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Letter to the Editor

The need for gentamicin adjunctive to cefuroxime as empirical sepsis therapy: a local protocol evaluation

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To the Editor,

The updated guideline of the national Dutch Working Party on Antibiotic Policy (SWAB) for antibacterial therapy of adult patients with sepsis recommends against the addition of an aminoglycoside to a β-lactam agent for patients with sepsis or septic shock, unless local distribution of pathogens associated with sepsis and their antimicrobial susceptibilities justify its additional use [1]. However, these data are generally not readily available, and adjunctive gentamicin is often given. From an antimicrobial stewardship perspective, we evaluated our local sepsis protocol by assessing the potential benefit and risk of gentamicin adjunctive to cefuroxime by studying the results of blood culture and the incidence of acute kidney injury (AKI).

Blood culture results and serum creatinine levels from 72 hours before gentamicin administration (baseline) and up to 7 days after gentamicin administration were analysed from all 1007 patients (aged >18 years) treated with gentamicin for sepsis at the emergency department (ED) between January 2018 and July 2019. Gentamicin was dosed 3 or 5 mg/kg once daily, with therapeutic drug monitoring in case of multiple administrations. Sepsis was diagnosed as a dysregulated systemic inflammatory and immune response to confirmed or suspected microbial invasion from the urinary tract, the abdomen, or an unknown origin; per-protocol gentamicin should not have been administered in cases of evident pneumonia as the cause of sepsis. Blood cultures taken at the ED were incubated in an automated microbial detection system (BacT/ALERT 3D bioMérieux) and growth was identified with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker); sensitivity to antibiotics was determined with VITEK (bioMérieux) or by disk diffusion. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC cut-off values were used to determine sensitivity.

In our large (850-bed) non-university teaching hospital, only 32/1007 patients (3.2%) with sepsis (mean age 72 years and 59% male) potentially benefitted from gentamicin based on their blood culture results, compared to 911/1007 patients (90.5%) for whom gentamicin treatment was most likely not beneficial (Table 1). For the remaining 64/1007 patients (6.3%), no blood culture was performed. Gentamicin-sensitive microorganisms with intrinsic resistance to cefuroxime were found in 11/32 patients; cefuroxime-resistant and gentamicin-sensitive microorganisms were found in blood cultures of the remaining 21/32 patients.

Regarding the occurrence of AKI classified using the KDIGO (Kidney Disease Improving Global Outcomes) criteria [2], both pre and post gentamicin administration serum creatinine levels were available for 863 patients, of whom 91 (10.5%) experienced stage 1 AKI, 17 (2.0%) stage 2 AKI, and another 17 (2.0%) stage 3 AKI. Most of the patients (689, 79.8%) were dosed at 5 mg/kg, and 590 (68.4%) of the patients received just one administration of gentamicin. Any-stage AKI incidence (n = 125, 14.5%) increased with increasing baseline creatinine values, where AKI incidence was 9.3%, 21.4% and 26.7% for baseline estimated glomerular filtration rate (eGFR) groups >50 mL/min, 31–50 mL/min and <30 mL/min, respectively (p for trend <0.0001).

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Table 1
Overview of number of isolated organisms identified in patients ($n = 296$) with positive blood cultures

	Total number	Cefuroxime R/ESBL	Gentamicin R	Gentamicin R and cefuroxime R
Enterobacterales	**174**			2
Escherichia coli	125	18/6	6	1
Klebsiella species	28	5/2	1	1
Proteus mirabilis	12	0	1	0
Other[a]	9	7 (all AmpC)	0	0
Pseudomonas aeruginosa	**4**	4	1	1
Gram-positive cocci	**140**			
Staphylococcus aureus (methicillin-sensitive)	26	0	n/a	n/a
Coagulase-negative staphylococci (CNS)	36	n/r	n/r	n/r
Streptococcus pneumoniae (penicillin-sensitive)	21	0	n/a	n/a
Streptococci viridans group	20	0	n/a	n/a
Haemolytic streptococci[b]	25	0	n/a	n/a
Enterococci[c]	12	n/a	n/a	n/a
Other	**17**			
Bacteroides species	4	n/a	n/a	n/a
Neisseria meningitidis	3	0	n/a	n/a
Aerococcus urinae	3	0	n/a	n/a
Other[d]	8	1	0	n/a

In 37 patients two and in six patients three different isolates were identified in the same blood draw.
R, resistant; ESBL, extended-spectrum β-lactamase; S, sensitive; n/r, not relevant (all CNS cultured were determined to be the result of contaminated blood cultures); n/a, not applicable.
[a] *Enterobacter cloacae (5), Citrobacter koseri (1), Citrobacter freundii (1), Raoultella ornithinolytica (1), Serratia marcescens (1).*
[b] Group A (11), group B (7), C en G (7).
[c] *E. faecalis* (7), E. *faecium* (3), *E. gallinarum* (1), *E. cassiliflavus* (1).
[d] *Gemella morbilorum* (1), *Actinobaculum schaalii* (1), *Moraxella osloensis* (1), *Haemophilus parainfluenzae* (1), *Pseudomonas stutzeri* (1), *Ruminococcus species* (1), *Vibrio cholerae* (1), *Clostridium perfringens* (1).

Altogether, our evaluation demonstrated that only 3.2% of all patients receiving gentamicin at the ED had a bacteraemia with a pathogen resistant to cefuroxime and sensitive to gentamicin, yielding a number needed to treat of 31. Conversely, for at least 90.5% of our patients, the addition of gentamicin to cefuroxime did not add pathogen coverage. A recent scenario-based survey study identified physicians' minimum acceptable threshold of adequate pathogen coverage to be between 80% and 90% in the management of patients with mild and severe sepsis [3]. Applying this cut-off, our local protocol evaluation substantiates the removal of gentamicin from the empirical treatment protocol. In addition, removal is supported by a recently published analysis demonstrating that co-administration of an aminoglycoside as part of empirical therapy for Gram-negative sepsis did not result in improved outcomes, despite some improved pathogen coverage [4]. Whether this finding is also true for sepsis of unknown origin will follow from a study currently being undertaken [5].

Together with a substantial number needed to treat, we observed that one out of seven patients developed AKI after gentamicin. Although we cannot distinguish between AKI caused by sepsis and AKI caused by gentamicin toxicity, the incidence of AKI was as high as 27% in patients with a baseline eGFR <30 mL/min, suggesting an even more compromised risk–benefit balance in these patients. Considering these observations, we decided to remove adjunctive gentamicin from our protocol and treat patients with sepsis empirically with β-lactam monotherapy (ceftriaxone) and, in cases of suspicion for abdominal origin, with adjunctive metronidazole. This straightforward study design is a good example of how to implement one of the key objectives for antimicrobial stewardship: optimization of local guidelines based on local resistance patterns.

Ethics approval

This study was approved by the hospital ethics committee (MEC-U W20.012).

Author contributions

Authorship eligibility is based on the four ICMJE authorship criteria. All authors certify that they have participated sufficiently in the work to take public responsibility for the content. Study concept and design: AdVS, BS,NR, and EvdG. Data acquisition: AdVS, BS, and NR. Analysis and/or interpretation of data: AdVS, BS, NR, and EvdG. Drafting the manuscript: AdVS. Revising the manuscript critically for important intellectual content: AdVS, BS, AJM, NR, and EG. We have not received substantial contributions from non-authors.

Transparency declaration

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