Decontamination of cephalosporin-resistant Enterobacteriaceae during selective digestive tract decontamination in intensive care units

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Objectives: Prevalences of cephalosporin-resistant Enterobacteriaceae are increasing globally, especially in intensive care units (ICUs). The effect of selective digestive tract decontamination (SDD) on the eradication of cephalosporin-resistant Enterobacteriaceae from the intestinal tract is unknown. We quantified eradication rates of cephalosporin-resistant and cephalosporin-susceptible Enterobacteriaceae during SDD in patients participating in a 13 centre cluster-randomized study and from a single-centre cohort.

Methods: All SDD patients colonized with Enterobacteriaceae in the intestinal tract at ICU admission were included. Cephalosporin resistance was defined as resistance to ceftazidime, cefotaxime or ceftriaxone and aminoglycoside resistance as resistance to tobramycin or gentamicin. Duration of rectal colonization was determined by screening twice weekly during ICU stay. Swabs were inoculated on selective medium supplemented with tobramycin or cefotaxime.

Results: Five hundred and seven (17%) of 2959 SDD patients with at least one rectal sample were colonized with Enterobacteriaceae at ICU admission: 77 (15%) with cephalosporin-resistant Enterobacteriaceae and 50 (10%) with aminoglycoside-resistant Enterobacteriaceae. Fifty-six (73%) patients colonized with cephalosporin-resistant Enterobacteriaceae were successfully decontaminated before ICU discharge, as were 343 (80%) patients colonized with cephalosporin-susceptible Enterobacteriaceae (P=0.17). For aminoglycoside resistance, 31 (62%) patients were decontaminated, as were 368 patients (81%) colonized with aminoglycoside-susceptible Enterobacteriaceae (P<0.01). On average, decolonization was demonstrated after 4 days if colonized with cephalosporin-susceptible Enterobacteriaceae and aminoglycoside-susceptible Enterobacteriaceae, and after 5 and 5.5 days if colonized with cephalosporin-resistant Enterobacteriaceae and aminoglycoside-resistant Enterobacteriaceae, respectively (log-rank test P=0.053 for cephalosporin resistance and P=0.03 for aminoglycoside resistance). If eradication failed, no associations were found with increased resistance in time (P>0.05 for all comparisons).

Conclusions: SDD can successfully eradicate cephalosporin-resistant Enterobacteriaceae from the intestinal tract.

Keywords: SDD, ICUs, antibiotic resistance, selective decontamination

Introduction

Over the last decade, the epidemiology of antibiotic resistance in intensive care units (ICUs) is changing rapidly. Especially, the global emergence of (multi)resistant Gram-negative bacteria (GNB) is worrisome. After the finding of mobile genetic elements conferring resistance to most cephalosporins [extended-spectrum β-lactamases (ESBLs)] in the 1980s,¹ GNB are now capable of producing carbapenemases able to hydrolyse carbapenems. As the antibiotic pipeline is virtually empty,² infection prevention is becoming increasingly important, especially in ICU medicine.
Selective decontamination of the digestive tract (SDD) is a preventive antibiotic strategy aiming to eradicate so-called potential pathogenic microorganisms, such as Enterobacteriaceae, colonizing the respiratory and intestinal tract. SDD consists of topical antibiotics applied in the oropharynx and intestinal tract every 6 h throughout ICU stay and of systemic prophylaxis, usually cefotaxime, which is administered during the first 4 days after ICU admission. In Dutch ICUs, SDD was associated with a 13% reduction in day 28 mortality and with a 38% reduction in acquisition of antibiotic-resistant GNB in the respiratory tract, including cephalosporin-resistant Enterobacteriaceae, as compared with standard care. In another study, also from the Netherlands, acquisition rates of cephalosporin-resistant Enterobacteriaceae in the intestinal tract were similarly low in patients receiving and not receiving SDD. Furthermore, SDD has been successfully used to control an outbreak of multiresistant Enterobacteriaceae colonizing the intestinal tract in ICU patients in France. Moreover, successful eradication of intestinal carriage of GNB during SDD was associated with lower rates of ICU-acquired bacteremia. Nevertheless, there are hardly any data on the effects of SDD on the eradication of cephalosporin-resistant Enterobacteriaceae from the intestinal tract. Most cephalosporin-resistant Enterobacteriaceae are susceptible to colistin in vitro and many are still susceptible to tobramycin. Effective eradication of intestinal carriage of cephalosporin-resistant Enterobacteriaceae could, therefore, reduce both cephalosporin-resistant Enterobacteriaceae colonization pressure in the unit and the risk of ICU-acquired bacteraemia for the individual patient. Yet, controversy exists whether SDD can be applied safely to patients colonized with cephalosporin-resistant Enterobacteriaceae in terms of prolonged carriage and cumulating antibiotic resistance as compared with carriage of susceptible Enterobacteriaceae. We, therefore, quantified eradication rates of cephalosporin-susceptible and -resistant Enterobacteriaceae during SDD.

Methods

We used rectal culture results from all patients receiving SDD in a Dutch cluster-randomized study comparing SDD with selective oropharyngeal decontamination (SOD) and standard care (i.e., no SDD/SOD) in 13 ICUs from 2004 to 2006. In addition, from one participating hospital we included data from 19 extra months of SDD use from all SDD patients admitted to the ICU from January 2008 until August 2009. All patients with an expected length of ICU stay of >48 h were eligible to participate in the trial. The SDD regimen has been described previously. In short, it consisted of oropharyngeal application of a paste containing colistin, tobramycin and amphotericin B, each at a concentration of 2%, and administration of 10 mL of a suspension containing 100 mg of colistin, 80 mg of tobramycin and 500 mg of amphotericin B via a nasogastric tube. Topical antibiotics were applied four times daily until ICU discharge. In addition, cefotaxime (1000 mg, every 6 h) was administered intra-vously during the first 4 days of study. Rectal carriage of Enterobacteriaceae was determined at admission and twice weekly during ICU stay. For the present analysis we included all SDD patients with at least two rectal culture results and with the first sample obtained after 2 days in the ICU. If colonization with Enterobacteriaceae was present at ICU admission, antimicrobial susceptibility was determined for ceftazidime, cefotaxime and ceftriaxone, and isolates being resistant or intermediate resistant (MIC >8 mg/L) to any of these agents were considered to be cephalosporin-resistant Enterobacteriaceae. In addition, resistance or intermediate resistance to either tobramycin or gentamicin was determined (MIC >4 mg/L) and, if present, the isolate was considered to be resistant to aminoglycosides. The duration of the first episode of colonization was determined for all patients. Decolonization was defined as two consecutive cultures without growth of the particular colonization-defining bacteria. A single negative culture (or a single positive result with another bacterial species) in-between two positive cultures was not considered as decolonization. A patient was considered to be colonized with a certain Gram-negative species at discharge if the last culture obtained in the ICU grew that particular species. A detailed description of the microbiological methods can be found in the Supplementary data (available at JAC Online). The χ² test was used to test for significant differences. A P value of <0.05 was used to denote statistical significance. Kaplan–Meier analysis was performed to determine differences in colonization duration. Patients were censored when decontamination occurred or when discharged from the ICU. Data were analysed with SPSS version 15.0 (SPSS, Chicago, IL, USA) and GraphPad Prism version 5.0 for Windows® (GraphPad Software, San Diego, CA, USA).

Results

In all, 3187 patients received SDD; at least one rectal sample was obtained from 2959 patients and 507 were colonized with Enterobacteriaceae at ICU admission and had at least one follow-up rectal culture result. Of these 507 patients, 77 (15%) were colonized with cephalosporin-resistant Enterobacteriaceae and 50 (10%) with aminoglycoside-resistant Enterobacteriaceae on ICU admission. Coreistance occurred in 25 patients (5%). Fifty-six (73%) of the patients colonized with cephalosporin-resistant Enterobacteriaceae were successfully decontaminated before ICU discharge, as were 343 (80%) of the patients colonized with non-cephalosporin resistant Enterobacteriaceae (Table 1). Among those 50 patients with aminoglycoside-resistant Enterobacteriaceae, 31 (62%) were decontaminated, as were 368 patients (81%) with aminoglycoside-susceptible Enterobacteriaceae (P<0.01). On average, decolonization was demonstrated after 4 days in the ICU if colonized with cephalosporin-susceptible Enterobacteriaceae and aminoglycoside-susceptible Enterobacteriaceae, and after 5 and 5.5 days if colonized with cephalosporin-resistant Enterobacteriaceae and aminoglycoside-resistant Enterobacteriaceae, respectively (log-rank test P=0.053 for cephalosporin resistance and P=0.03 for aminoglycoside resistance) (Figure 1). Escherichia coli was the most prevalent species among patients carrying cephalosporin-susceptible Enterobacteriaceae (78%), but accounted for only 27% of the species among patients colonized with cephalosporin-resistant Enterobacteriaceae. In these patients, Enterobacter spp. were most prevalent (43%) (Table S1, available as Supplementary data at JAC Online). Eradication was not achieved in 108 patients (21%). To investigate the occurrence of cumulating antibiotic resistance during persistent colonization, resistance to ciprofloxacin, cephalosporins, aminoglycosides and carbapenems (imipenem or meropenem) was determined in the first and the last culture obtained in the ICU from these 108 patients. Colonization was demonstrated on admission and discharge in 24 (22%) and 21 (19%) patients, respectively, for ciprofloxacin-resistant Enterobacteriaceae, in 20 (19%) and 23 (21%) patients, respectively, for aminoglycosides, and in 7 (6%) and 9 patients (8%), respectively, for carbapenems. Cephalosporin-resistant Enterobacteriaceae were present in 25 (23%) admission cultures as compared with 24 (22%)
discharge cultures. Resistance to at least one of the tested antibiotic classes in the first and the last culture was detectable in 23 (21%) and 24 (22%) patients on admission and discharge, respectively. None of these differences between admission and discharge prevalence were statistically significant (P values all ≥ 0.6) (Table S2, available as Supplementary data at JAC Online).

**Discussion**

In this nested post hoc analysis of a cluster-randomized study supplemented with single-centre data, SDD appeared to be equally effective in eradicating intestinal carriage of cephalosporin-resistant and cephalosporin-susceptible Enterobacteriaceae, with an average time to eradication of 5 days and with successful eradication in 80% and 73% of the patients, respectively. Yet, for aminoglycoside-resistant Enterobacteriaceae eradication rates were lower than for aminoglycoside-susceptible isolates, though the majority of patients were successfully decontaminated in the ICU during SDD (62% versus 81%, respectively). If eradication failed, no associations were found with increased resistance in time.

We used ceftazidime, cefotaxime and ceftriaxone as marker antibiotics to classify cephalosporin-resistant Enterobacteriaceae. These marker antibiotics can be considered as a proxy for ESBL production in Enterobacteriaceae. Unfortunately, ESBL production was not confirmed during the period of study to distinguish ESBL-producing Enterobacteriaceae from non-ESBL-producing Enterobacteriaceae.

In the analysis we did not take into account the intravenously administered antibiotics as a separate factor, as we considered the high intraluminal concentrations of the topical antibiotics to be the most important factor in decontaminating colonized patients. In addition, part of the SDD regimen is the 4 day course of cefotaxime that all patients received. Furthermore, most of the systemic antibiotics with activity against cephalosporin-resistant Enterobacteriaceae are excreted via the
kidneys, therefore hardly influencing intestinal decontamination rates.\textsuperscript{8,9} None of the patients received tigecycline, which is mostly excreted in bile, affecting the intestinal flora.\textsuperscript{10}

Similar rates of effectiveness have been reported from other, much smaller studies in specific patient populations. In a paediatric ICU, 23 of 1101 children (2.1\%) were intestinal ESBL carriers at some point during ICU admission and received SDD.\textsuperscript{11} The overall decontamination rate was 54\%; however, no rate was provided for intestinal ESBL carriage only. In another study, all patients detected as ESBL carriers between 2000 and 2008 received an SDD regimen containing chlorhexidine mouth rinse and oral paromomycin for intestinal decolonization. Of the 18 patients that completed the SDD strategy, carriage was effectively eradicated in 15 (83\%).\textsuperscript{12}

The strength of the present study is the size of the study population, with 3187 SDD patients all subjected to the same screening schedule. Limitations include the absence of a control population not receiving SDD and the lack of detailed specific patient information to investigate determinants associated with failure of eradication.

Our findings demonstrate successful intestinal decontamination of cephalosporin-resistant Enterobacteriaceae, which may reduce both cross-transmission and infection rates. Failure of eradication was not associated with increased resistance during ICU stay. In view of the global increase in infections caused by ESBL-producing and carbapenemase-producing bacteria, this approach deserves careful evaluation, using stringent surveillance policies to monitor ecological safety.

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Transparency declarations
None to declare.

Supplementary data
A detailed description of the microbiological methods, Table S1 and Table S2 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References