Original article

The effects of topical antibiotics on eradication and acquisition of third-generation cephalosporin and carbapenem-resistant Gram-negative bacteria in ICU patients; a *post hoc* analysis from a multicentre cluster-randomized trial

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A B S T R A C T

Objectives: The aim was to quantify the effects of selective digestive tract decontamination (SDD) consisting of a mouth paste and gastro-enteral suspension, selective oropharyngeal decontamination with a mouth paste (SOD) and 1–2% chlorhexidine (CHX) mouthwash on eradication and acquisition of carriage of third-generation cephalosporin-resistant Enterobacterales (3GCR-E) and carbapenem-resistant Gram-negative bacteria (CR-GNB) in Intensive Care Unit (ICU) patients.
Methods: This was a nested cohort study within a cluster-randomized cross-over trial in six European countries and 13 ICUs with 8665 patients. Eradication and acquisition during ICU stay of 3GCR-E and CR-GNB were investigated separately in the rectum and respiratory tract for the three interventions and compared with standard care (SC) using Cox-regression competing events analyses.
Results: Adjusted cause specific hazard ratios (CSHR) for eradication of rectal carriage for SDD were 1.76 (95% CI 1.31–2.36) for 3GCR-E and 3.17 (95% CI 1.60–6.29) for CR-GNB compared with SC. For the respiratory tract, adjusted CSHR for eradication of 3GCR-E were 1.47 (0.98–2.20) for SDD and 1.38 (0.92–2.06) for SOD compared with SC, and for eradication of CR-GNB these were 0.77 (0.41–1.45) for SDD and 0.81 (0.44–1.51) for SOD, compared with SC. Adjusted CSHRs for acquisition of rectal carriage during SDD (compared with SC) were 0.51 (0.40–0.64) for 3GCR-E and of 0.56 (0.40–0.78) for CR-GNB. Adjusted CSHRs for acquiring respiratory tract carriage with 3GCR-E compared with SC were 0.38 (0.28–0.50) for SDD and 0.55 (0.42–0.71) for SOD, and for CR-GNB 0.46 (0.33–0.64) during SDD and 0.60 (0.44–0.81) during SOD, respectively. SOD was not associated with eradication or acquisition of 3GCR-E and CR-GNB in the rectum.
Conclusions: Among mechanically ventilated ICU patients, SDD was associated with more eradication and less acquisition of 3GCR-E and CR-GNB in the rectum than SC. SDD and SOD were associated with less acquisition of both 3GCR-E and CR-GNB than SC in the respiratory tract. **N.L. Plantinga, Clin Microbiol Infect 2020;26:485**

Introduction

The incidence of infections caused by third-generation cephalosporin-resistant Enterobacterales (3GCR-E) and carbapenem-resistant Gram-negative bacteria (CR-GNB) is rising in ICU patients. Reducing carriage of these bacteria during ICU stay will aid in preventing infections and cross-transmission. Decontamination

regimens such as selective digestive decontamination (SDD) and selective oropharyngeal decontamination (SOD) have been associated with reduced prevalence of carriage with antibiotic-resistant Gram-negative bacteria (GNB) in settings with low resistance levels [1,2], have been used in control strategies for outbreaks of ESBL and CR-GNB and for decontamination of colonized patients [3–5] with different results [6–10]. There is, however, considerable heterogeneity across studies in terms of study populations, clinical settings, definitions of decolonization, length of follow-up and decontamination regimens applied. Moreover, the efficacy of chlorhexidine (CHX) mouthwash without concomitant topical antibiotics for reducing carriage in the respiratory tract has not been determined. A recently performed systematic review on decolonization of multidrug-resistant Gram-negative bacteria carriers emphasized the absence of scientific data in this field, leading to recommendation for not using 'routine decolonization' of 3GCR-E and CR-GNB [11]. We, therefore, aimed to determine the efficacy SDD, SOD and CHX 1–2% mouthwash on eradication of 3GCR-E and CR-GNB from the rectum and respiratory tract and on acquisition of these bacteria during Intensive Care Unit (ICU) stay.

Methods

Study populations

We analysed data from 13 European ICUs with moderate-to-high prevalence of antibiotic resistance (>5% of Gram-negative bacteraemia in ICU caused by ESBL in 2011) that included mechanically ventilated patients in a cluster randomized cross-over trial between December 2013 and May 2017, in which the effect of SDD, SOD and CHX 1–2% mouthwash on patient outcome and antibiotic resistance were compared with a baseline period of standard care (SC) (www.clinicaltrials.gov, NCT02208154) [12]. Protocolized infection control measures throughout the R-GNOSIS ICU study were the daily use of chlorhexidine 2% bodywash and hand hygiene according to the WHO protocol with weekly observations. Moreover, 11 out of 13 ICUs used chlorhexidine 0.12/0.20% mouthwash (four per day) during standard care (please see supplementary material)

Rectum and respiratory tract surveillance samples (endotracheal aspirates, sputum or throat swabs) were obtained twice weekly (Monday and Thursday) during mechanical ventilation; results from rectum and respiratory samples obtained for clinical reasons were also part of the analyses.
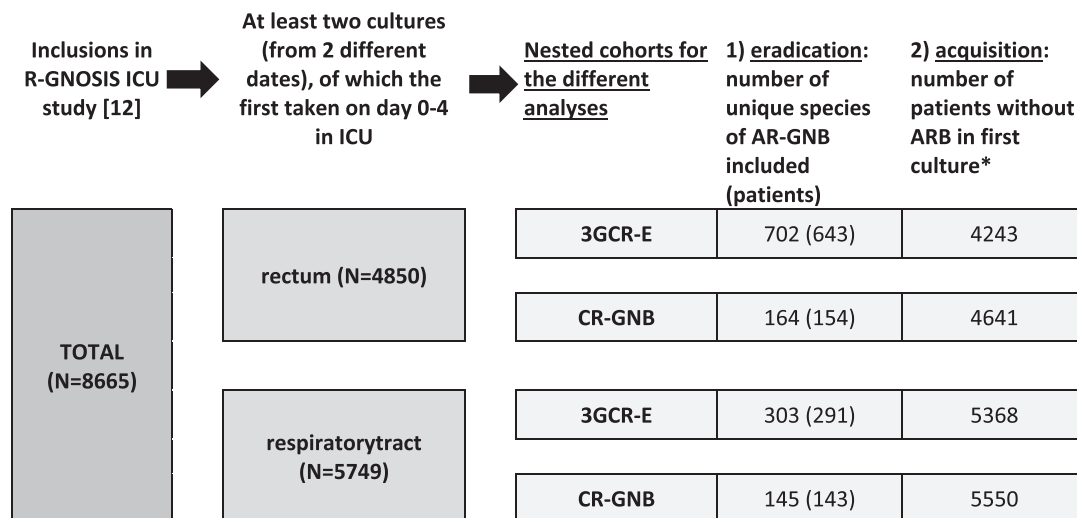
From the main study, eight nested cohorts were created, one for each outcome (eradication and acquisition) for different antibiotic-resistant GNB (3GCR-E and CR-GNB) separately in two body sites (the rectum and respiratory tract) (Fig. 1 and Fig. S1). 3GCR-E was defined as any species of Enterobacterales with resistance to cefotaxime, ceftriaxone and/or ceftazidime, whichever antibiotic was tested. CR-GNB was defined as any species of Enterobacterales or glucose non-fermenting Gram-negative bacteria (NF-GNB) with resistance to imipenem, meropenem or doripenem.

For eradication, all unique species with documented resistance to 3GCR or carbapenems in the rectum or respiratory tract at any time during the first 5 days in ICU, labelled as 'initial ICU stay', and with at least one rectum or respiratory culture following the index culture, were included. These species were at risk until eradication was reached, which was defined as the day of the first culture without the resistant species of interest (3GCR-E or CR-GNB), with all − if any − subsequent cultures negative for that resistant species.

For acquisition, we included patients (instead of species) with at least two cultures for the specific body site (rectum or respiratory tract), of which the first was taken on day 0–4 in ICU and not yielding the antibiotic-resistant GNB for which acquisition was studied; hence all relevant species detected in the first culture had to be susceptible to 3GC or carbapenems. These patients were at risk from ICU admission until the day of acquisition, which was defined as the day of the first culture yielding any 3GCR-E, or CR-GNB, from the body site of interest. For those not meeting the study endpoint (eradication or acquisition) follow-up ended at the day of death or discharge from ICU. The need for informed consent was waived by the local ethics committees.

Microbiology

Surveillance samples were inoculated on selective chromogenic media (ESBL chrom-ID, bioMérieux, Marcy-l'Étoile, France) and

		1) eradication: number of unique species of AR-GNB included (patients)	2) acquisition: number of patients without ARB in first culture*
rectum (N=4850)	**3GCR-E**	702 (643)	4243
	CR-GNB	164 (154)	4641
respiratory tract (N=5749)	**3GCR-E**	303 (291)	5368
	CR-GNB	145 (143)	5550

Inclusions in R-GNOSIS ICU study [12] → At least two cultures (from 2 different dates), of which the first taken on day 0-4 in ICU → Nested cohorts for the different analyses

TOTAL (N=8665)

Fig. 1. Flowchart nested cohorts for eradication and acquisition of 3GCR-E and CR-GNB in rectum and respiratory tract. AR-GNB, antibiotic-resistant Gram-negative bacteria; 3GCR-E, third-generation cephalosporin-resistant Enterobacterales; CR-GNB, carbapenem-resistant Gram-negative bacteria. *If multiple species of GNB were present in the first culture, all needed to have documented absence of resistance, i.e. at least one susceptible result in absence of a resistant result for the antibiotic class under study (ceftriaxone, cefotaxim or ceftazidim for 3GCR-E; imipenem, meropenem or doripenem for CR-GNB).

Table 1
Number of antibiotic-resistant GNB species included for eradication analyses per tractus over all study periods

	Acinetobacter baumannii	Citrobacter freundii	Enterobacter species	Escherichia coli	Hafnia alvei	Klebsiella oxytoca	Klebsiella pneumoniae	Morganella morganii	Proteus species	Pseudomonas aeruginosa	Serratia marcescens	Other	Total
Rectum													
3GC-resistant Enterobacterales													
Unique species	N/A	27	88	346	5	25	157	3	8	N/A	1	42	702
Row %		3.8%	12.5%	49.3%	0.7%	3.6%	22.4%	0.4%	1.1%		0.1%	6.0%	
Carbapenem-resistant Gram-negative bacteria													
Unique species	12	3	11	5	0	4	44	2	2	72	0	9	164
Row %	7.3%	1.8%	6.7%	3.0%	0.0%	2.4%	26.8%	1.2%	1.2%	43.9%	0.0%	5.5%	
Respiratory tract													
3GC-resistant Enterobacterales													
Unique species	N/A	13	56	73	12	10	91	4	2	N/A	13	29	303
Row %		4.3%	18.5%	24.1%	4.0%	3.3%	30.0%	1.3%	0.7%		4.3%	9.6%	
Carbapenem-resistant Gram-negative bacteria													
Unique species	20	1	6	0	0	0	23	1	0	79	1	14	145
Row %	13.8%	0.7%	4.1%	0.0%	0.0%	0.0%	15.9%	0.7%	0.0%	54.5%	0.7%	9.7%	

Number of species that were eradicated in the eradication cohorts. Row percentages represent the proportion of all eradicated species in that tractus.
3GCR-E: third-generation cephalosporin; GNB: Gram-negative bacteria.

Table 2
Number of antibiotic-resistant GNB species acquired during ICU-stay per tractus over all study periods

	Acinetobacter baumannii	Citrobacter freundii	Enterobacter species	Escherichia coli	Hafnia alvei	Klebsiella oxytoca	Klebsiella pneumoniae	Morganella morganii	Proteus species	Pseudomonas aeruginosa	Serratia marcescens	Other	Total
Rectum													
3GC-resistant Enterobacterales													
Unique species	N/A	49	231	221	12	30	253	13	7	N/A	12	25	853
Row %		5.7%	27.1%	25.9%	1.4%	3.5%	29.7%	1.5%	0.8%		1.4%	2.9%	
Carbapenem-resistant Gram-negative bacteria													
Unique species	18	3	33	8	2	7	104	2	2	149	4	11	343
Row %	5.2%	0.9%	9.6%	2.3%	0.6%	2.0%	30.3%	0.6%	0.6%	43.4%	1.2%	3.2%	
Respiratory tract													
3GC-resistant Enterobacterales													
Unique species	N/A	20	157	55	16	26	162	16	11	N/A	37	10	510
Row %		3.9%	30.8%	10.8%	3.1%	5.1%	31.8%	3.1%	2.2%		7.3%	2.0%	
Carbapenem-resistant Gram-negative bacteria													
Unique species	43	1	23	3	0	3	65	1	2	217	4	21	383
Row %	11.2%	0.3%	6.0%	0.8%	0.0%	0.8%	17.0%	0.3%	0.5%	56.7%	1.0%	5.5%	

Number of species acquired during ICU stay in the acquisition cohorts. Row percentages represent the proportion of all acquired species in that tractus.
3GC, third-generation cephalosporin; GNB, Gram-negative bacteria.

clinical samples were analysed according to local protocols. Species identification and resistance determination was done by disc diffusion or automated methods using VITEK (bioMérieux) or Phoenix (BD diagnostics, Franklin Lakes, NJ, USA) according to local protocols. The methods of susceptibility testing per hospital did not change during the study. When multiple samples from one body site were taken on one day, results were interpreted as a single culture result.

Statistical analysis

For all outcomes, crude incidence rates per 1000 days at risk, and incidence rate ratios (IRR) with 95% confidence intervals (CI) were calculated to compare the interventions with standard care. Survival analyses were performed using Cox regression, adjusting for disease severity score on ICU admission, antibiotic use at the time of ICU admission, the Charlson comorbidity index and clustering within ICU (using a random effect in eradication analyses, stratum for acquisition analyses) [13]. Moreover, analyses accounted for ICU discharge and death in ICU as competing events, and for left truncation.

Two different disease severity scores were used by ICUs, either APACHE II score or SAPS II score. We standardized both scores and included an interaction term between the standardized score and a dummy variable for ICU using APACHE or ICU using SAPS in the Cox models. For statistical analyses we used IBM SPSS statistics version 21 and R software version 3.2.2 (R project for Statistical Computing).

Results

Study populations

Among the 8665 ICU admissions enrolled in the main study, there were 4850 patients with two or more rectal and 5749 with two or more respiratory tract cultures of which the first was taken during initial ICU-stay (days 0–4) (Fig. 1 and Fig. S1). From these, four cohorts were created to study eradication including 1314 unique micro-organisms, from 936 unique patients (Table 1; Table S2). Similarly, four cohorts were created for acquisition, including 4243 and 4641 *patients* at risk for rectal acquisition of 3GCR-E and CR-GNB, respectively, and 5368 and 5550 patients at risk for respiratory tract acquisition of 3GCR-E and CR-GNB, respectively (Fig. S1). The numbers of antibiotic-resistant GNB acquired in the acquisition cohorts are described in Table 2. Patient characteristics of the different cohorts are listed in Tables S1a and b. Hospital-level characteristics, infection control and outcome measures as well as the (relative) contribution of patients from hospitals to the current cohorts is presented in Table S3.

Eradication of rectal carriage

Eradication rates for 3GCR-E and CR-GNB species were 40.6 and 31.8/1000 days, respectively, during SC and 69.4 and 99.3/1000 days for 3GCR-E and CR-GNB, respectively, during SDD (Table 3, Figs. S2 and S3). The adjusted cause specific hazard rates (CSHRs) for eradication of rectal carriage during SDD, compared with SC, were 1.76 (95% CI 1.31–2.36) for 3GCR-E and 3.17 (95% CI 1.60–6.29) for CR-GNB (Table 3). CSHRs for SOD and CHX were not statistically significantly different from SC (Table 3).

Eradication of respiratory tract carriage

Eradication rates for 3GCR-E and CR-GNB were 61.1 and 76.2/1000 days, respectively, during SC, 102.1 and 67.9/1000 days for 3GCR-E and CR-GNB, respectively, during SDD, and were 102.8 and 62.3/1000 days for 3GCR-E and CR-GNB, respectively, during SOD (Table 3). Adjusted CSHRs for eradication of 3GCR-E were, compared with SC, 1.47 (95% CI 0.98–2.20) during SDD and 1.38 (95%CI 0.92–2.06) during SOD. Proportions of 3GCR-E and CR-GNB species identified during initial ICU stay persisting in respiratory

Table 3
Eradication of 3GCR-E and CR-GNB from the rectum and respiratory tract

	SC	CHX	SOD	SDD
Rectum				
3GC-resistant Enterobacterales				
Number of unique isolates in cohort	177	168	180	177
Number of events (eradication rate/1000 days at risk)	76 (40.6)	69 (28.6)	74 (41.0)	105 (69.4)
Comparison with standard care				
Crude: eradication rate ratio (95% CI)		0.70 (0.50 – 0.99)	1.01 (0.72 – 1.41)	1.71 (1.26 – 2.33)
Adjusted: cause specific hazard ratio (95% CI)		0.82 (0.58 – 1.14)	0.95 (0.68 – 1.33)	1.76 (1.31 – 2.36)
Carbapenem-resistant Gram-negative bacteria				
Number of unique isolates in cohort	44	36	38	46
Number of events (eradication rate/1000 days at risk)	46 (31.8)	15 (40.4)	16 (43.2)	31 (99.4)
Comparison with standard care				
Crude: Eradication rate ratio (95% CI)		1.27 (0.59 – 2.75)	1.36 (0.64 – 2.90)	3.12 (1.66 – 6.11)
Adjusted: cause specific hazard ratio (95% CI)		1.12 (0.51 – 2.45)	1.09 (0.51 – 2.34)	3.17 (1.60 – 6.29)
Respiratory tract				
3GC-resistant Enterobacterales				
Number of unique isolates in cohort	79	77	75	72
Number of events (eradication rate/1000 days at risk)	49 (61.1)	49 (49.6)	52 (102.8)	53 (102.1)
Comparison with standard care				
Crude: eradication rate ratio (95% CI)		0.81 (0.54 – 1.23)	1.68 (1.12 – 2.54)	1.67 (1.11 – 2.52)
Adjusted: cause specific hazard ratio (95% CI)		0.86 (0.57 – 1.30)	1.38 (0.92 – 2.06)	1.47 (0.98 – 2.20)
Carbapenem resistant Gram-negative bacteria				
Number of unique isolates in cohort	37	32	42	34
Number of events (eradication rate/1000 days at risk)	24 (76.2)	14 (41.5)	21 (62.3)	18 (67.9)
Comparison with standard care				
Crude: eradication rate ratio (95% CI)		0.55 (0.26–1.10)	0.82 (0.43–1.53)	0.89 (0.46–1.71)
Adjusted: cause specific hazard ratio (95% CI)		0.61 (0.31–1.20)	0.81 (0.44–1.51)	0.77 (0.41–1.45)

SC, standard care; CHX, chlorhexidine mouthwash; CI, confidence interval; *n*, number; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination.

tract cultures during ICU stay are depicted in the supplement (Figs. S4 and S5).

Acquisition of rectal carriage

Acquisition rates with 3GCR-E and CR-GNB were 14.1 and 5.6/1000 days at risk, for 3GCR-E and CR-GNB, respectively, during SC, and were 7.6 and 3.3/1000 days at risk, for 3GCR-E and CR-GNB, respectively, during SDD yielding adjusted CSHRs (for SDD compared with SC) of 0.51 (95% CI 0.40—0.64) for 3GCR-E and of 0.56 (95% CI 0.40—0.78) for CR-GNB (Table 4). SOD did not reduce rectal acquisition of 3GCR-E and CR-GNB, whereas the adjusted CSHR for rectal acquisition of CR-GNB during CHX (compared with SC) was 0.69 (95% CI 0.50—0.93) (Table 4). Cumulative rectal acquisition of 3GCR-E and CR-GNB throughout the first 21 days in ICU and from the first negative culture for these microorganisms (taken in day 0—4) are visualized in Figs. S6 and S7.

Acquisition of respiratory tract carriage

Acquisition rates for 3GCR-E and CR-GNB were 8.4 and 5.8/1000 days at risk, respectively, during SC, 3.5 and 2.7/1000 days for 3GCR-E and CR-GNB, respectively, during SDD, and were 4.7 and 3.7/1000 days for 3GCR-E and CR-GNB, respectively, during SOD (Table 4). Adjusted CSHRs for acquiring carriage with 3GCR-E, compared with SC, were 0.38 (95% CI 0.28—0.50) for SDD and 0.55 (95% CI 0.42—0.71) for SOD, and these were 0.46 (95% CI 0.33—0.64) and 0.60 (95% CI 0.44—0.81) for acquisition of CR-GNB during SDD and SOD, respectively. Acquisition rates with 3GCR-E and CR-GNB during CHX did not differ significantly from SC. Cumulative respiratory tract acquisition of 3GCR-E and CR-GNB throughout the first 21 days in ICU and from the first negative culture for these microorganisms (taken in day 0—4) are visualized in Figs. S8 and S9.

Including the competing events ICU-death and ICU-discharge in analyses did not change interpretation (Table S4).

Discussion

In this study, where patients with an expected duration of mechanical ventilation of 24 hours or more were treated with SDD, SOD or CHX mouthwash, or received none of these interventions, SDD was associated with more eradication of 3GCR-E and CR-GNB from the rectum than SC. Moreover, SDD was associated with less acquisition of both 3GCR-E and CR-GNB, compared with SC, in the respiratory tract and rectum, and SOD was associated with less acquisition of these bacteria in the respiratory tract. Although these findings did not translate to effects on clinical outcomes [12], the current findings strongly suggest that the use of high levels of both colistin and tobramycin in the topical components of selective decontamination are effective against GNB resistant to 3GC and/or carbapenems. Increased decolonization and reduced acquisition of such bacteria most probably reduces the risk of cross-transmission, as well as the risk of so-called endogenous infections for individual patients [14,15]. Rectal eradication rates with SDD — when using both topical colistin and an aminoglycoside — among adults in previous studies were 52% for ESBL Enterobacterales at 28 days (vs. 37% without SDD, p 0.27) [3], 73% for 3GCR-E (vs. 80% for 3GC-susceptible Enterobacterales, also with SDD, p >0.05) [16], 43% for KPC-2-producing *Klebsiella pneumoniae* (vs. 30% without SDD, p 0.102) [7], and 58.5% for carbapenem-resistant *Klebsiella pneumoniae* after 6 weeks of follow-up (vs. 33.3% without SDD) [4]. These studies differ from each other with regard to the study population, duration and type of antibiotic regimens and length of follow-up, and the 2019 guideline of the European Society of Clinical Microbiology and Infectious Diseases on decolonization of multidrug-resistant Gram-negative bacteria qualifies the evidence from controlled studies as of 'very low to moderate certainty for microbiological eradication of 3GCR-E' [11].

SOD and SDD effectively reduced acquisition of 3GCR-E and CR-GNB in the respiratory tract, but did not cause eradication of these AR-GNB in the respiratory tract, possibly because oropharyngeal

Table 4
Acquisition of 3GCR-E and CR-GNB in the rectum and respiratory tract

	SC	CHX	SOD	SDD
Rectum				
3GC-resistant Enterobacterales				
Number in cohort	1113	1031	1047	1052
Number of events (acquisition rate/1000 days)	216 (14.1)	206 (15.3)	215 (15.6)	111 (7.6)
Comparison with standard care				
Crude: acquisition rate ratio (95%-CI)		1.06 (0.87—1.28)	1.10 (0.91—1.33)	0.53 (0.42—0.67)
Adjusted: cause specific hazard ratio (95% CI)		1.02 (0.84—1.24)	1.11 (0.91—1.35)	0.51 (0.40—0.64)
Carbapenem-resistant Gram-negative bacteria				
Number in cohort	1215	1131	1147	1148
Number of events (acquisition rate/1000 days)	104 (5.6)	69 (4.1)	88 (5.2)	57 (3.3)
Comparison with standard care				
Crude: acquisition rate ratio (95% CI)		0.72 (0.53—0.98)	0.92 (0.69—1.22)	0.59 (0.43—0.82)
Adjusted: cause specific hazard ratio (95% CI)		0.69 (0.50—0.93)	0.83 (0.62—1.12)	0.56 (0.40—0.78)
Respiratory tract				
3GC-resistant Enterobacterales				
Number in cohort	1369	1304	1380	1315
Number of events (acquisition rate/1000 days)	163 (8.4)	144 (8.1)	94 (4.7)	65 (3.5)
Comparison with standard care				
Crude: acquisition rate ratio (95% CI)		0.96 (0.77—1.20)	0.56 (0.43—0.72)	0.41 (0.31—0.54)
Adjusted: cause specific hazard ratio (95% CI)		0.94 (0.74—1.18)	0.55 (0.42—0.71)	0.38 (0.28—0.50)
Carbapenem-resistant Gram-negative bacteria				
Number in cohort	1411	1359	1414	1366
Number of events (acquisition rate/1000 days)	118 (5.8)	94 (4.8)	77 (3.7)	54 (2.7)
Comparison with standard care				
Crude: acquisition rate ratio (95% CI)		0.84 (0.64—1.11)	0.65 (0.49—0.86)	0.48 (0.35—0.66)
Adjusted: cause specific hazard ratio (95% CI)		0.82 (0.62—1.09)	0.60 (0.44—0.81)	0.46 (0.33—0.64)

3GC, third-generation cephalosporin; SC, standard care; CHX: chlorhexidine mouthwash; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination.

mouth paste does not reach effective concentrations in the lower parts of the respiratory tract. The observed reduction in rectal acquisition of CR-GNB during CHX mouthwash cannot be biologically explained as it is unlikely that chlorhexidine reached the lower digestive tract, and is, therefore, considered a spurious finding.

The current study adds information coming from a large cohort of patients treated with SDD, SOD and CHX as part of a cluster-randomized intervention and a control group. It provides evidence that topical antibiotic regimens containing colistin and an aminoglycoside reduce detectable carriage of 3GCR-E and CR-GNB in the rectum and respiratory tract in ICU-patients, through both eradication and prevention of acquisition in settings with moderate to high-levels of carriage with 3GCR-E and CRE.

However, justification of the use of selective decontamination should be based on improved patient outcomes, which could not be demonstrated in the main study [12], nor has it been demonstrated in comparable ICUs with moderate-to-high levels of antibiotic resistance. Failure to eradicate Gram-negative bacteria from the respiratory tract or rectum during SDD has been associated with higher incidences of ICU-acquired bloodstream infection (BSI) in patients receiving SDD [14]. Conversely, eradication of carriage and prevention of acquisition could be expected to reduce acquired BSI rates. In the main study, the incidence of ICU-acquired BSI caused by antibiotic-resistant GNB tended to be lower with SDD than during SC, although statistical significance was not reached (CSHR 0.70; 95% CI 0.43–1.14) [12]. Associations between carriage of resistant GNB and ICU-acquired BSI, as well as possible explanations for absence of clinical effectiveness in the R-GNOSIS ICU study (effect modification) are subjects of further evaluation.

Selection of colistin-resistant isolates could be an important adverse event of using this antibiotic for decontamination purposes. Indeed, an increase in resistance against colistin and gentamicin following eradication treatment for KPC-2-producing *Klebsiella pneumoniae* isolates has been reported [7]. In the current study the prevalence of colonization with colistin-resistant Enterobacterales was low during all study periods (<2.4% in the rectum and <1.0% in the respiratory tract during unit-wide point prevalence surveys), as were incidences of ICU-acquired BSI caused by species intrinsically resistant to colistin (ten episodes during SDD, 30 episodes during standard care) [12]. Yet, SOD was temporarily interrupted in one ICU because of clonal transmission of colistin-resistant *Klebsiella pneumoniae*.

Strengths of this study are its sample size, a standardized surveillance protocol reducing information bias, the cluster-randomized allocation of interventions and the presence of patients not receiving any intervention for reference. The last one allowed determination of the natural history of bacterial carriage during ICU-stay, i.e. in the absence of interventions that aim to modulate bacterial carriage. During SC, more than half of all unique species of 3GCR-E or CR-GNB initially colonizing the respiratory tract became undetectable during ICU-stay. Carriage may have been affected by intravenous antibiotics, but absence of patient-specific antibiotic use precluded such analyses.

Study limitations include the absence of confirmation of carbapenemase or ESBL production in phenotypically resistant bacteria, as this was not routine practice in most participating microbiology laboratories. Furthermore, the duration of follow-up was limited to ICU-stay. In four other studies investigating the effects of topical antibiotics on carriage with antibiotic-resistant GNB in ICU patients, follow-up ranged from 2 to 7 weeks and carriage tended to reappear after initial decontamination [3,4,9,17]. Finally, we used surveillance cultures to determine eradication and acquisition. Naturally, this approach suffers from incomplete detection, potentially leading to misclassification of endpoints.

Also, the inability of bacteria to grow in cultures may be a consequence of suppression, rather than eradication. Yet, methodology was standardized across all study periods, thereby limiting detection bias.

Conclusion

Among mechanically ventilated ICU patients, SDD was associated with more eradication and less acquisition of 3GCR-E and CR-GNB in the rectum than SC, and SDD and SOD were associated with less acquisition of both 3GCR-E and CR-GNB than SC in the respiratory tract.

Transparency Declaration

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.08.001.

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