05); and mortality, 0.93 (95% CI, 0.62–1.41). The pooled nephrotoxicity risk ratio was 0.78 (95% CI, 0.31–1.94). Only one study assessed ototoxicity. Although our study was limited by the small number of trials available for review, the results suggest that SDD of aminoglycosides may be efficacious for febrile, immunocompromised patients. Additional studies are necessary for more precise quantification of the mortality and toxicity risk ratios.**

Aminoglycoside antibiotics have traditionally had an adjunctive, synergistic role in the empirical treatment of febrile, neutropenic patients [1–3]. Consensus guidelines and proposed algorithms for these empirical regimens have included recommendations that aminoglycosides be combined with $\beta$-lactam antibiotics to provide adequate coverage for infections due to $\beta$-lactam–resistant gram-negative organisms [4]. Specific treatment guidelines for febrile neutropenic patients recommend early combination therapy with an aminoglycoside for patients with severe granulocytopenia (granulocyte count, $<100/mm^3$), persistent granulocytopenia (duration, >7 days), and/or the presence of a clinical focus of infection [5]. However, the reported efficacy of $\beta$-lactam monotherapy, which is equal to that of synergistic antibiotic combinations, and concern regarding the toxicity of the combination regimens have limited the widespread use of aminoglycosides in this population [6].

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The results of recent studies suggest that single daily dosing (SDD) of aminoglycosides (also known as once-daily aminoglycoside therapy), as opposed to standard dosing regimens, may obviate many of these concerns [7–9]. Meta-analyses have demonstrated equivalent efficacy and a trend towards reduced toxicity with SDD regimens [10–12]. This novel method of drug administration results in higher peak serum concentrations relative to conventional dosing strategies and in improved efficacy by optimizing aminoglycoside concentration-dependent bactericidal activity [7, 8]. Moreover, because of extended dosing intervals and reduced drug accumulation, SDD regimens may result in reduced ototoxicity and nephrotoxicity [7, 9]. The convenience of SDD may also facilitate the outpatient treatment of febrile neutropenic patients at low risk for infection [13, 14].

However, in the previously published meta-analyses, both immunocompetent and immunocompromised patients were examined [11, 12], or only immunocompetent patients were examined [10]. It is unlikely that the results are applicable to the immunocompromised patient population, as there is a clear relationship between the severity of neutropenia and the incidence of infection [15]. Of the randomized, controlled trials that have addressed SDD in immunocompromised patients, there has been one large study in which microbiological cure was not examined and clinical cure and toxicity estimates were not conclusive [16].

We combined the smaller randomized trials with this larger study in a meta-analysis to systematically review the current evidence supporting the SDD of aminoglycosides in immunocompromised patients [17–19]). We examined both efficacy and toxicity outcomes for SDD and for the standard dosing regimen.

## Methods

The methodology used for this review has been reported previously [10].

*Data* sources. To identify relevant studies, we used MEDLINE to search the literature published from 1966 to October 1994; the key words for the search were *aminoglycosides, drug administration schedule,* and *adult.* In addition, we manually searched selected infectious diseases journals for relevant articles published from November 1994 to April 1995. Two of us (R.H. and T.T.D.) independently reviewed the literature

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searches and identified the relevant studies. Further articles were identified from the bibliographies of review articles and position papers and the bibliographies of the selected articles. We also asked the primary investigators in the studies we identified to forward any potentially relevant articles that we might have missed. All articles that either reviewer identified as relevant were retrieved.

*Study selection.* We included studies in our review if the following criteria were met: (1) the study was a randomized controlled trial; (2) an intravenous SDD regimen was compared with a standard aminoglycoside dosing regimen; (3) the study included immunocompromised adults with infections (immunocompromised patients were defined as those with a malignancy or febrile neutropenia, and those who had received surgical prophylaxis were excluded); (4) any of the outcomes, including bacteriologic or clinical cure, mortality, or nephrotoxicity or ototoxicity, were measured; and (5) <50% of the study sample had lower urinary tract infections. The two reviewers examined all potentially relevant articles for adherence to these selection criteria.

*Methodological quality.* The two independent reviewers applied a standardized, weighted methodological-quality grading system to all studies that met the inclusion criteria; scores ranged between 0 and 1.0. Kappa, which measures the agreement between observers beyond that expected by chance [20], was calculated for study selection and methodological quality criteria, and disagreement was resolved by consensus.

*Data extraction.* The outcome measures assessed were bacteriologic cure (as defined by the investigators in a particular study), clinical cure (as defined by the investigators in a particular study), mortality (all causes), nephrotoxicity (defined as an increase in the serum creatinine level of >35–45 μmol/L during the study period [21]), and ototoxicity (defined as an audiometrically determined 15-dB change in hearing at any frequency).

The two independent reviewers extracted the data, and disagreements pertaining to outcome data were resolved by consensus. When information regarding either the methodological quality criteria or the outcome measures was not explicitly provided in the published report, the primary author of the selected article was asked to supply the missing information.

**Table 1.** Characteristics of studies of single daily dosing of aminoglycosides in immunocompromised adults.

| Reference | Study population | Control population | Aminoglycoside regimen | Concomitant therapy | Principal site of infection | Outcomes |
|---|---|---|---|---|---|---|
| [16] | 283 Patients; mean age, 29.5 y; febrile neutropenic; 56%, granulocytes <100/mm$^3$*; 71%, hematologic malignancy | 256 Patients; mean age, 28 y; febrile neutropenic; 54%, granulocytes <100/mm$^3$; 71%, hematologic malignancy | Amikacin, 20 mg/kg q.d. vs. 6.6 mg/kg q8h | Ceftriaxone, 2 g q.d. (study population) or ceftazidime, 2 g q8h (control population) | Miscellaneous (oral cavity and pharynx, upper and lower respiratory tracts, skin and soft tissues, other sites) | Clinical cure, mortality, nephrotoxicity and ototoxicity |
| [17] | 47 Patients; mean age, 55 y; febrile neutropenic; 57%, neutrophils <0.5 × 10$^9$/L; 85%, hematologic malignancy | 45 Patients; mean age, 47 y; febrile neutropenic; 60%, neutrophils <0.5 × 10$^9$/L; 91%, hematologic malignancy | Tobramycin, 5 mg/kg q.d. vs. 1.5 mg/kg q8h | Ceftriaxone, 2 g q.d. (study population) or azlocillin, 4 g q6h (control population) and flucloxacillin, 1–2 g q4h (17 patients in each group) | Septicemia, miscellaneous (skin and soft tissues, gastrointestinal tract, upper and lower respiratory tracts, other sites) | Bacteriologic cure, clinical cure, mortality |
| [18] | 61 Patients; mean age, 48 y; febrile neutropenic; 84%, hematologic malignancy | 55 Patients; mean age, 50 y; febrile neuropenic; 82%, hematologic malignancy | Netilmicin, 6 mg/kg q.d. vs. 2 mg/kg q8h | Piperacillin, 4 g q8h or azlocillin, 5 g q8h | Septicemia, miscellaneous (upper and lower respiratory tracts, skin and soft tissues) | Clinical cure, mortality, nephrotoxicity |
| [19] | 31 Patient-episodes; mean age, 61 y; 18, febrile neutropenic; median neutrophil count, <0.1 × 10$^9$/L; 72%, hematologic malignancy | 33 Patient-episodes; mean age, 62 y; 17, febrile neutropenic; median neutrophil count, <0.1 × 10$^9$/L; 72%, hematologic malignancy | Netilmicin, 300 mg q.d. vs. 100 mg q8h | Cefuroxime, 750 mg q8h | Miscellaneous (respiratory tract, urinary tract, gastrointestinal tract, skin and soft tissues) | Bacteriologic cure, clinical cure, nephrotoxicity |

* Granulocyte count on enrollment in study.

*Analysis of data.* We assessed the heterogeneity between individual study risk ratios with use of the $\chi^2$ test for homogeneity and by visual inspection. For each outcome in which there was homogeneity of the individual study risk ratios, a pooled risk ratio was calculated with use of a random effects model [22]. We also analyzed clinical cure for the subgroups of patients with and without bacteremia by using data from the three trials in which results were reported according to bacteremic status [16–18].

## Results

*Trial characteristics.* We reviewed six independent studies for our meta-analysis [16–19, 23–25]; we excluded two studies because they were not randomized controlled trials [23, 24]. One trial was reported both in an abstract and in a complete report [16, 25]; therefore, data were extracted from the complete report for our study. Thus, four individual studies were included in this review. For study selection, the raw agreement between the two reviewers was 100%, and $\kappa$ was 1.0, indicating complete agreement between the reviewers.

The characteristics of the individual trials as well as their combined outcomes (those that met the prespecified definitions) are shown in table 1. For the efficacy and toxicity risk ratio estimates, differences in the pooled sample sizes were due to different sample sizes for each outcome within individual studies and different studies pooled for each outcome (table 2). Data pertaining to patient-episodes (as opposed to individual patients) were available for two trials [16, 19]. We did not find significant heterogeneity between individual study risk ratios for any of the outcomes analyzed.

The mean methodological quality score for the trials was 0.77 (range, 0.66–0.91). The $\kappa$ for methodological-quality score ascertainment was 0.87.

*Efficacy outcomes.* For the outcomes bacteriologic cure and clinical cure, the pooled risk ratios indicated equivalence of the two dosing regimens (figure 1). The pooled risk ratio for bacteriologic cure was 1.00 (95% CI, 0.86–1.16). As shown in figure 1, the pooled risk ratio for clinical cure was 0.97 (95% CI, 0.91–1.05). The pooled risk ratio for mortality was 0.93 (95% CI, 0.62–1.41) (figure 2).

Further efficacy analyses for patients with bacteremic and nonbacteremic infections did not yield significant differences in the pooled risk ratios for clinical cure. For bacteremic patients, the pooled risk ratio for clinical cure was 1.03 (95% CI, 0.81–1.32), while the pooled risk ratio was 0.93 (95% CI, 0.86–1.01) for nonbacteremic patients.

*Toxicity outcomes.* Examination of nephrotoxicity yielded a pooled risk ratio of 0.78 (95% CI, 0.31–1.94) (figure 2). Ototoxicity data were available only from one study [16]. The risk ratio for ototoxicity in this trial was 1.69 (95% CI, 0.49–5.86). The wide confidence intervals around this estimate, which reflected the small sample size, indicates that additional studies are needed to ascertain the true risk of ototoxicity with either regimen.

## Discussion

In this analysis, we found equivalent efficacy and a trend towards reduced mortality and nephrotoxicity when an SDD regimen of aminoglycosides, rather than a standard dosing regimen, was given to immunocompromised patients. There are

**Table 2.** Data used for calculating pooled risk ratios in a meta-analysis of trials evaluating single daily dosing of aminoglycosides in immunocompromised adults.

| | No. of patients with indicated outcome/total no. assessed (%) | | | | |
|---|---|---|---|---|---|
| Reference, regimen | Bacteriologic cure* | Clinical cure* | Mortality† | Nephrotoxicity‡ | Ototoxicity§ |
| [16] | | | | | |
| SDD | ... | 249/350 (71) | 34/282 (12) | 11/283 (4) | 6/55 (11) |
| Standard dosing | ... | 256/344 (74) | 33/255 (13) | 8/256 (3) | 3/50 (6) |
| [17] | | | | | |
| SDD | 7/15 (47) | 42/47 (89) | 4/47 (9) | ... | ... |
| Standard dosing | 7/17 (41) | 41/45 (91) | 4/41 (10) | ... | ... |
| [18] | | | | | |
| SDD | ... | 44/61 (72) | 1/61 (2) | 2/61 (3) | ... |
| Standard dosing | ... | 38/55 (69) | 1/55 (2) | 4/54 (7) | ... |
| [19] | | | | | |
| SDD | 11/11 (100) | 14/28 (50) | ... | 0/31 | ... |
| Standard dosing | 14/14 (100) | 13/31 (42) | ... | 3/33 (10) | ... |

NOTE. SDD = single daily dosing.
* As defined in particular study.
† All causes.
‡ Defined as an increase in the serum creatinine level of >35–45 μmol/L during the study.
§ Defined as a 15-dB change in hearing at any frequency, as determined by audiometry.

limitations to our systematic review that preclude widespread application of the results. Only four studies were available for inclusion in this review, and the combined patient sample was small (803 patients). The small sample size, combined with a low incidence of toxicity, resulted in wide confidence intervals around the toxicity risk ratio estimates. Only one study assessed ototoxicity.

In addition, since the investigators in prior studies of febrile neutropenic patients may have selected patients at low risk for infection [26], other investigators have advocated stratification of efficacy and toxicity analyses by underlying risk factors for mortality such as the degree of neutropenia (<100 cells/mm$^3$) and the duration of neutropenia (>7 days), the presence of leukemia vs. solid tumors, the presence of gram-negative bacteremia, and older patient age [27, 28]. However, aside from the outcomes for bacteremic vs. nonbacteremic subgroups, the trials included in the present review did not consistently report outcome data stratified by these risk factors, which prevented us from performing such subgroup analyses.

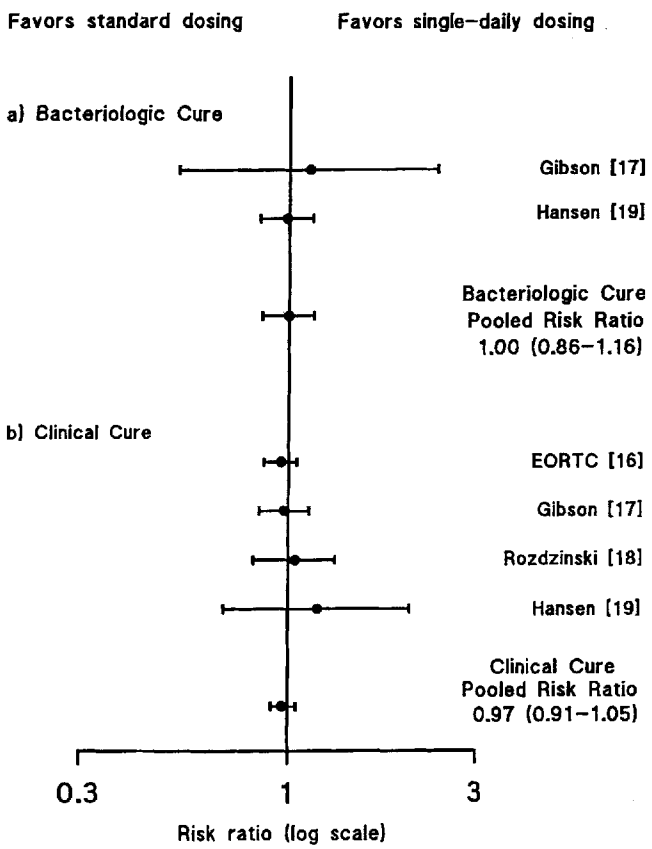


**Figure 1.** Efficacy outcomes with single daily dosing vs. standard aminoglycoside dosing. The individual study risk ratios and the pooled risk ratios for the outcomes of a) bacteriologic cure and b) clinical cure are shown with 95% confidence intervals. Risk ratios to the left of 1.0 favor standard aminoglycoside dosing; those to the right of 1.0 favor single daily aminoglycoside dosing. Statistical analysis for heterogeneity of the outcome bacteriologic cure revealed the following values: $X^2 = 0.10$, df = 2, and $P = .75$; statistical analysis for heterogeneity of the outcome clinical cure revealed the following values: $X^2 = 1.00$, df = 4, and $P = .80$. EORTC = European Organization for Research and Treatment of Cancer.

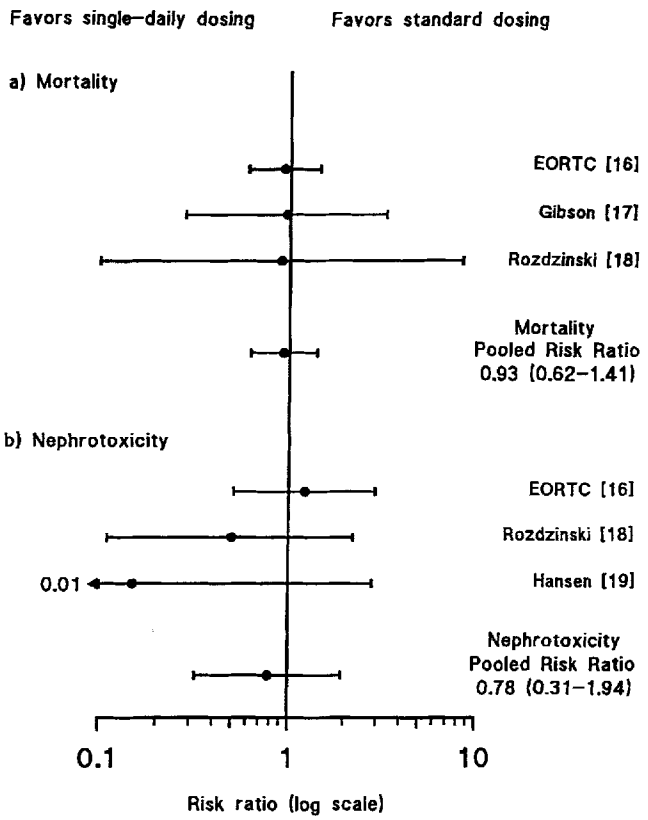


**Figure 2.** Mortality and nephrotoxicity outcomes with single daily dosing vs. standard aminoglycoside dosing. The individual study risk ratios and pooled risk ratios for a) mortality and b) nephrotoxicity are shown with 95% confidence intervals (lower confidence interval extends beyond scale of figure [*arrow*]). Risk ratios to the left of 1.0 favor single daily dosing of aminoglycosides; those to the right of 1.0 favor standard aminoglycoside dosing. Statistical analysis for heterogeneity of the outcome mortality revealed the following values: heterogeneity $X^2 = 0.003$, df = 3, and $P = 1.0$; statistical analysis for heterogeneity of the outcome nephrotoxicity revealed the following values: $X^2 = 2.47$, df = 3, and $P = .29$.

Despite the lack of subgroup analyses, examination of the individual trials indicates that a significant proportion of patients had these risk factors for mortality. Most of the patients in this sample (71%–91%) had febrile neutropenia due to hematologic malignancies (table 1) and severe neutropenia (50%–66% of the patients had <100 neutrophils/mm$^3$). No difference in the efficacy of the antibiotic regimens was found for patients with hematologic malignancies vs. those with solid tumors in the trial that stratified patients according to underlying malignancy [16]. Although they did not include outcome data stratified by degree of neutropenia, three of the trials we reviewed indicated no difference in clinical response rates to aminoglycoside therapy when analyzed by neutrophil count at study entry [16, 18, 19].

The median duration of neutropenia for patients in the largest trial was 18 days [16]. The rates of gram-negative bacteremia were equivalent between the studies, although the overall incidence of pseudomonas infections, which are associated with significantly higher mortality among neutropenic patients, was low (1.4%–1.7%) [29]. None of the studies included outcome data stratified or analyzed by patient age. Without subgroup analyses, the exact impact of each of these risk factors on the efficacy and toxicity estimates cannot be ascertained, although the lack of heterogeneity between individual studies suggests uniformity of patient response.

Our assessment of the efficacy of SDD of aminoglycosides was based on the outcomes bacteriologic cure, clinical cure, and mortality (all causes). Despite variability in the definition of successful therapy, no significant heterogeneity was found for any of the outcomes. The SDD regimen appears equally efficacious in both bacteremic and nonbacteremic patients, although cautious interpretation of this subgroup analysis is necessary given that data for this analysis were available from only three of the studies included in this review. Neutropenia may be more profound and severe in patients with hematologic malignancies who have received induction chemotherapy than it is in patients with solid tumors; thus, it is reassuring that the efficacies of the two aminoglycoside dosing regimens were equivalent despite the severity of the patients' illnesses [30].

The risk of nephrotoxicity is often a deterrent to the use of aminoglycosides in immunocompromised patients, particularly if the patients are receiving concomitant nephrotoxic medications such as amphotericin B, cisplatin, or nonsteroidal anti-inflammatory drugs. Although the confidence intervals around the nephrotoxicity risk ratio do not exclude the possibility of equivalent or increased toxicity with the SDD regimen, the pooled risk ratio indicates a clinically relevant trend towards reduced nephrotoxicity with the SDD regimen. This potential reduction in nephrotoxicity is consistent with the rationale that SDD results in less renal accumulation through a reduction in saturable binding of the drug to the renal proximal tubular cells [31].

The effect of aminoglycosides on ototoxicity was evaluated in only one study with a small sample size ($n$ = 105) that resulted in wide confidence intervals around the ototoxicity risk ratio estimate [16]. The trend towards increased ototoxicity in this study is at variance with the relative risk reduction of 0.67 (95% CI, 0.35–1.28) demonstrated in a previous meta-analysis of SDD in immunocompetent patients [10]. Clearly, further studies in immunocompromised patients are required to provide a more precise estimate of the risk of ototoxicity.

In clinical practice, clinicians are faced with many choices for the initial empirical antimicrobial treatment of febrile neutropenic patients, including monotherapy with a broad-spectrum agent or combination therapy with either two $\beta$-lactam antibiotics or a synergistic aminoglycoside and a $\beta$-lactam antibiotic [26, 28]. However, $\beta$-lactam monotherapy may lead to the induction of resistance in certain gram-negative strains that are initially susceptible to the $\beta$-lactam at the onset of therapy [32–34], and therapy with two $\beta$-lactams may be antagonistic or prolong the duration of neutropenia [35–37].

The findings of the present review suggest that SDD of aminoglycosides may be safe and efficacious for synergistic use in immunocompromised patients, although these findings must be interpreted cautiously because of the small sample size and the limited patient characteristics outlined previously, which may have affected the efficacy estimates. If results consistent with those of this review are obtained in future studies, SDD would afford several clinical advantages over standard aminoglycoside dosing regimens. For example, less frequent accessing of a patient's intravenous line may decrease the risk of catheter-related sepsis. In addition, the reduction in nursing time, the ease of administration, and the reduction in drug-level monitoring associated with the SDD regimen could result in cost savings.

Finally, the simplified SDD regimen may facilitate outpatient antibiotic therapy. Additional studies that compare SDD with standard dosing regimens and that specifically examine the associated risk of ototoxicity will further clarify the clinical usefulness of SDD aminoglycoside therapy in immunocompromised patients.

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