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Original Article

Nephrotoxicity associated with short-term gentamicin therapy in community-acquired bacteraemia: risk of nephrotoxicity

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ABSTRACT

INTRODUCTION. Hesitancy towards the use of aminoglycosides persists among clinicians due to the perceived risk of nephrotoxicity.

METHODS. This retrospective cohort study included adults with community-acquired bacteraemia and no pre-existing renal failure. The patients were divided into two groups matched 1:1 by age (± 5 years): 1) patients treated with short-term (≤ 3 days) once-daily gentamicin within 24 hours of admission and 2) non-gentamicin-treated patients. The primary endpoint was an increase in plasma creatinine levels of ≥ 40 µmol/l from baseline. Cause-specific Cox regression was used to compute hazard ratios (HR) with 95% confidence intervals (CI) for prognostic factors of acute kidney injury (AKI) and death.

RESULTS. A total of 310 adults with bacteraemia were included, among whom 159 (49%) were treated with gentamicin and 151 (51%) with other antibiotics. No significant between-group differences were observed in sex distribution, comorbidities, biochemical variables and vital signs at admission. In the gentamicin-exposed group, 11 (7%) patients developed AKI compared with 12 (8%) patients in the non-exposed group. Gentamicin was neither associated with increased risk of AKI (HR = 0.86; 95% CI: 0.38-1.96) nor with 30-day mortality (HR = 0.73; 95% CI: 0.38-1.41) compared with other antibiotic regimens.

CONCLUSIONS. Our study showed no increase in the risk of developing AKI and no increase in all-cause mortality in patients treated with short-term once-daily gentamicin for community-acquired bacteraemia compared with other antibiotic regimens.

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Community-acquired bacteraemia is common among patients admitted to the emergency department, and appropriate antibiotic treatment initiated before the result of blood cultures is recommended to reduce complications and mortality [1]. It is impossible to recommend a universal therapy applicable to all regions of the world since the pathogen distribution and susceptibility patterns vary considerably. In Denmark, empirical treatment of suspected community-acquired bacteraemia is often ampicillin plus gentamicin or piperacillin/tazobactam [2]. However, the renal safety of aminoglycosides has been questioned, and ambivalence persists among clinicians towards using antibiotic regimens consisting of aminoglycosides such as gentamicin.

The primary aim of this study in patients with community-acquired bacteraemia was to examine whether the empirical short-term use of a gentamicin regimen administered within 24 hours of admission is associated with a higher incidence of acquired acute kidney injury (AKI) under hospital admission than other antibiotic treatments. The secondary aim was to evaluate all-cause 30-day mortality.

Methods

Patient cohort

We established a retrospective cohort counting 1,011 adults with a positive blood culture retrieved from the regional microbiology information system (WWBakt, Autonik AB, Sweden). All patients were admitted to the Emergency Department at Aalborg University Hospital between 1 January 2022 and 28 February 2023 and received empiric intravenous antibiotic treatment within 24 hours of admission. In the cohort, 203 patients had gentamicin as part of the regimen, whereas 808 patients had not received gentamicin during hospitalisation. Each of the 203 patients was individually age-matched (± 5 years) with a patient in the non-gentamicin group. The subgroup of 406 patients was then reduced by exclusion of patients with any of the following criteria: 1) chronic kidney disease (CKD), defined as a chronically increased plasma creatinine level for at least three months and/or known renal impairment diagnosed by a nephrologist, 2) malignant disease in active treatment, 3) haematological disorder, 4) diagnosed bacteraemia within 90 days before admission, 5) more than three gentamicin doses and 6) less than two plasma creatinine measurements. After applying the exclusion criteria, a final cohort of 310 patients was analysed (159 had gentamicin exposure and 151 did not have gentamicin exposure).

Data collection

We retrieved the following data from the Patient Registry System (NordEPJ, Systematic, Denmark): vital signs on admission, prescribed medicine, blood biochemistry and haematology, intensive care unit (ICU) therapy, and mortality. The time (hours;minutes) that the vital signs were first recorded was used to determine the time of admission. Vital signs included blood pressure, heart rate, temperature, respiratory frequency, oxygen saturation, oxygen supply and Glasgow Coma Scale. Plasma creatinine measurements were retrieved within the entire admission period, and we used the first measured plasma creatinine level as a baseline. Previous measurements were explored to indicate possible CKD in case of a baseline above normal creatinine levels. If AKI was detected during admission, it was noted whether there was a record of normalised creatinine levels thereafter.

Bacteriology data were gathered using WWBakt. This system contained data specifying bacterial species, antimicrobial susceptibility testing, and recommendations from clinical microbiologists.

Information on patient comorbidities at the time of admission was retrieved with the help of the Business Intelligence Group at Aalborg University Hospital, and the comorbidities used in this study were established based on the Charlson Comorbidity Index (CCI). Lastly, whether the patient received haemodialysis and/or intensive care during hospitalisation was noted.

All variables were included in a data registration system (REDCap, Vanderbilt University, USA).

Outcomes

The primary endpoint was the incidence of acquired AKI during admission. The Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI is an increase in plasma creatinine of ≥ 26.5 µmol/l from the baseline value [3]. To lessen measurement uncertainty, we modified the definition slightly and used an increase in plasma creatinine of ≥ 40 µmol/l from the baseline within 14 days after admission. The secondary outcome was 30-day all-cause mortality after admission.

Statistical analysis

Between the two groups, numerical data were assessed using the Mann-Whitney test and categorical data with the Pearson χ^2 or Fisher's exact test. The numerical findings were reported as medians and interquartile range,

and the categorical findings as frequency (n (%)). The Cox proportional hazards regression was used as a survival analysis for mortality. The Cox cause-specific hazard rate ratio was used as a time-to-event analysis for acquired AKI to consider the conflicting risk of death. Sub-group analyses of the Cox regression included gentamicin treatment, sex, comorbidities and the quick Sequential Organ Failure Assessment (qSOFA) score as covariates to detect hazard ratios (HR), including a 95% confidence interval (CI).

Statistical significance was considered in the case of p values < 0.05. All statistical analyses were performed using STATA/MP 17 (STATA Corp. TX, USA).

Ethical considerations

The study was approved by the Danish Data Protection Agency (R. No. 2023-010027). Informed patient consent was not required for this study.

Trial registration: not relevant.

Results

The age-matching of patients produced two groups with no significant differences in most baseline characteristics, such as sex, duration of hospitalisation and comorbidities. However, a significant difference was found in the share of patients receiving immunomodulatory treatment (**Table 1**).

TABLE 1 Baseline demographics of patients with community-acquired bacteraemia.

	Exposed to gentamicin?		
	yes (N_y = 159)	no (N_n = 151)	p value
Sex, n (%)	0.872		
Male	87 (55)	84 (56)	
Female	72 (45)	67 (44)	
Age, median (IQR)			
Females	76	77	0.466
Age groups, n (%)			
< 50 yrs	10 (6)	9 (6)	0.904
50-59 yrs	16 (10)	14 (9)	0.814
60-69 yrs	28 (18)	19 (13)	0.217
70-79 yrs	41 (26)	42 (28)	0.687
≥ 80 yrs	64 (40)	67 (44)	0.463
Comorbidities, n (%)			
Myocardial infarction	11 (7)	11 (7)	0.900
Congestive heart failure	18 (11)	18 (12)	0.869
Peripheral arterial disease	10 (6)	13 (9)	0.436
Cerebrovascular disease	34 (21)	22 (15)	0.119
Dementia	3 (2)	4 (3)	0.652
Chronic pulmonary disease	31 (20)	32 (21)	0.711
Connective tissue disease	9 (6)	11 (7)	0.561
Peptic ulcer disease	9 (6)	11 (7)	0.561
Mild liver disease	2 (1)	5 (3)	0.224
Diabetes without chronic complications	25 (16)	26 (17)	0.723
Diabetes with chronic complications	5 (3)	6 (4)	0.693
Paraplegia and hemiplegia	1 (1)	2 (1)	0.532
Renal disease	3 (2)	7 (5)	0.171
Cancer	40 (25)	28 (19)	0.160
Moderate or severe liver disease	0	0	-
Metastatic carcinoma	7 (4)	5 (3)	0.619
HIV/AIDS	0	1 (1)	0.304
Charlson Comorbidity Index Score, n (%)			
0	53 (33)	41 (27)	0.237
1	46 (29)	48 (32)	0.584
≥ 2	60 (38)	62 (41)	0.549
Immunomodulating treatment[a], n (%)	7 (4%)	21 (20)	0.004

IQR = interquartile range.
a) fingolimod, hydrocortisone, hydroxychloroquine, interferon beta-1b, leflunomide, mycophenolatmofetil, prednisolone/methylprednisolone, tacrolimus, tofacitinib.

At the time of admission, no significant differences between the two groups were observed in most vital signs and blood chemistry. However, there were minor differences in temperature and oxygen supply (**Table 2**). There was no significant difference when comparing the median baseline creatinine levels (p = 0.424) or eGFR (p = 0.610) of the two groups (Table 2). Very few patients (15/310 = 5%) had surgery during hospitalisation.

TABLE 2 Clinical and laboratory characteristics of patients with community-acquired bacteraemia.

	Exposed to gentamicin?		
	yes (N_y = 159)	no (N_n = 151)	p value
Duration of hospitalization median (IQR), days	6 (4-19)	8 (4-13)	0.080
Vital signs			
BP, median (IQR), mmHg:			
Systolic	126 (112-140)	123 (104-143)	0.321
Diastolic	64 (55-76)	66 (58-77)	0.152
Heart rate, median (IQR), /min.	98 (86-112)	96 (82-108)	0.637
Temperature, median (IQR), °C	38.5 (37.7-39.0)	37.7 (37.0-38.6)	< 0.001
Respiratory frequence, median (IQR), /min.	18 (16-22)	19 (16-24)	0.120
O_2 saturation, median (IQR), %	96 (95-97)	96 (93-98)	0.552
Need for O_2 supply, n[a] (%)	32 (20)	47 (31)	0.026
Glasgow Coma Scale, median (IQR)	15 (15-15)	15 (15-15)	0.997
Laboratory findings, median (IQR)			
Platelets, × 10^9/l	213 (158-271)	200 (152-271)	0.578
Bilirubin, mmol/l	15 (10-22)	15 (10-23)	0.734
CRP, mg/l	131 (48-206)	143 (57-238)	0.209
Leukocytes, × 10^9/l	13.4 (9.9-17.3)	13.6 (8.8-19.0)	0.966
Kidney function at admission, median (IQR)			
Creatinine, µmol/l	93 (73-119)	95 (76-120)	0.424
eGFR, ml/min.	62 (48-80)	58 (44-83)	0.610
Organ failure, n (%)			
qSOFA	12 (8)	15 (10)	0.456
SOFA	55 (34)	59 (39)	0.350
Focus of infection, n (%)			
Lower airways	1 (1)	16 (11)	< 0.001
Abdominal	25 (16)	23 (15)	0.905
Urinary tract	94 (59)	35 (23)	< 0.001
Skin	4 (3)	18 (12)	0.001
Other[b]	7 (4)	13 (9)	0.211
Unknown	28 (18)	48 (32)	0.004

BP = blood pressure; eGFR = estimated glomerular filtration rate; IQR = interquartile range; qSOFA = quick sequential organ failure assessment.
a) Number of total patients.
b) Cardiac, central nervous system, bones and joints, permanent intravascular access, upper airways, mediastinum.

Urinary tract infections were the most frequent infection type in the group administered gentamicin (59%). In contrast, an unknown focus of infection was the most frequent infection type in the patients not administered gentamicin (32%).

Using qSOFA scores, 27 patients were at increased risk of severe sepsis at admission. Among these, there was no significant difference in the risk of sepsis between the two study groups (p = 0.456). Furthermore, when scoring patients using the SOFA scores, an increased risk was found for 55 patients (34%) in the gentamicin group and 59 patients (39%) in the non-gentamicin group. This difference is insignificant (p = 0.350) (Table 2).

The most frequently used antibiotic in patients not administered gentamicin was piperacillin/tazobactam (56%)

(**Table 3**). In the group exposed to gentamicin, 93 patients were administered one dose, 50 patients two doses, and 16 patients three doses (Table 3). Table 3 presents the overall distribution of the bacterial pathogens found in the blood cultures.

TABLE 3 Antibiotic regimens and distribution of bacterial pathogens in positive blood cultures. Data are presented as n (%).

	Exposed to gentamicin?		
	yes (N_y = 159)	no (N_n = 151)	p value
Doses of gentamicin, n (%)			
1	93 (58)	-	
2	50 (31)	-	
3	16 (10)	-	
Non-gentamicin regimens, n (%)			
Piperacillin/tazobactam	15 (9)	84 (56)	-
Benzylpenicillin	23 (14)	22 (14)	-
Cephalosporins	14 (9)	17 (11)	-
Metronidazol	28 (18)	9 (6)	-
Ampicillin	103 (65)	3 (2)	-
Other[a]	0	34 (23)	-
Pathogens, n (%)			
Staphylococcus aureus	11 (7)	17 (11)	0.183
Coagulase-negative staphylococci	3 (2)	3 (2)	0.949
Streptococci:			
Streptococcus pneumoniae	2 (1)	12 (8)	0.005
β-haemolytic	9 (6)	22 (15)	0.009
Non-haemolytic	5 (3)	12 (8)	0.063
Enterococci	11 (7)	5 (3)	0.151
Other gram-positive[b]	1 (1)	6 (4)	0.048
Escherichia coli	79 (5)	43 (28)	< 0.001
Klebsiella spp.	22 (14)	11 (7)	0.062
Enterobacterales: non-*E.coli*/*Klebsiella* spp.	14 (9)	10 (7)	0.472
Pseudomonas aeruginosa	7 (4)	1 (1)	0.038
Other gram-negative[c]	5 (3)	9 (6)	0.233
Anaerobes, all	6 (4)	11 (7)	0.175
Polybacteraemia	12 (8)	8 (5)	0.420

a) Cloxacillin, dicloxacillin, clindamycin, clarithromycin, meropenem, amoxicillin/clavulanic acid, ciprofloxacin, doxycyclin, pivmecillinam.
b) *Actinotignum schaalii*, *Aerococcus urinae*, gram-positive rods
c) *Acinetobacter* species, *Aeromonas* species, *Campylobacter jejuni*, *Capnocytophaga canimorsus*, *Haemophilus influenzae*, *Stenotrophomonas maltophilia*.

There was no significant difference in the incidence of acquired AKI during hospitalisation between the exposed and non-exposed group (p = 0.338) (**Table 4**). Furthermore, two patients who developed AKI during their admission required the initiation of dialysis (Table 4). Concerning AKI, four patients (36%) of the exposed group and six patients (50%, p = 0.851) of the non-exposed groups showed normalisation of creatinine values within the follow-up period. Furthermore, the observed 30-day incidence of all-cause mortality between the exposed group

(n = 16) and the non-exposed group (n = 21) showed no significant difference (p = 0.280) (Table 4). Regarding admittance to the ICU, a total of seven patients from the gentamicin group and a total of 17 from the non-gentamicin group were admitted. This difference reached statistical significance (p = 0.024) (Table 4).

TABLE 4 Nephrotoxicity, intensive care and mortality in patients with community-acquired bacteraemia. Data are presented as n (%).

	Exposed to gentamicin?		
	yes (N_y = 159)	no (N_n = 151)	p value
AKI: creatinine increase > 40 µmol/l	11 (7)	12 (8)	0.715
Dialysis	0	2 (13)	0.207
Normalized creatinin values	4 (36)	6 (50)	0.851
AKI by KDIGO staging			
1	8 (8)	5 (3)	0.450
2	2 (1)	0	0.167
3	2 (1)	4 (3)	0.374
All-cause mortality 0-30 days	16 (10)	21 (14)	0.280
Intensive care	7 (4)	17 (11)	0.024

AKI = acute kidney injury; KDIGO = Kidney Disease Improving Global Outcomes.

When assessing the cause-specific hazard rate ratio for developing AKI, gentamicin treatment (HR = 0.86; 95% CI: 0.38-1.96), sex (HR = 0.79; 95% CI: 0.34-1.82), CCI score (HR = 1.01; 95% CI: 0.72-1.41) and qSOFA score (HR = 1.07; 95% CI: 0.25-4.56) could not be considered risk factors. Similar results were seen in the survival analysis as gentamicin treatment (HR = 0.73; 95% CI, 0.38-1.41) and sex (HR = 0.91; 95% CI: 0.47-1.77) could not be considered risk factors for higher mortality. As expected from previous literature, the survival analysis showed that a higher CCI score (HR = 1.45; 95% CI: 1.13-1.87) and qSOFA score (HR = 5.65; 95% CI: 2.77-11.54) were associated with an increased risk of mortality.

Discussion

In the present cohort of community-acquired bacteraemia, the 30-day mortality was 12%, which agrees with previous studies from Denmark of similar cohorts [4, 5] and from Sweden [6]. Patient survival was independent of the use of gentamicin. Notably, the primary end-point of AKI was not different between the two patient groups, reflecting that aminoglycosides administered once daily in the short term had no nephrotoxicity. The safety of short-term aminoglycoside treatment in sepsis has previously been reported for Sweden [6], Denmark [5] and the Netherlands [7]. Freundlich et al. [8] showed a moderate increase in serum creatinine levels but not the development of AKI. A Danish study reported a similar lack of nephrotoxicity, but the daily dose of gentamicin was 240 mg [9], which is lower than currently recommended, raising concerns about whether a higher dose of 5 mg/kg is safe. The results of our study confirm 5 mg/kg renal safety.

The Cochrane review by Paul et al. [1] concluded that aminoglycosides in combination with a β-lactam antibiotic should be discouraged. However, several of the studies in the review did not report short-term and single-dose gentamicin use, which is the currently recommended antibiotic regimen and the focus of our study. It is established practice in our region to use gentamicin as the preferred aminoglycoside. Moreover, during the study period, tobramycin was in limited supply, restricting its use to targeted therapy for *Pseudomonas aeruginosa* only.

It should be acknowledged that the previous tradition of administering multiple doses daily, reflected in the Cochrane review, is indeed associated with an increased risk of AKI [10]. Another review by Hayward et al. [11] described a significant number of patients with a transient rise in creatinine levels after only a one-off dose of gentamicin. However, the study itself identified some limitations and possible influential biases. Thus, they were unable to adjust for well-established AKI factors, such as comorbidities, age, other nephrotoxic drugs, defining and reporting adverse events, and surgical procedures. In fact, in the studies reporting a statistically significant increase in AKI, all patients were undergoing orthopaedic prophylactic arthroplasty surgery, with which older age and nonsteroidal anti-inflammatory drugs (NSAIDs) are highly associated.

The studies reporting increased renal injury in patients administered aminoglycosides differ in several ways from our study. Firstly, Ong et al. [12] used data from patients already admitted to the ICU, which indicates that patients' overall vital status at this point was severely compromised. This could mean that multi-factorial causes of acute renal impairment were present. In contrast, our study used data from patients with positive blood cultures, with only a tiny minority of patients admitted to the ICU. The complex and multi-factorial aspect of AKI in patients with severe sepsis or septic shock compared to patients with less severe sepsis was also addressed in Boyer et al. [13].

Our study had several strengths. The patient cohort reflects clinical practice with unselected patients admitted to the emergency department for suspected sepsis and should be generalisable to other hospitals in countries with the same pathogen distribution. The demographics, vital status and kidney function at admission were comparable between the two groups, the only significant differences being immunomodulatory treatment, temperature and need for oxygen. The study based the AKI definition on the KDIGO criteria, which are known for high sensitivity and specificity to ensure that acute renal impairment is identified [3].

However, our study also carries some limitations. Firstly, gentamicin dose is prescribed by weight, but weight is mostly estimated by the clinician or the patient, which brings uncertainty to the recommended dosage of 5 mg/kg. Secondly, to detect a gentamicin-induced AKI, patients must survive for a certain amount of time, which is not always the case, leading to potential survivorship bias. Cobussen et al. [7] mentioned this but also stated that AKI would develop within the first week of admission. Therefore, patients dying shortly after gentamicin-induced AKI should have a minimal statistical effect. Furthermore, since mortality was low in our cohort, this bias does not strongly influence our conclusions. To isolate gentamicin as the inducing factor for AKI, this study lacks information on other well-known nephrotoxic medications such as loop-diuretics, angiotensin-converting enzyme inhibitors-inhibitors and non-steroidal inflammatory drugs [5].

Furthermore, smoking, excessive use of alcohol and patient delay have not been noted, which are potential risk factors for developing AKI [6]. The major significant differences between the two groups lie within the focus of infection and, consequently, the type of pathogen. This results from the regional guidelines as gentamicin is primarily recommended for abdominal, urinary tract and unknown focus. We cannot exclude confounding by indication in the choice of antibiotic treatment, although the first dose was administered before the biochemistry results were available. With a retrospective study design, selection bias is inevitable, which could be solved by adopting a prospective study design. Lastly, it should be noted that this study cannot be used to describe the risk of AKI in patients excluded due to certain risk factors.

Conclusions

Short-term, once-daily treatment with gentamicin is safe with respect to mortality and nephrotoxicity. This study's results underpin the current national guidelines.

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