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Original article

# Short-course aminoglycosides as adjunctive empirical therapy in patients with Gram-negative bloodstream infection, a cohort study

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ABSTRACT

*Objective:* Short-course aminoglycosides as adjunctive empirical therapy to β-lactams in patients with a clinical suspicion of sepsis are used to broaden antibiotic susceptibility coverage and to enhance bacterial killing. We quantified the impact of this approach on 30-day mortality in a subset of sepsis patients with a Gram-negative bloodstream infection.

*Methods:* From a prospective cohort study conducted in seven hospitals in the Netherlands between June 2013 and November 2015, we selected all patients with Gram-negative bloodstream infection (GN-BSI). Short-course aminoglycoside therapy was defined as tobramycin, gentamicin or amikacin initiated within a 48-hour time window around blood-culture obtainment, and prescribed for a maximum of 2 days. The outcome of interest was 30-day all-cause mortality. Confounders were selected a priori for adjustment using a propensity score analysis with inverse probability weighting.

*Results:* A total of 626 individuals with GN-BSI who received β-lactams were included; 156 (24.9%) also received aminoglycosides for a median of 1 day. Patients receiving aminoglycosides more often had septic shock (31/156, 19.9% versus 34/470, 7.2%) and had an eight-fold lower risk of inappropriate treatment (3/156, 1.9% versus 69/470, 14.7%). Thirty-day mortality was 17.3% (27/156) and 13.6% (64/470) for patients receiving and not receiving aminoglycosides, respectively; yielding crude and adjusted odds ratios for 30-day mortality for patients treated with aminoglycosides of 1.33 (95% CI 0.80–2.15) and 1.57 (0.84–2.93), respectively.

*Conclusions:* Short-course adjunctive aminoglycoside treatment as part of empirical therapy with β-lactam antibiotics in patients with GN-BSI did not result in improved outcomes, despite better antibiotic coverage of pathogens. **J.W. Timotëus Deelen, Clin Microbiol Infect 2021;27:269**



## Introduction

The global emergence of antibiotic resistance is increasingly complicating the selection of antibiotics for empirical treatment in patients with a clinical suspicion of sepsis. One strategy to reduce

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the impact of resistance is the addition of aminoglycosides to empirical β-lactam therapy.

Based on accumulating evidence, combination therapy with aminoglycosides does not provide a benefit for patients with sepsis compared with β-lactam monotherapy [1]. However, this combination is recommended in the *Surviving Sepsis* guidelines and several national guidelines, including those of Sweden and France [2–4]. In the Netherlands, the sepsis guideline suggests the addition of a short course (one or two doses) of empirical aminoglycosides when the patient is at increased risk of infection with an extended-spectrum β-lactamase-producing pathogen. This increased risk is defined as previous cephalosporin/fluoroquinolone use and/or colonization with an extended-spectrum β-lactamase-producing pathogen in the last year. Yet, in locally adapted guidelines in Dutch hospitals, recommendations range from no aminoglycosides at all to a short 1- to 2-day course of aminoglycosides in every patient with sepsis. This strategy is therefore widely but inconsistently employed, and aside from differences in local guidelines, drivers for this heterogeneity are unknown.

In critically ill individuals admitted with sepsis to intensive care units (ICU), a short course of aminoglycosides as adjunct to β-lactam antibiotics was associated with an increased risk for kidney injury and a non-significant trend towards increased mortality [5]. It is unclear whether this strategy is beneficial in a non-ICU population. We therefore determined in seven Dutch hospitals the effect of short-term empirical aminoglycoside treatment as adjunct to β-lactam antibiotics on 30-day mortality in individuals with Gram-negative bloodstream infection (GN-BSI), a subset of individuals with sepsis in whom the expected benefits of this strategy are expected to be largest.

## Materials and methods

### *Study, setting and participants*

This study was nested in a prospective cohort in eight hospitals in the Netherlands (seven secondary-care hospitals, one tertiary-care hospital). In this study, data of 2000 patients with a Gram-negative infection and 2000 non-infected control individuals were collected to assess the burden of antibiotic resistance in Gram-negative infections in the Netherlands. (ClinicalTrials.gov identifier: NCT02007343, (Rottier WC, in preparation)) Patients were included between June 2013 and November 2015. Every week, trained research nurses consecutively screened clinical cultures (excluding screening cultures of rectum or throat) and included the first five patients (age ≥18 years) with a positive culture that met the following criteria: (a) involved *Enterobacterales* and/or non-fermenters; (b) constituted a new infection according to the respective CDC criteria for infection [6]; (c) was the index culture of a new infection episode. Individuals being treated for Gram-negative infection at the time of blood-culture obtainment were not eligible. From this cohort we selected individuals with BSI from seven hospitals, because medication data were not available from one secondary-care hospital. Individuals who died on day 0 and those who did not receive β-lactam antibiotics on day 0 or 1 were excluded from the analysis. The Ethics Committee of the University Medical Centre Utrecht waived the requirement of informed consent.

### *Outcome and definitions*

The study outcome is 30-day all-cause mortality, which was determined from medical records supplemented with mortality data from the Municipal Personal Records Database.

Empiric aminoglycosides were defined as the prescription of gentamicin, tobramycin or amikacin on the day before, on and/or after the index culture. Dose per kg was calculated with an average weight of 80 kg, which was based on data from a Dutch study conducted in ICU. Exposure was ascertained by extraction of medication data from the local pharmacy system and confirmed with prescription data in the digital patient records. Appropriate empirical antibiotic therapy was defined as an antibiotic, or a combination of antibiotics, administered on day 0 and/or 1 of which at least one had *in vitro* activity based on antibiotic susceptibility testing. Day 0 is the calendar date of blood-culture obtainment. Local antibiotic policies for empirical antibiotic treatment in patients with sepsis are listed in the Supplementary material (Table S1). First choice treatments included a second-generation cephalosporin plus aminoglycoside in five hospitals and monotherapy with a third-generation cephalosporin in two hospitals.

We use the term 'bloodstream infection' (BSI) interchangeably with bacteraemia. For further definitions of variables, see Supplementary material (Appendix S2).

### *Statistical analysis*

All analyses were performed in R version 3.4.3, using the JTOOLS version 2.0.0 [7].

Missing values occurred rarely (<0.1% of all variables in the cohort), so no imputation or other strategies were deemed necessary; a complete case analysis was performed.

To determine the casual effect of short-course aminoglycosides, we created a propensity score and used inverse probability weighting of this score to adjust for pre-selected confounders. A full description of this process is given in the Supplementary material (Appendix S3).

### *Sensitivity analyses*

We performed four sensitivity analyses to increase robustness of our findings: (a) excluding patients with treatment restriction/do not resuscitate; (b) excluding patients in whom blood cultures had been obtained in ICU; (c) excluding emergency room patients from one hospital where it was unclear whether all aminoglycoside administrations at the emergency room were registered; (d) an analysis without patients with a BSI caused by *Pseudomonas aeruginosa*, which has intrinsic resistance to commonly used cephalosporins and may bias the results.

The study was reported according to the STROBE guideline for reporting of observational studies [8].

## Results

Among the 1721 patients in the total cohort with Gram-negative infections, 690 (40.1%) had a BSI, of whom six died on day 0, and 58 did not receive β-lactam antibiotics, leaving 626 patients (Fig. 1). Of these, 156 received adjunctive aminoglycosides (24.9%) for a median of 1 day (Table 1). All received gentamicin or tobramycin. There was no loss to follow up.

Among the patients receiving aminoglycosides, 31/156 (19.9%) had septic shock, compared with 34/470 patients (7.2%) who did not receive aminoglycosides. Treatment restrictions were more prevalent among patients not receiving aminoglycosides (143/470 (30.4%) compared with 30/156 (19.2%) among those without aminoglycosides). Colonization/infection with third-generation-cephalosporin-resistant pathogens in the previous year was similar in both groups (5.8% and 6.4% in aminoglycoside and non-aminoglycoside groups, respectively).

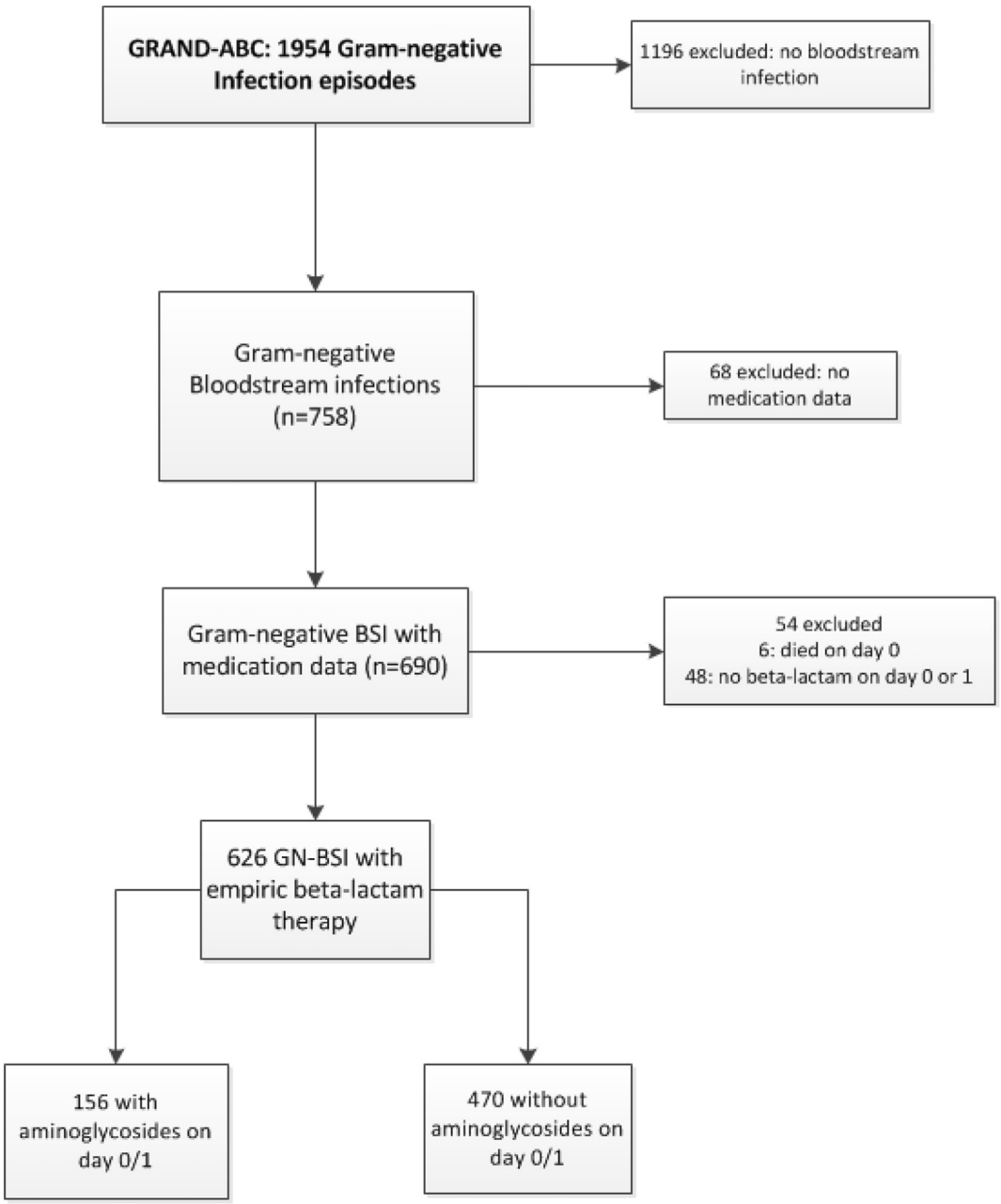


**Fig. 1.** Flow chart.

Most episodes of GN-BSI were caused by *Escherichia coli* (376/626; 59.6%), followed by *Klebsiella pneumoniae* (54/626; 8.5%) and *Pseudomonas aeruginosa* (35/626; 5.6%). Multiple Gram-negative species (e.g. *E. coli* plus *K. pneumoniae* from index cultures) were involved in 97/626 BSI (13.3%), of which 62% included *E. coli*.

Proportions of patients with aminoglycosides per hospital ranged from 12% to 54% (see Supplementary material, Table S1). Types of β-lactams used differed between the aminoglycoside group and no-aminoglycoside group. In the aminoglycoside group, 60.9% (95/156) of prescribed β-lactams were second-generation cephalosporins, and 22.4% (35/156) were third-generation cephalosporins. In the no-aminoglycoside group, 36.8% (173/470) and 36.0% (169/470) of prescribed β-lactams were second- and third-generation cephalosporins, respectively. The proportion of patients receiving carbapenem therapy was similar in the non-aminoglycoside and aminoglycoside groups (5.5% versus 5.1%). Mean aminoglycoside dosages were similar between hospitals and ranged from 3.7 mg/kg to 4.3 mg/kg for gentamicin and from 4.6 mg/kg to 4.7 mg/kg for tobramycin. Overall, 72 of 626 patients received inappropriate empirical therapy; three (1.9%) patients of the 156 that received aminoglycosides and 69 (14.7%) of the 470 that did not receive aminoglycosides.

Study site, sepsis severity and Charlson co-morbidity were the major predictors of aminoglycoside use in the propensity score model (Table 2). After weighting, all covariates were balanced, with an SD of <0.1. The overall explained variance (McFadden's $R^2$) of aminoglycoside use was 15.3%, and study site explained 51.4% of this variance in aminoglycoside use, followed by sepsis severity (12.9%).

**Table 1**
Baseline data of patients with and without empirical aminoglycoside therapy

| | Patients not treated with aminoglycosides ($n = 470$) | Patients treated with aminoglycosides ($n = 156$) |
|---|---|---|
| Age (years), mean (+SD) | 72.7 (14.0) | 69.6 (14.7) |
| Female sex, *n* (%) | 205 (43.6) | 78 (50.0) |
| Charlson co-morbidity score, median (interquartile range) | 2 (1–4) | 2 (0–3) |
| Hospital, *n* (%) | | |
| A | 56 (11.9) | 23 (14.7) |
| B | 41 (8.7) | 49 (31.4) |
| C | 109 (23.2) | 15 (9.6) |
| D | 100 (21.3) | 15 (9.6) |
| E | 68 (14.5) | 20 (12.8) |
| F | 56 (11.9) | 25 (16.0) |
| G | 40 (8.5) | 9 (5.8) |
| Origin, *n* (%) | | |
| Community-onset | 193 (41.1) | 74 (47.4) |
| Healthcare-associated | 193 (41.1) | 56 (35.9) |
| Hospital-onset | 84 (17.9) | 26 (16.7) |
| Chronic kidney disease, *n* (%) | 29 (6.2) | 5 (3.2) |
| Immunocompromised, *n* (%) | 54 (11.5) | 22 (14.1) |
| Sepsis severity, *n* (%) | | |
| Sepsis | 381 (81.1) | 103 (66.0) |
| Severe sepsis | 55 (11.7) | 22 (14.1) |
| Septic shock | 34 (7.2) | 31 (19.9) |
| Infection source, *n* (%) | | |
| Primary bloodstream infection | 50 (10.6) | 22 (14.1) |
| Urinary tract | 250 (53.2) | 88 (56.4) |
| Abdominal | 111 (23.6) | 32 (20.5) |
| Respiratory | 14 (3.0) | 5 (3.2) |
| Skin and soft tissue | 13 (2.8) | 3 (1.9) |
| Other | 32 (6.8) | 6 (3.8) |
| Pathogens, *n* (%) | | |
| *Escherichia coli* | 281 (59.8) | 92 (59.0) |
| *Klebsiella pneumoniae* | 42 (8.9) | 11 (7.1) |
| Other *Enterobacterales* | 60 (12.7) | 22 (14.1) |
| *Pseudomonas aeruginosa* | 26 (5.4) | 9 (5.8) |
| Multiple species | 61 (13.0) | 22 (14.1) |
| Resistance, *n* (%)[a] | | |
| Second-generation cephalosporins | 128 (23.0) | 31 (21.1) |
| Third-generation cephalosporins | 43 (9.7) | 15 (10.2) |
| Aminoglycosides | 36 (7.9) | 12 (8.2) |
| Ward where culture obtained, *n* (%) | | |
| Surgical | 70 (14.9) | 14 (9.0) |
| Intensive care unit | 23 (4.9) | 6 (3.8) |
| Internal medicine | 101 (21.5) | 40 (25.6) |
| Emergency department | 276 (58.7) | 95 (60.9) |
| Colonization/infection with third-generation cephalosporin-resistant pathogen in previous year, *n* (%) | 30 (6.4) | 9 (5.8) |
| Treatment restriction, *n* (%) | 143 (30.4) | 30 (19.2) |
| Empirical treatment, *n* (%)[b] | | |
| First-generation cephalosporin | 9 (1.9) | 4 (2.6) |
| Second-generation cephalosporin | 173 (36.8) | 95 (60.9) |
| Third-generation cephalosporin | 169 (36.0) | 35 (22.4) |
| Amoxicillin (+clavulanic acid) | 118 (25.1) | 36 (23.1) |
| Piperacillin/tazobactam | 30 (6.4) | 9 (5.8) |
| Carbapenem | 26 (5.5) | 8 (5.1) |
| Inappropriate day 0 and 1 | 69 (14.7) | 3 (1.9) |
| Median duration of aminoglycoside therapy (days) | — | 1 (1–2) |
| Mean dose of gentamicin[c] | — | 3.9 mg/kg |
| Mean dose of tobramycin | — | 4.7 mg/kg |

Data are given as *n* (%) unless otherwise indicated.
[a] Resistance in *Enterobacterales* infection episodes (excluding *Pseudomonas*). Resistance in *Pseudomonas* is 3/35 (8.6%) to ceftazidime and 1/35 (2.9%) to aminoglycosides.
[b] Numbers do not add up to 100% because of escalation/de-escalation on day 1, a patient may start with ceftriaxone on day 0 and escalate to carbapenems on day 1.
[c] Calculated with an average weight of 80 kg.

### *Outcomes*

Overall 30-day mortality was 14.6% ($n = 91$)—17.3% and 13.6% for those receiving and not receiving aminoglycosides, respectively. The unadjusted odds ratio for 30-day mortality for patients receiving aminoglycosides was 1.33 (95% CI 0.80–2.15). The adjusted odds ratio of aminoglycoside use for 30-day mortality was 1.57 (95% CI 0.84–2.92). The median time to death was 5 days (interquartile range 1.5–10.5 days) and 7.5 days (interquartile range 2–16 days) for patients receiving and not receiving aminoglycosides, respectively. Length of stay after infection onset was similar in both groups (median 8 days, interquartile range 6–13 days).

Seventy-four patients were treated in ICU, of whom 52 were admitted to the ICU within 24 hours. ICU admission within 24 hours occurred more frequently in the aminoglycoside group (10.2% versus 5.5%). ICU admission >24 hours after obtaining blood

cultures occurred in seven patients in the aminoglycoside group (4.4%) and 15 patients in the non-aminoglycoside group (2.7%).

Adjusted odds ratios in the performed sensitivity analyses did not change our interpretation (Table 3).

## Discussion

In this study of 626 sepsis patients with documented GN-BSI, we were unable to demonstrate an improved clinical outcome for a short-term course of aminoglycosides added to β-lactams as part of empirical therapy. These results add to an increasing body of evidence regarding the absence of clinical benefits of short-term adjunctive aminoglycosides as part of empirical treatment strategies.

Up to now, three studies have determined the effects of short-course aminoglycoside therapy as part of empirical antibiotic treatment in individuals with severe sepsis and septic shock. These studies, though, focused primarily on the occurrence of acute kidney injury, not mortality. Two were retrospective single-centre studies, with 317 and 341 patients, respectively, and one was a prospective study of 648 individuals in two Dutch ICU [5,9,10]. In the retrospective studies, exposure to aminoglycosides was <3 days in one (ICU-based) study and a single dose in the other study. In both studies, aminoglycosides were not associated with either acute kidney failure or clinical benefits. In the prospective ICU-based study, a short-course of aminoglycoside therapy in individuals with sepsis was associated with an increased incidence of acute kidney injury, without evidence of clinical benefits. The current study extends this absence of clinical benefits towards a general hospital population with GN-BSI.

**Table 2**
Propensity score model, odds ratio for aminoglycoside use versus no aminoglycoside use

| | Odds ratio (95% CI) |
|---|---|
| Hospital | |
| A | 3.02 (1.40–6.68) |
| B | 7.90 (3.90–16.77) |
| C | Reference |
| D | 2.13 (0.88–5.22) |
| E | 1.95 (0.89–4.33) |
| F | 3.03 (1.43–6.61) |
| G | 2.74 (0.99–7.41) |
| Sepsis severity | |
| Sepsis | Reference |
| Severe sepsis | 1.59 (0.86–2.89) |
| Septic shock | 3.17 (1.68–6.02) |
| Treatment restriction | 0.88 (0.51–1.50) |
| Second-generation cephalosporin use | 2.56 (1.56–4.28) |
| Culture ward | |
| Surgical | Reference |
| Internal medicine | 1.01 (0.63–1.65) |
| Intensive care unit | 0.86 (0.34–2.06) |
| Age (per year) | 0.98 (0.97–1.00) |
| Sex (female) | 1.17 (0.77–1.79) |
| Kidney disease | 0.49 (0.15–1.36) |
| Charlson Co-morbidity Index | |
| 0 | Reference |
| 1 | 0.48 (0.24–0.93) |
| 2 | 0.99 (0.54–1.80) |
| 3–4 | 0.70 (0.36–1.35) |
| >4 | 0.78 (0.40–1.51) |
| Origin | |
| Community onset | Reference |
| Health-care-associated | 0.96 (0.60–1.53) |
| Hospital onset | 0.85 (0.46–1.55) |

Propensity score model. These variables are included in the propensity score, for calculating the chance (propensity) of aminoglycoside use. Propensity score was calculated using a logistic regression analysis.

Despite similar local antibiotic policies in the participating hospitals, aminoglycoside use varied widely between hospitals. In our propensity score, study site contributed 51% to the explained variance in aminoglycoside use. Our findings also suggest that physicians include the clinical severity of disease and co-morbidities in their clinical decision-making. Patients that received aminoglycosides were twice as likely to have severe sepsis or septic shock and less frequently had chronic kidney disease or treatment restrictions.

Broadening the antibiotic spectrum of empirical treatment is an important reason for adjunctive use of a short-course of aminoglycosides [11]. In the six non-academic centres, resistance among *Enterobacterales* to second-generation cephalosporins ranged from 16% to 23%, and resistance to third-generation cephalosporins from 6.4% to 10.3%, whereas resistance to gentamicin ranged from 3.8% to 11.7%. Indeed, adjunctive use of aminoglycosides was associated with an eight-fold lower risk of inappropriate empirical therapy, mainly by mitigating resistance to second-generation cephalosporins. However, despite the lower risk of inappropriate empirical therapy, aminoglycoside use was not, also after adjusting for confounding (including use of second-generation cephalosporins), associated with a higher survival rate at day 30.

The absence of an effect of inappropriate empirical antibiotic therapy on mortality has been reported before in similar patient populations, both in the Netherlands and the United Kingdom [12,13]. Faster recognition of sepsis through implementation of sepsis guidelines [2], higher quality of supportive care [14], potentially reduced bacterial virulence due to resistance genes [15] and shorter duration of inappropriate therapy due to faster diagnostic procedures may all contribute to mitigating the effect of inappropriate therapy. Additionally, there might still be an *in vivo* effect of β-lactams in *in vitro* non-susceptible bacteria, which may also mitigate the harmful effects of what is considered inappropriate therapy [16]. Another argument might be that a low severity of infections reduces the impact of inappropriate therapy on patient outcome. However, overall 30-day mortality in our study population was 15%, which is comparable to other cohorts of patients with GN-BSI [17,18].

Underdosing of aminoglycosides may also contribute to the observed absence of beneficial effects [19,20]. The average doses of 3.7–4.3 mg/kg for gentamicin and 4.6–4.7 mg/kg for tobramycin, were lower than currently recommended doses (which are 5 mg/kg for gentamicin and 5–7 mg/kg for tobramycin [1]). Yet, these recommendations are based on pharmacokinetic/pharmacodynamic principles and the consequences of suboptimal dosing on patient outcome are unknown [21]. As short-course aminoglycosides often constitute one single dose of aminoglycoside, therapeutic drug monitoring cannot be used to optimize dosing.

The absence of benefit, combined with widespread but heterogeneous use of short-term aminoglycosides calls for a randomized clinical trial, as we discussed before [22]. In such a study we would propose to use higher dosages of gentamycin and tobramycin. The current study was performed in individuals with GN-BSI, but this is not a suitable population for a randomized controlled trial, as the presence of GN-BSI is unknown at the initiation of empirical therapy. However, one of the reasons to use aminoglycosides is to reduce inappropriate therapy in GN-BSI, so improvements in outcomes are expected to be the largest in this GN-BSI population. For further studies, the more relevant study population would be patients with sepsis, potentially caused by Gram-negative bacteria, and with an a priori risk of 30-day mortality of, for instance, 20%. In such a population we would argue that the addition of aminoglycosides should yield an absolute reduction of 30-day mortality of at least 2%. In such a study, the effects on kidney failure should be carefully monitored.

**Table 3**
Regression analyses—30-day mortality

| | Mortality: no aminoglycosides | Mortality: Aminoglycosides | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|---|
| Full analysis ($n = 626$) | 64/470 (13.6%) | 27/156 (17.3%) | 1.33 (0.80–2.15) | 1.57 (0.84–2.92) |
| Excluding patients with infection onset at ICU ($n = 597$) | 57/447 (12.8%) | 22/145 (15.3%) | 1.24 (0.72–2.07) | 1.52 (0.76–3.05) |
| Excluding CO/HA cases hospital B ($n = 558$) | 58/441 (13.1%) | 24/117 (20.5%) | 1.70 (0.99–2.86) | 1.84 (0.96–3.55) |
| Excluding patients with treatment restriction ($n = 453$) | 29/327 (8.9%) | 19/126 (15.1%) | 1.82 (0.97–3.37) | 1.93 (0.92–4.10) |
| Excluding patients with *Pseudomonas aeruginosa* BSI ($n = 591$) | 59/444 (13.2%) | 23/147 (15.6%) | 1.21 (0.71–2.02) | 1.43 (0.75–2.71) |

BSI, bloodstream infection; CO, community-onset; HA, health-care-associated/hospital onset; ICU, intensive care unit; OR, odds ratio.
We report the crude and adjusted odds ratios of the impact of short-term adjunctive aminoglycosides on 30-day mortality, along with five sensitivity analyses (further explained in the methods). The adjusted OR was calculated by a logistic regression analysis, using inversed probability weighting to adjust for confounding. The confounders age, sex, culture ward, sepsis severity, Charlson co-morbidity score, chronic kidney disease, second-generation cephalosporin use, treatment restriction and community-onset/health-care-associated/hospital onset were included in the propensity score. Odds ratios reported with 95% confidence interval.

We would like to discuss several study limitations. Naturally, our analysis is susceptible to confounding, even after adjustment. We, therefore, performed four sensitivity analyses, to both account for uncertainties in the data and to better understand several confounders. These analyses support our findings and point at a potentially more harmful effect of aminoglycosides, although the confidence intervals are wide. Furthermore, we adjusted for several important confounders, including sepsis severity. Although existence of an unknown confounder that explains the lack of a beneficial effect of aminoglycosides on mortality seems unlikely, more specific data on disease severity would have increased the study validity. Second, the average dose of aminoglycosides was lower than guideline recommendations. Although there is no conclusive evidence with regards to effectivity of higher dosages, this may have impacted the effect on mortality. Third, we did not register creatinine levels either before or after infection. Although chronic kidney disease is included as a confounder, we could not explore associations between creatinine levels and mortality. Additionally, the definition of chronic kidney disease in this study does not include milder forms of chronic kidney disease, hence putative confounding caused by this variable may have been incompletely adjusted.

In conclusion, we were unable to demonstrate beneficial effects of a short-course of aminoglycosides added to β-lactam antibiotics on 30-day mortality in individuals with GN-BSI. Considering the widespread use of aminoglycosides and uncertainty about its benefits, a randomized trial is warranted.

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## Author contributions

JD devised the study, collected data and drafted the manuscript, CHvW and MB aided in devising the study and critically reviewed the manuscript, all other authors aided in collecting data and critically reviewed the manuscript.

## Transparency declaration

All authors state no conflicts of interests.

Parts of the results have been presented at the ECCMID 2019 conference in Amsterdam, Oral presentation #1187.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.04.041.

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