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Associations Between Enteral Colonization With Gram-Negative Bacteria and Intensive Care Unit–Acquired Infections and Colonization of the Respiratory Tract

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Background. Enteral and respiratory tract colonization with gram-negative bacteria may lead to subsequent infections in critically ill patients. We aimed to clarify the interdependence between gut and respiratory tract colonization and their associations with intensive care unit (ICU)–acquired infections in patients receiving selective digestive tract decontamination (SDD).

Methods. Colonization status of the rectum and respiratory tract was determined using twice-weekly microbiological surveillance in mechanically ventilated subjects receiving SDD between May 2011 and June 2015 in a tertiary medical-surgical ICU in the Netherlands. Acquisition of infections was monitored daily by dedicated observers. Marginal structural models were used to determine the associations between gram-negative rectal colonization and respiratory tract colonization, ICU-acquired gram-negative infection, and ICU-acquired gram-negative bacteremia.

Results. Among 2066 ICU admissions, 1157 (56.0%) ever had documented gram-negative carriage in the rectum during ICU stay. Cumulative incidences of ICU-acquired gram-negative infection and bacteremia were 6.0% (n = 124) and 2.1% (n = 44), respectively. Rectal colonization was an independent risk factor for both respiratory tract colonization (cause-specific hazard ratio [CSHR], 2.93 [95% confidence interval {CI}, 2.02–4.23]) and new gram-negative infection in the ICU (CSHR, 3.04 [95% CI, 1.99–4.65]). Both rectal and respiratory tract colonization were associated with bacteremia (CSHR, 7.37 [95% CI, 3.25–16.68] and 2.56 [95% CI, 1.09–6.03], respectively). Similar associations were observed when Enterobacteriaceae and glucose nonfermenting gram-negative bacteria were analyzed separately.

Conclusions. Gram-negative rectal colonization tends to be stronger associated with subsequent ICU-acquired gram-negative infections than gram-negative respiratory tract colonization. Gram-negative rectal colonization seems hardly associated with subsequent ICU-acquired gram-negative respiratory tract colonization.

Keywords. colonization; translocation; ICU-acquired infection; gram-negative bacteria; bacteremia.

Disruption of the normal microbiota during critical illness can lead to overgrowth of aerobic gram-negative bacteria (GNB) in the gut and respiratory tract, which may lead to subsequent infectious complications, such as bacteremia [1]. This hypothesis is supported by previous findings that gram-negative (GN) colonization of the gut was associated with intensive care unit (ICU)–acquired GN bacteremia [2]. Moreover, selective digestive tract decontamination (SDD) was associated with a lower incidence of respiratory tract colonization with antibiotic-resistant bacteria than was selective oropharyngeal decontamination (SOD), also suggesting that the intestinal tract serves as a reservoir for GNB colonizing the respiratory tract during ICU stay [3]. The potential pathophysiological mechanisms leading to bacteremia include direct translocation of bacteria from the gut into the bloodstream (systemic translocation) and indirect transmission via the mesenteric lymph nodes (gut–lymph translocation), which may be facilitated by altered intestinal permeability and possibly changes in virulence of the gut microbiota in critically ill patients [1, 4]. Alternatively, bacteremia may result from aspiration of gastric contents leading to respiratory tract colonization and subsequent pneumonia. Indeed, SOD (without affecting the intestinal flora) has also been associated with reduced incidences of ventilator-associated pneumonia [5] and ICU-acquired bacteremia with Enterobacteriaceae [6]. However, the relative importance of respiratory tract and intestinal colonization for ICU-acquired infections is unknown, as is the association between rectal colonization and acquisition of respiratory tract colonization.

We aimed to clarify the interdependence between gut and respiratory tract colonization and their associations with

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ICU-acquired infections and ICU-acquired bacteremia. To this end, we quantified the associations between gut colonization with GNB and the occurrence of ICU-acquired infections, between the occurrence of gut and respiratory tract colonization and ICU-acquired bacteremia and between gut colonization with GNB and subsequent respiratory tract colonization in a large cohort of patients admitted to the ICU (Figure 1).

MATERIALS AND METHODS

Study Design

We studied consecutive patients admitted to the ICU of the University Medical Center Utrecht between May 2011 and June 2015, who were mechanically ventilated, had a length of stay of at least 2 days, and received SDD. The SDD regimen has been described previously [6] and consisted of 3 components: (1) a gastrointestinal suspension containing colistin, tobramycin, and amphotericin B, administered 4 times daily via a nasogastric tube; (2) a paste with the same antimicrobials, applied 4 times daily in the mouth; and (3) cefotaxime administered 4 times daily intravenously for a duration of 4 days. As part of the SDD protocol, surveillance cultures of the rectum and respiratory tract were performed twice weekly; patients without rectum or respiratory tract samples were excluded from this analysis. Patients with persistent or newly acquired GNB colonization in their second or later surveillance samples received an intensified SDD regimen, with 8 times daily application of the antibiotic suspension or paste and nebulization with tobramycin or colistin.

Clinical data were prospectively collected as part of the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project [7], including information on patient demographics, medication use, physiological parameters, and organ failure scores. Patients were screened daily for the presence of infections during their ICU stay by dedicated physician observers. Infection and bacteremia events were considered ICU-acquired if they occurred 2 days or more after ICU admission. The likelihood of infection was defined according to adapted Centers for Disease Control and Prevention and International Sepsis Forum criteria based on a post hoc review of all available clinical data [8]. For the current analysis we included all infections where the likelihood was rated as at least possible [7]. The medical ethical committee approved an opt-out consent procedure (protocol number 10-056C).

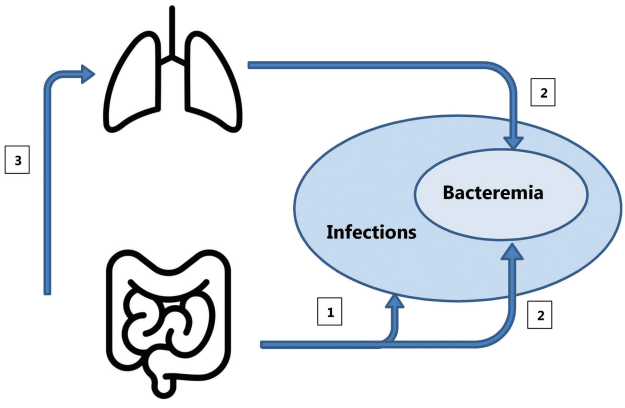

Figure 1. Possible associations between rectal and respiratory tract colonization and infections. (1) First objective: the association between rectal colonization with gram-negative bacteria (GNB) and intensive care unit (ICU)–acquired infections with GNB. (2) Second objective: The association between rectal and/or respiratory tract colonization with GNB and ICU-acquired bacteremia. (3) Third objective: The association between rectal colonization with GNB and acquisition of respiratory tract colonization.

Study Objectives

The first objective was to determine the association between rectal colonization with GNB and development of an ICU-acquired infection with GNB (Figure 1). Infections were considered to be associated with colonization if the diagnosis was established on a day with GNB colonization. We did not determine the association between respiratory tract colonization and ICU-acquired infections, because colonization of the respiratory tract is a diagnostic criterion for ventilator-associated pneumonia and this would, therefore, introduce bias.

The second objective was to determine the association between both respiratory tract and rectal colonization with GNB and ICU-acquired bacteremia due to GNB.

The third objective was to determine the association between rectal colonization with GNB and subsequent acquisition of respiratory tract colonization with GNB. This analysis was limited to subjects having respiratory cultures yielding no GNB growth during the first 2 days in ICU, and at least 1 complete set of rectum and respiratory surveillance cultures available later. As sensitivity analyses, all objectives were also studied for Enterobacteriaceae and glucose-nonfermenting (GNF) GNB separately.

Colonization Status

Surveillance samples from the respiratory tract (consisting of throat swabs and/or endotracheal aspirates) as well as the rectum were taken upon ICU admission and twice weekly thereafter, and inoculated on MacConkey agar, blood agar, and Mout media. Cultures were analyzed semiquantitatively for growth of GNB, followed by species identification using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) and susceptibility testing according to local protocols. GNB colonization was defined as the presence of ≥1 GNB species in a single surveillance sample. Changes in colonization status could thus occur if a positive culture was followed by a negative culture or vice versa, in which case the switch was assumed to have occurred in the middle of the interval between 2 subsequent cultures (See Supplementary Figure 1 for a detailed explanation of colonization definition).

For the third objective, only complete surveillance culture sets (ie, concomitant rectum and respiratory surveillance

samples) were analyzed. Respiratory cultures performed at discretion of the treating physician were excluded to prevent information bias (as rectal cultures were only performed for surveillance purposes). Acquisition of GNB respiratory tract colonization was attributed to rectal colonization if the rectum was colonized with any GNB prior to the first positive respiratory culture.

Statistical Analyses

We performed Cox regression analyses with marginal structural models (MSMs) to assess the associations of interest. A MSM was used because time-varying confounders, such as antibiotic exposure, may influence both the outcome (infection) and the determinant (GNB colonization) but in addition, the inverse relation is also present (GNB colonization may influence future antibiotic use). An explanation of MSMs can be found in the Supplementary Materials (Supplementary Appendix, rationale for using MSM analyses). We estimated the cause-specific hazard ratio (CSHR) for the endpoints of interest and competing events. This hazard ratio can be interpreted as the (relative) change in the instantaneous probability of acquiring an infection on a colonized vs a noncolonized day. Death and discharge from ICU were both considered competing endpoints, as they preclude the later occurrence of colonization and infection in the ICU.

Confounders were selected a priori using clinical judgment. Age, medical or surgical admission type, the presence of immunodeficiency, comorbidities, and infection upon ICU admission were treated as baseline (ie, time-fixed) confounders, whereas Sequential Organ Failure Assessment (SOFA) score, use of antibiotics with an effect on GNB, and mechanical ventilation status were included as time-varying confounders (ie, values could vary per day) in all models. In addition, the presence of surgical drains was included as a time-varying confounder in the model for the outcomes ICU-acquired bacteremia and infection. Multiple ICU admissions were analyzed separately if patients had been readmitted to the ICU during the study period; therefore, a random effect was added to the Cox regression models to account for correlation caused by readmission of patients. SAS version 9.4 (SAS Institute, Cary, North Carolina) and R version 3.2.2 (R foundation for Statistical Computing, 2015) were used to perform statistical analyses.

RESULTS

Of 3184 admissions during which SDD was used, 2066 ICU episodes (in 1874 unique patients) were included for the analysis of objectives 1 and 2 (all having 1 or more rectum and respiratory samples and a length of stay >2 days) and 1457 (in 1345 patients) for objective 3 (having both a rectal and respiratory surveillance sample on admission and during follow-up) (Figure 1 and Supplementary Figure 2, inclusion flow chart). The median length of stay was 7 (interquartile range [IQR], 4–13) days. A total of 8465 rectum and 10 087 respiratory tract cultures were taken during 25 766 ICU days, averaging 1.0 and 1.2 cultures every 3 days, respectively. In 97% and 99% of ICU episodes, a first rectum and respiratory tract culture, respectively, had been obtained within 4 days. There was a decrease in the proportion of rectal cultures yielding GNB growth from 45.4% at admission, to 9.3% by day 10 in the ICU. For respiratory samples, this was 28.9% and 17.2%, respectively.

In 1157 (56.0%) ICU episodes, at least 1 rectum culture grew GNB during ICU admission, and 804 (38.9%) had 1 or more respiratory cultures with GNB. The median duration of colonization was 4 (IQR, 3–8) days and 4 (IQR 3–6) days in patients who (ever) had respiratory and/or rectal GNB colonization, respectively, whereas the median number of noncolonized days under observation in these patients was 7 (IQR, 4–13) days and 7 (IQR 4–14) days. Patients without GNB in any rectum culture, referred to as "never colonized," stayed in ICU for a median of 8 (IQR 6–14) days and more frequently had a history of hematologic malignancy and immune deficiency or an infection upon ICU admission, and were less often admitted to ICU for a surgical reason than ever-colonized patients (Table 1).

Rectal Colonization and Intensive Care Unit-Acquired Infections With Gram-Negative Bacteria

There were 124 ICU-acquired GNB infections during 27 890 observation-days (incidence rate, 4.4 per 1000 days). The majority were respiratory tract infections (n = 70 [57%]), followed by primary or catheter-related bloodstream infections (n = 28 [23%]), abdominal infections (n = 8 [7%]), and other (n = 18 [15%]). Of these, 45 (36%) were diagnosed during simultaneous rectal GNB colonization, and in 32 (71%) of these episodes the species causing infection and colonization were identical. The incidence rate of infections was 8.2 per 1000 colonized days, vs 3.5 per 1000 noncolonized days. The most common causative pathogens were *Pseudomonas aeruginosa* (29%), *Enterobacter cloacae* (14%), and *Serratia marcescens* (14%).

After adjustment for confounders in a MSM, the estimated CSHR for developing new infection during rectal colonization with GNB was 3.04 (95% confidence interval [CI], 1.99–4.65; $P < .001$; Table 2). The CSHR for Enterobacteriaceae and GNF GNB separately were similar (Supplementary Table 1, result of MSM analyses for Enterobacteriaceae and GNF GNB). The increased CSHR for ICU discharge and death indicate that being colonized increased the rate of being discharged from ICU or dying in the ICU, leading to shorter length of stay and shorter exposure to the risk of infection. Nevertheless, colonization was associated with an increased hazard for infection, as expressed by the increased CSHR (Table 2).

Respiratory Tract and Rectal Colonization and Bacteremia With Gram-Negative Bacteria

We observed 44 episodes of ICU-acquired GN bacteremia during 27 890 observation days (incidence rate, 1.6/1000 days) with 45 species. Of the 44 episodes, 20 (45%) occurred during

Table 1. Characteristics of Intensive Care Unit Admissions That Were Noncolonized Versus Colonized With Gram-Negative Bacteria in the Rectum During Intensive Care Unit Admission (n = 2066)

Characteristics	Rectum Colonization With GNB		
	Never Colonized (n = 909)[a]	Ever Colonized (n = 1157)[b]	*P* Value
Patient characteristics			
Age, y, median (IQR)	61 (48–71)	62 (50–71)	.056
Male sex	598 (66)	744 (64)	.562
Chronic renal insufficiency	63 (7)	102 (9)	.111
Congestive heart failure	85 (9)	162 (14)	.001
Myocardial infarction	88 (10)	139 (12)	.087
COPD	102 (11)	136 (12)	.683
Diabetes mellitus	146 (16)	202 (18)	.378
Immune deficiency	152 (17)	150 (13)	.018
Hematologic malignancy	63 (7)	34 (3)	<.001
Cerebrovascular disease	99 (11)	149 (13)	.158
Charlson comorbidity index, median (IQR)	1 (0–2)	1 (0–2)	.71
ICU admission characteristics			
Surgical admission	308 (34)	506 (44)	<.001
Readmission	177 (20)	139 (12)	<.001
Infection at admission	491 (54)	508 (44)	<.001
APACHE-IV score, median (IQR)	76 (61–98)	78 (62–99)	.322

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; GNB, gram-negative bacteria; ICU, intensive care unit; IQR, interquartile range.

[a]11 242 patient-days at risk.

[b]16 648 patient-days at risk, of which 5513 colonized.

concurrent rectal colonization (incidence rate, 3.6/1000 colonized days vs 1.1/1000 noncolonized days), with the same species causing infection and colonization in 18 per 20 cases. For respiratory tract colonization, 16 bacteremia episodes (36%) occurred during concurrent respiratory tract colonization (same species in 15/16). The incidence rate was 2.7 per 1000 colonized days, vs 1.3 per 1000 non-colonized days in the respiratory tract. Bacteremia was most frequently caused by *P. aeruginosa* (15 [33%]), *Escherichia coli* (8 [18%]), and *S. marcescens* (5 [11%]). The adjusted CSHR for bacteremia with GNB was 7.37 (95% CI, 3.25–16.68; $P < .001$) for GNB rectal colonization; 2.56 (95% CI, 1.09–6.03; $P = .032$) for GNB respiratory tract colonization; and 10.84 (95% CI, 4.23–27.77; $P < .001$) for concurrent GNB colonization at both sites (Table 3). Results were similar for Enterobacteriaceae and GNF GNB when analyzed separately (Supplementary Table 2, result of MSM analyses for Enterobacteriaceae and GNF GNB).

Rectal Colonization and Acquisition of Respiratory Tract Colonization

There were 999 ICU episodes with respiratory cultures not growing GNB on ICU admission; these patients thus remained at risk for subsequent colonization (Supplementary Figure 2, inclusion flow chart). Baseline characteristics can be found in the Supplementary Materials (Supplementary Table 3, characteristics of ICU admissions for objective 3).

There were 119 episodes of ICU-acquired GNB respiratory tract colonization during 13 389 observation days (incidence rate, 8.9/1000 days); 31 (26%) of these occurred during

Table 2. Results of Marginal Structural Model Analyses for Objective 1: The Association Between Rectum Colonization With Gram-Negative Bacteria and Intensive Care Unit–Acquired Infections (n = 2066)

Model	Outcome					
	ICU-Acquired GNB Infection		ICU Death		ICU Discharge	
	CSHR (95% CI)	*P* Value	CSHR (95% CI)	*P* Value	CSHR (95% CI)	*P* Value
Crude[a]	4.38 (2.92–6.57)	<.001	2.05 (1.56–2.69)	<.001	1.12 (.98–1.28)	.085
MSM[b]	3.04 (1.99–4.65)	<.001	1.73 (1.26–2.36)	.001	1.39 (1.16–1.55)	<.001

Abbreviations: CI, confidence interval; CSHR cause-specific hazard rate; GNB, gram-negative bacteria; ICU intensive care unit; MSM, marginal structural model.

[a]Results from Cox regression model with colonization as a time-dependent variable (not adjusted for confounders).

[b]Results from MSM with correction for time-fixed and time-dependent confounders (age, immune deficiency, Charlson comorbidity index, surgical admission, infection at admission, mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score, SOFA change, gram-negative antibiotic, surgical drains.

Table 3. Association Between Rectum or Respiratory Tract Colonization With Gram-Negative Bacteria and Intensive Care Unit-Acquired Bacteremia (n = 2066)

	Outcome					
	ICU-Acquired Bacteremia		ICU Death		ICU Discharge	
Model	CSHR (95% CI)	*P* Value	CSHR (95% CI)	*P* Value	CSHR (95% CI)	*P* Value
Rectum colonization						
Crude[a]	9.07 (3.94–20.86)	<.001	1.86 (1.38–2.52)	<.001	1.12 (.97–1.30)	.013
MSM[b]	7.37 (3.25–16.68)	<.001	1.78 (1.29–2.46)	<.001	1.18 (1.01–1.39)	.039
Respiratory tract colonization						
Crude[a]	2.63 (1.14–6.03)	.023	0.93 (.68–1.28)	.657	0.84 (.72–0.79)	.020
MSM[b]	2.56 (1.09–6.03)	.032	0.90 (.64–1.27)	.552	0.87 (.74–1.02)	.090
Rectum and respiratory tract colonization						
Crude[a]	11.13 (4.50–27.58)	<.001	2.32 (1.54–3.50)	<.001	0.87 (.68–1.14)	.270
MSM[b]	10.84 (4.23–27.77)	<.001	2.24 (1.43–3.51)	<.001	0.95 (.72–1.24)	.685

Abbreviations: CI, confidence interval; CSHR, cause-specific hazard rate; ICU, intensive care unit; MSM, marginal structural model.

[a]Results from Cox regression model with colonization as a time-dependent variable (not adjusted for confounders).

[b]Results from MSM with correction for time-fixed and time-dependent confounders (age, immune deficiency, Charlson comorbidity index, surgical admission, infection at admission, mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score, SOFA change, gram-negative antibiotic, surgical drains.

concurrent rectal GNB colonization, with identical species present in 11 of 31 (35%) episodes. There were 61 episodes of ICU-acquired respiratory tract colonization with Enterobacteriaceae, of which 19 (31%) occurred during rectal colonization, with identical species in 8 episodes (42%). For GNF GNB, there were 104 episodes of ICU-acquired respiratory tract colonization of which 6 (6%) occurred during GNF GNB rectum colonization, in 5 episodes (83%) with *P. aeruginosa* carriage at both sites.

The CSHR for acquiring GNB respiratory tract colonization was 2.93 (95% CI, 2.02–4.23; $P < .001$) and similar for Enterobacteriaceae and GNF GNB separately. (Table 4 and Supplementary Table 4, result of MSM analyses for Enterobacteriaceae and GNF GNB).

DISCUSSION

In this study among patients receiving SDD, colonization of the gut with GNB was associated with an increased risk of ICU-acquired infection. These findings confirm and extend previously reported associations between gut colonization and ICU-acquired GNB bacteremia [2], and between gut colonization and infection with *P. aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* [9–11]. Mechanisms that may explain these associations include bacterial translocation from the gut, exogenous translocation via the fecal patina leading to respiratory tract colonization, vascular catheter–associated bacteremia through the colonized skin, and microaspiration of gut flora colonizing the stomach [12].

In our study, both rectal and respiratory carriage were associated with an increased risk of ICU-acquired bacteremia. However, the association for rectal carriage was stronger than for respiratory tract carriage, indicating that the gut is a more important reservoir for GNB bacteremia. Yet, simultaneous colonization at *both* body sites had the highest hazard rate for acquiring bacteremia. This is in line with clinical observations that SDD, which targets carriage in the respiratory tract and in the gut, was more effective in reducing the incidence of ICU-acquired GNB bacteremia than SOD, which only targets carriage in the respiratory tract [6, 13].

Migration of GNB from the gut to the respiratory tract may occur through endogenous and exogenous routes. Indeed, rectal carriage with GNB in our study was associated with subsequent acquisition of GNB respiratory tract colonization. However, whereas congruence between species colonizing rectum and causing ICU-acquired infections was 71%, congruence was only 35% for rectal and

Table 4. Association Between Rectum Colonization With Gram-Negative Bacteria and Acquisition of Respiratory Tract Colonization

	Outcome					
	ICU-Acquired Respiratory Tract Colonization		ICU Death		ICU Discharge	
Model	CSHR (95% CI)	*P* Value	CSHR (95% CI)	*P* Value	CSHR (95% CI)	*P* Value
Crude[a]	2.28 (1.44–3.63)	<.001	2.83 (1.78–4.50)	<.001	0.91 (.71–1.17)	.461
MSM[b]	2.93 (2.02–4.23)	<.001	1.92 (1.10–3.35)	.021	1.17 (.91–1.51)	.218

Abbreviations: CI, confidence interval; CSHR, cause-specific hazard rate; ICU, intensive care unit; MSM, marginal structural model.

[a]Results from MSM (Cox model accounting for repeated admission by a random nested effect, but not for confounders).

[b]Results from MSM with time-fixed and time-dependent confounders (age, immunodeficiency, Charlson comorbidity index, surgical admission, infection at admission, mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score, SOFA change, gram-negative antibiotic, inhalation antibiotics.

respiratory tract colonization. This low congruence at the species level questions a causal relationship between rectal colonization and acquisition of respiratory tract colonization, and suggests unmeasured confounding. The size of our study precluded species-specific analyses, which could have resulted in more accurate estimates of associations between rectal and respiratory tract colonization. Furthermore, colonization at other body sites or exogenous sources may also be associated with respiratory tract colonization and ICU-acquired infections. For instance, 38 of 48 ICU-acquired infections caused by *Pseudomonas* and *Stenotrophomonas* species occurred without documented rectal colonization with GNB, suggesting the gut was not the source of these infections.

In our cohort of mechanically ventilated patients treated with SDD, the incidence rate of ICU-acquired GN infections (4.4/1000 days) was low compared to other cohorts. For example, in a French cohort without SDD, the incidence of all-cause ICU acquired GN infections in mechanically ventilated patients was 14 per 1000 patient-days [14]. Also, the incidence rate of ICU-acquired bacteremia (1.6/1000 days) was low compared with a Taiwanese study including mechanically ventilated ICU patients [15], and similar to the rate observed in a meta-analysis on the effect of chlorhexidine (CHX) bathing (1.1/1000 days), although nonventilated ICU patients were also included in the latter study [16].

In some patients treated with SDD, intestinal colonization with GNB persisted despite application of laxative agents and intensified administration of SDD. Apparently, achieved concentrations of topical antibiotics in the distal parts of the gastrointestinal tract remained too low. It is unknown whether further increasing the frequency of SDD administration (to more than 8 times per day) is safe. Absorption of tobramycin leading to toxic levels has been described in patients receiving continuous venovenous hemofiltration (CVVH) [17].

Strengths of this study include the c ohort size, the protocolized surveillance for carriage, the prospective adjudication of infections by independent research physicians, and the use of advanced methodology to account for time-dependent confounders. Limitations of this study include absence of screening for GNB carriage at other body sites and the absence of molecular typing of bacteria, which precludes assessment of genotypic relatedness of species colonizing and infecting patients. Our assumption of relatedness based on species identification most likely overestimated associations. In a recently published study, though, it was concluded based on whole-genome sequencing results that in 80% of infections, the genome of *K. pneumoniae* was identical to that of the *K. pneumoniae* carried in the rectum [10]. Finally, misclassification may have occurred (most notably falsely categorizing patients as noncolonized) as the sensitivity of rectal swabs and perianal swabs to detect GNB colonization is <100% [18, 19]. This may have influenced the strength and accuracy of the associations.

In conclusion, rectal colonization with GNB is associated with an increased risk of ICU-acquired GNB infection and respiratory tract colonization. Future studies are warranted to determine whether the protective effects of SDD on the occurrence of ICU-acquired bacteremia can be safely augmented in patients with persistent intestinal carriage.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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