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Systematic Review of Measurement and Adjustment for Colonization Pressure in Studies of Methicillin-Resistant *Staphylococcus aureus*, Vancomycin-Resistant Enterococci, and *Clostridium difficile* Acquisition

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Abstract

OBJECTIVE—Colonization pressure is an important infection control metric. The aim of this study was to describe the definition and measurement of and adjustment for colonization pressure in nosocomial-acquisition risk factor studies of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Clostridium difficile*.

METHODS—We performed a computerized search of studies of nosocomial MRSA, VRE, and *C. difficile* acquisition published before July 1, 2009, through MEDLINE. Studies were included if a study outcome was MRSA, VRE, or *C. difficile* acquisition; the authors identified risk factors associated with MRSA, VRE, or *C. difficile* acquisition; and the study measured colonization pressure.

RESULTS—The initial MEDLINE search yielded 505 articles. Sixty-six of these were identified as studies of nosocomial MRSA, VRE, or *C. difficile* acquisition; of these, 18 (27%) measured colonization pressure and were included in the final review. The definition of colonization pressure varied considerably between studies: the proportion of MRSA- or VRE-positive patients (5 studies), the proportion of MRSA- or VRE-positive patient-days (6 studies), or the total or mean number of MRSA-, VRE-, or *C. difficile*–positive patients or patient-days (7 studies) in the unit over periods of varying length. In 10 of 13 studies, colonization pressure was independently associated with MRSA, VRE, or *C. difficile* acquisition.

CONCLUSION—There is a need for a simple and consistent method to quantify colonization pressure in both research and routine clinical care to accurately assess the effect of colonization pressure on cross-transmission of antibiotic-resistant bacteria.

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Colonization pressure is an important infection control metric that was first described by Bonten et al.[1] in 1994. It is defined as the proportion of patients colonized with a particular organism in a defined geographic area within a hospital during a specified time period. Therefore, colonization pressure can be used to quantify the burden of antibiotic-resistant bacteria in a hospital unit and can also represent an estimate of the probability of cross-transmission of antibiotic-resistant bacteria within the unit. For example, the risk of transmission is likely higher when 80% of the patients are already colonized than when only 10% of the patients are colonized.[2] Thus, colonization pressure may potentially provide a method for adjusting for the burden of antibiotic-resistant bacteria while assessing the independent associations of other hypothesized causal factors with acquisition of antibiotic-resistant bacteria in epidemiology studies.

Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Clostridium difficile* are prevalent antibiotic-resistant bacteria in healthcare settings, and there is strong evidence that these organisms can be transmitted from patient to patient.[3,4] Thus, colonization pressure is likely an important risk factor for acquisition of these antibiotic-resistant bacteria, and these species are the subject of this review. The aim of this study was to describe the definition and measurement of and adjustment for colonization pressure in nosocomial-acquisition risk factor studies of MRSA, VRE, and *C. difficile*.

METHODS

Identification of Relevant Articles

We performed a computerized search of studies of nosocomial MRSA, VRE, and *C. difficile* acquisition published before July 1, 2009. The search terms “MRSA acquisition,” “VRE acquisition,” *“Clostridium difficile* acquisition,” “colonization pressure,” “MRSA acquisition AND colonization pressure,” “VRE acquisition AND colonization pressure,” and “*Clostridium difficile* acquisition AND colonization pressure” were used for the search in MEDLINE. MRSA, VRE, and *C. difficile* acquisition was defined as isolation of MRSA or VRE or a positive toxin assay for *C. difficile* from a surveillance culture sample, a clinical culture sample, or both after the first 24 hours of admission if a patient had a negative culture result for MRSA, VRE, or *C. difficile* or no stool culture positive for *C. difficile* on admission to the hospital unit.

Additional studies were identified by a review of cited references from all retrieved articles. The complete set of titles and abstracts from the search was independently reviewed by one investigator (A.O.A.) to identify those that met the inclusion and exclusion criteria. The studies selected for the final review were further reviewed by another author (J.P.F.) to ensure that they met the inclusion criteria. Because this study did not involve patient or research subject data, it did not require approval by the Institutional Review Board.

Inclusion and Exclusion Criteria

Studies were included if all three of the following criteria were met: (1) a study outcome was MRSA, VRE, or *C. difficile* acquisition; (2) the authors aimed to identify risk factors associated with MRSA, VRE, or *C. difficile* acquisition, that is, the study used epidemiologic and statistical methods to identify variables (eg, antibiotic exposures, medical devices, patient comorbidities) associated with MRSA, VRE, or *C. difficile* acquisition; and (3) the study measured colonization pressure. Studies were excluded if the study described only the demographic and clinical characteristics of patients colonized or infected with MRSA, VRE, or *C. difficile*; described only the risk factors for patients colonized or infected with MRSA, VRE, or *C. difficile* on hospital admission; described only the

molecular subtypes of the colonizing or infecting MRSA, VRE, or *C. difficile* isolates; reported only the prevalence of MRSA, VRE, or *C. difficile*; or reported only the effect of an intervention on the incidence of MRSA, VRE, or *C. difficile* but did not explore factors associated with MRSA, VRE, or *C. difficile* acquisition. In addition, studies were excluded if they did not have humans as subjects, were not written in English, or were review articles (Figure 1).

Data Extraction

The following information was extracted for each study that met the inclusion criteria: author(s) and year of publication; country of study origin; study design; hospital setting (eg, intensive care unit [ICU]); body sites of culture samples and organisms isolated; definition of colonization pressure; culture type (eg, surveillance or clinical) used to determine MRSA, VRE, or *C. difficile* acquisition; methods of statistical analysis; and study results.

RESULTS

The initial search yielded 505 articles: 378 on MRSA, 72 on VRE, and 55 on *C. difficile*. Following initial review and application of the inclusion criteria, 66 studies (31 of MRSA, 18 of VRE, and 17 of *C. difficile*) were identified as nosocomial-acquisition studies. Of these 66 studies, 18 (27%) measured colonization pressure and were included in the final review (Figure 1).

General Description of the Studies Included in the Systematic Review

Of the 18 studies, 10 were conducted in the United States, 6 in Europe, 1 in Canada, and 1 in Hong Kong. Thirteen studies were prospective cohort studies, 3 were retrospective cohort studies, and 2 were case-control studies (Table 1). Fourteen studies included ICU patients only, 1 included only general medical patients, and 3 included both ICU and general medical patients. Seven studies assessed only MRSA acquisition, 7 assessed only VRE acquisition, 1 assessed both MRSA and VRE acquisition, and 3 assessed only *C. difficile* acquisition.

Of the 8 MRSA studies, 7 defined MRSA acquisition using surveillance and clinical cultures, while 1 did so using only surveillance cultures. Seven of the 8 MRSA studies indicated that the nares were the primary body site for culture samples to determine MRSA colonization. Five studies used culture samples from other body sites, such as the perineum,[5,6,21] throat,[16] groin,[12] and axilla,[21] in addition to the nares, to determine MRSA colonization. Clinical cultures used to determine MRSA acquisition included blood, sputum, and wound cultures.[6,11,12]

Of the 8 VRE studies, 3 defined VRE acquisition using both surveillance and clinical cultures,[15,19,20] while 5 defined VRE acquisition using only surveillance cultures.[2,7,14,16,20] All 8 VRE studies indicated that the rectum was the primary body site for culture samples to determine VRE colonization. Three studies used stool samples in addition to rectal swab samples to determine VRE colonization.[7,19,20]

All 3 *C. difficile* studies defined *C. difficile* acquisition using only clinical cultures.[8–10] None of the 3 studies used stool cultures in asymptomatic patients to identify those who were colonized with *C. difficile*. Unformed clinical stool samples were used for *C. difficile* toxin assay to determine *C. difficile* acquisition in all 3 studies.

Definitions of Colonization Pressure

The definition of colonization pressure varied considerably between studies (Table 1). The three broad definitions of colonization pressure used were the proportion of MRSA- or

VRE-positive patients (5 studies), the proportion of MRSA-or VRE-positive patient-days (6 studies), and the total or mean number of MRSA-, VRE-, or *C. difficile*–positive patients or patient-days (7 studies) in the unit over study periods of varying length.

Of the 5 studies that defined colonization pressure as the proportion of MRSA- or VRE-positive patients in the unit, 1 defined colonization pressure as the proportion of MRSA-or VRE-colonized patients on entry to the ICU.[16] Two studies defined colonization pressure as the daily proportion of patients in the unit colonized with VRE prior to VRE acquisition or discharge.[2,7] Two studies defined colonization pressure as the daily proportion of patients in the unit colonized with VRE throughout a patient's ICU stay.[14,15]

Of the 6 studies that defined colonization pressure as the proportion of MRSA- or VRE-positive patient-days in the unit, 1 defined colonization pressure as the proportion of MRSA-positive patient-days in the unit during the week preceding acquisition or discharge.[13] Two studies defined colonization pressure as the weekly proportion of MRSA-positive patient-days in the unit.[11,21] One study defined colonization pressure as the monthly proportion of MRSA-positive patient-days in the unit.[6] Two studies defined colonization pressure as the proportion of MRSA-positive patient-days in the unit during the entire study period.[17,18]

Of the 7 studies that defined colonization pressure as the total or mean number of MRSA-, VRE-, or *C. difficile*–positive patients or patient-days in the unit, 1 defined colonization pressure as the mean number of MRSA-positive patients on the unit in the 3 days preceding MRSA acquisition or discharge.[5] One study defined colonization pressure as the total number of MRSA-positive patients in the unit during a patient's ICU stay.[12] Two studies defined colonization pressure as the total number of VRE-positive patients or patient-days in the unit during a patient's ICU stay.[19,20] One study defined colonization pressure as the total number of *C. difficile*–positive patients present during a patient's susceptible days in the unit.[16] Two studies defined colonization pressure as the total number of *C. difficile*–positive patients present during a patient's stay in the unit or the mean number of *C. difficile*–positive patients present during a patient's susceptible days in the unit.[8,9]

MRSA Acquisition Study Results

Of the 8 MRSA studies, 3 did not include multivariable analysis.[5,6,11] Of the remaining 5 studies, 4 included colonization pressure in their multivariable analysis.[12,13,17,21] Three of the 4 studies found colonization pressure to be significantly associated with MRSA acquisition.[13,17,21]

The definitions of colonization pressure that yielded a significant association between colonization pressure and MRSA acquisition were the proportion of MRSA-positive patient-days in the unit during the week preceding MRSA acquisition or discharge, the weekly proportion of MRSA-positive patient-days in the unit, and the proportion of MRSA-positive patient-days in the unit during the entire study period. Risk factors identified as associated with MRSA acquisition when colonization pressure was controlled for in a multivariable analysis were age, admission to the ICU, severity of illness (Simplified Acute Physiology Score II), and ICU length of stay.[13,17]

VRE Acquisition Study Results

All 8 VRE studies measured colonization pressure, but only 6 included colonization pressure in their multivariable analysis. Four of the 6 studies found colonization pressure to be significantly associated with VRE acquisition.[2,7,19,20] One study found that colonization pressure modified the association between gown use and VRE acquisition, that is, that gown use was protective against VRE acquisition for patients exposed to a high level of VRE (odds ratio [OR], 0.43; 95% confidence interval [CI], 0.27–0.68) but that gown use was not

protective against VRE acquisition for patients exposed to a low level of VRE (OR, 1.50; 95% CI, 0.57–3.98).[19]

The definitions of colonization pressure that yielded a significant association between colonization pressure and VRE acquisition were the daily proportion of patients in the unit colonized with VRE prior to VRE acquisition or discharge and the total number of VRE-positive patients or patient-days in the unit during a patient's ICU stay. Risk factors identified as associated with VRE acquisition when colonization pressure was controlled for in a multivariable analysis were environmental contamination, enteral feeding, leukemia, end-stage renal disease, pre-ICU and ICU length of stay, and pre-ICU and ICU antibiotic use (anaerobic therapy, cephalosporin, ceftriazone, piperacillin-tazobactam, vancomycin, and quinolones).[2,14,15,19,20]

C. difficile Acquisition Study Results

All 3 *C. difficile* studies included colonization pressure in their multivariable analysis and found colonization pressure to be significantly associated with *C. difficile* acquisition.[8–10] The definitions of colonization pressure that yielded significant association between colonization pressure and *C. difficile* acquisition were the total number of *C. difficile*–positive patients present during a patient's susceptible days or during a patient's total stay in the unit and the mean number of *C. difficile*–positive patients present during a patient's susceptible days in the unit. Risk factors identified as associated with *C. difficile* acquisition when colonization pressure was controlled for in a multivariable analysis were age of at least 45 years; admission to the facility in the previous 60 days; mechanical ventilation; receipt of gastric acid suppressor, narcotic, or antidiarrheal agent; low albumin level; VRE colonization or infection; leukemia or lymphoma; Charlson comorbidity index of 1–2; Modified Acute Physiology Score of 3–5; and receipt of fluoroquinolone, vancomycin, metronidazole, or first-, third-, or fourth-generation cephalosporin.[8–10]

DISCUSSION

Colonization pressure is an important infection control metric that quantifies the burden of antibiotic-resistant bacteria in a hospital unit over a period of time. Colonization pressure has been shown to be an important risk factor for nosocomial acquisition of MRSA,[13,17,21] VRE,[2,7,19,20] and *C. difficile*.[8–10] Previous studies have also assessed risk factors for acquisition of other antibiotic-resistant bacteria, such as extended-spectrum β-lactamase–producing *Klebsiella* and *Escherichia coli*, and have concluded that patient-to-patient transmission is likely an important contributor.[22,23] However, these studies were not included in this review because of the limited data on colonization pressure and in an attempt to focus the manuscript. The aim of this study was to describe the definition and measurement of and adjustment for colonization pressure in nosocomial-acquisition risk factor studies of MRSA, VRE, and *C. difficile*.

We systematically reviewed the colonization pressure literature for MRSA, VRE, and *C. difficile* acquisition studies, and we found significant heterogeneity in the definition of and adjustment for colonization pressure. To summarize, colonization pressure was broadly defined as the proportion of antibiotic-resistant-bacteria-positive patients, the proportion of antibiotic-resistant bacteria–positive patient-days, or the total number of antibiotic-resistant bacteria–positive patients or patient-days in the unit or the mean number of antibiotic-resistant bacteria–positive patients in the unit daily, weekly, monthly, or for the duration of the study period. Positivity was determined using surveillance cultures, clinical cultures, or both. This review did not provide sufficient data to determine the most accurate definition of colonization pressure, but it is clear that there is a need for a simple and consistent but

optimal definition of colonization pressure for use in both research and routine clinical care.[24]

The majority of the studies included in this review were performed in ICUs, where patients are screened more often to identify asymptomatic carriers of antibiotic-resistant bacteria. However, there are other healthcare settings, such as non-ICU hospital wards and long-term care facilities, where MRSA, VRE, and *C difficile* are endemic but surveillance for these bacteria is not routinely performed. In these settings, clinical cultures from symptomatic patients may be the only data available to quantify colonization pressure, and a definition of colonization pressure that quantifies only asymptomatic carriers could be problematic. The use of a definition that incorporates clinical-culture positivity or possibly prior history of colonization or infection may be more applicable and may still provide some useful data in these settings.

However, it is important to note that using clinical cultures from symptomatic patients to quantify colonization pressure may be prone to ascertainment bias. Clinical cultures are requested by the treating physician as clinically indicated; therefore, sicker patients and patient populations are more likely to have clinical cultures collected. This may lead to a subgroup of the patient population who are less sick and thus are less likely to have clinical cultures collected. This would likely result in an underestimation of colonization pressure.

For a definition of colonization pressure to be useful, it should be applicable in both research and routine clinical care. For example, a useful definition of colonization pressure should be applicable in a healthcare unit to routinely monitor colonization pressure, and when colonization pressure is found to be especially high (ie, above an indicated level), for example, during an outbreak, more intensive infection prevention efforts can be implemented.

In summary, the optimal definition of colonization pressure would quantify asymptomatic carriers present in the unit daily. Colonization pressure would thus be defined as the average daily proportion of patients colonized with the bacterial species under study during the period prior to acquisition or discharge from the unit. However, because of limited resources in routine clinical care, daily surveillance cultures are not often feasible, and this definition of colonization pressure may not be applicable in every healthcare setting. In the absence of daily surveillance culture data, the best available data, such as weekly surveillance data, clinical cultures, or possibly prior history of colonization or infection, may prove useful for quantifying colonization pressure. Computer simulation models may also be useful in estimating colonization pressure. Readers interested in the use of computer simulation models to study transmission of antibiotic-resistant bacteria may benefit from several available resources.[25–27]

In conclusion, further study is needed to determine a simple and consistent method to quantify colonization pressure in research and routine clinical care to accurately assess the effect of colonization pressure on cross-transmission of antibiotic-resistant bacteria.

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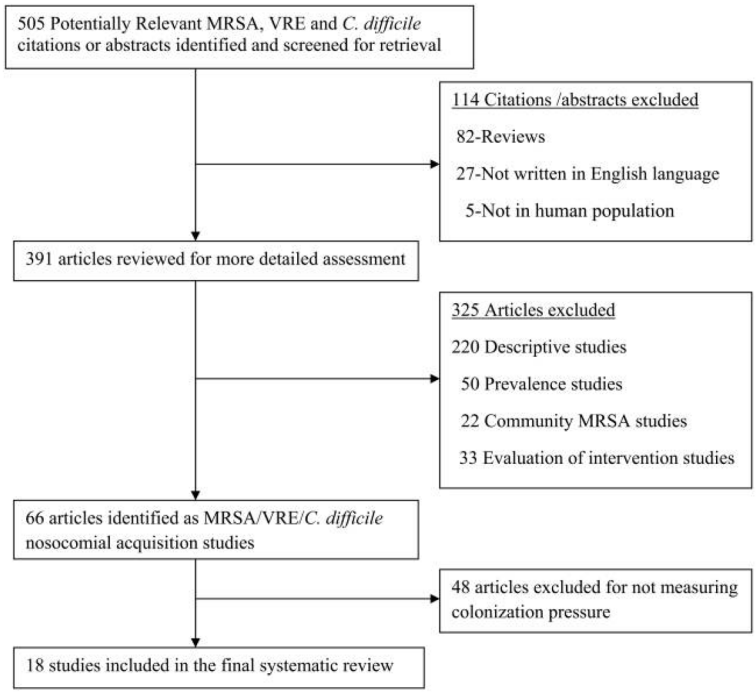

FIGURE 1.
Article selection tree for systematic review.

TABLE 1

Characteristics of Studies Included in the Final Review

First author, year	Country	Study design	Hospital setting	Organism isolated	Body sites of culture sample	Definition of colonization pressure	Culture type (frequency)	Reported adjusted measure[a]	Other factors[b]
Bloemendaal 2009[5]	Netherlands, France, Portugal, Spain, Italy	Prospective cohort	ICUs (77 beds)	MRSA	Nares, perineum, and clinical samples	No. of MRSA-positive patients in the unit during the 3 days preceding acquisition or during the study period for patients without acquisition	Surveillance (admission, twice weekly, discharge), clinical culture	Multivariable analysis not performed	
Williams 2009[6]	Canada	Prospective cohort	General medicine (36 beds)	MRSA	Nares, perineum, and clinical samples (wound)	Proportion of MRSA-positive patient-days among total patient-days in a month	Surveillance (admission, point prevalence every 4 months), clinical culture	Multivariable analysis not performed	
Drees 2008[7]	United States	Prospective cohort	ICU (20 beds)	VRE	Rectum, stool specimen	Average daily pro- portion of VRE-positive patients in the ICU until VRE acquisition or discharge	Surveillance (admission, twice weekly, discharge)	HR = 1.4 (95% CI, 1.12–1.84)	Environmental contamination, mean no. of antibiotics per day, leukemia
Dubberke 2007[8]	United States	Retrospective cohort	General hospital patients	*Clostridium difficile*	Stool specimen	Average daily no. of CDAD-positive patients present in the ward during patient's stay at risk in the ward	Clinical culture	OR = 2.9 (95% CI, 2.1–4.2) for mean CDAD pressure of 0.3–1.4; OR = 4.0 (95% CI, 2.9–5.6) for mean CDAD pressure of >1.4	Mechanical ventilation, low albumin level, leukemia/ lymphoma, antimobility agent, H2 blockers, PPI, >7-day course of FQ, vancomycin, or 1G or 3G cephalosporin, >0-day course of metronidazole or 4G cephalosporin
Dubberke 2007[9]	United States	Nested case-control	General hospital patients	*C. difficile*	Stool specimen	Total daily no. of CDAD-positive patients present in the ward during patient's stay in the ward; average daily no. of CDAD-positive patients present in the ward during	Clinical culture	OR = 2.9 (95% CI, 2.0–4.3) for sum CDAD pressure of 2–8; OR = 4.0 (95% CI, 2.7–6.0) for sum CDAD pressure of >8; OR = 3.9 (95% CI, 2.6–5.8) for mean CDAD	Age ≥45 years; admission to the facility in the previous 60 days; CMI of 1–2; modified APS of 3–5; receipt of gastric acid suppressor, narcotic, or antidiarrheal agent; low albumin level; receipt of FQ or 3G or 4G cephalosporin

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First author, year	Country	Study design	Hospital setting	Organism isolated	Body sites of culture sample	Definition of colonization pressure	Culture type (frequency)	Reported adjusted measure[a]	Other factors[b]
						patient's stay at risk in the ward		pressure of 0.3–1.4; OR = 5.4 (95% CI, 3.4–8) for mean CDAD pressure of >1.4	
Lawrence 2007[10]	United States	Retrospective cohort	ICU (19 beds)	*C. difficile*	Stool specimen	Total daily no. of CDAD-positive patients in the ICU unit during patient's time at risk in the ICU	Clinical culture	OR = 3.77 (95% CI, 1.14–12.49) for CCP of >30 case-days of exposure	VRE colonization or infection
Dancer 2006[11]	Scotland	Retrospective cohort	ICU (8 beds)	MRSA	Blood	Proportion of MRSA-positive patient-days per total patient-days in the unit for the week	Surveillance (admission, alternate days), clinical culture	Multivariable analysis not performed	
Cepeda 2005[12]	United Kingdom	Prospective cohort	ICU (28 beds)	MRSA	Nares, groin, and clinical samples (sputum, wound, blood)	Total daily no. of MRSA-positive patients present in the ICU during patient's ICU stay	Surveillance (admission, weekly, discharge), clinical culture	HR = 1.19 (95% CI, 0.86–1.65)	Anti-MSSA antibiotic use
Lucet 2005[13]	France	Prospective cohort	ICU (47 beds)	MRSA	Nares	Proportion of MRSA-positive patient-days per total patient-days in the unit during the week preceding acquisition or discharge	Surveillance (admission, weekly), clinical culture	OR = 1.019; $P < .0001$	Age, severity of illness (SAPS II) ICU LOS
Winston 2004[14]	United States	Prospective cohort	ICU (30 beds)	VRE	Rectum	Average daily pro- portion of VRE-positive patients in the ICU during each patient's ICU stay	Surveillance (twice weekly)	CP not significant in multivariable analysis (HR not reported)	End-stage renal disease, ICU LOS, ceftria-zone and piper-acillin-tazobactam use
Martínez 2003[15]	United States	Case-control	ICU (10 beds)	VRE	Rectum, clinical sample	Average daily pro- portion of VRE-positive patients in the ICU during each	Surveillance (admission, weekly), clinical culture	CP not significant in multivariable analysis	Pre-ICU LOS, pre-ICU vancomycin and quinolone use, location in high-risk MICU room

First author, year	Country	Study design	Hospital setting	Organism isolated	Body sites of culture sample	Definition of colonization pressure	Culture type (frequency)	Reported adjusted measure[a]	Other factors[b]
						patient's ICU stay			
Ho 2003[16]	Hong Kong	Prospective cohort	ICU (92–170 beds)	MRSA, VRE	Nares, throat, rectum	Proportion of MRSA-positive patients at ICU entry	Surveillance (admission, discharge)	CP not included in multivariable analysis	
Muller 2003[17]	France	Prospective cohort	ICU, general medical, surgical unit	MRSA	Nares, clinical sample	Proportion of MRSA-positive patient-days per total patient-days in the unit during the study period	Surveillance (admission), clinical culture	OR = 1.02 (95% CI, 1.02–1.03)	Admission to the ICU; antibiotic exposure to β-lactams, FQ, and macrolides during ICU stay
Srinavasan 2002[18]	United States	Prospective cohort	ICU (16 beds)	VRE	Perineum, rectum	Proportion of VRE-positive patient-days per total patient-days in the unit during the study period	Surveillance (admission, weekly)	CP not included in multivariable analysis	
Puzniak 2002[19]	United States	Quasi-experimental prospective cohort	ICU (19 beds)	VRE	Rectum, stool sample	Total no. of VRE-positive patients present during each patient's ICU stay	Surveillance (admission, weekly, discharge)	CP significant in multivariable analysis but OR not reported	Anaerobic therapy duration
Puzniak 2001[20]	United States	Quasi- experimental prospective cohort	ICU (19 beds)	VRE	Rectum, stool sample, blood	Total no. of VRE-positive patients present during each patient's ICU stay	Surveillance (admission, weekly, discharge), clinical culture	OR = 1.06 (95% CI, 1.00–1.12)	Enteral feeding, anaerobic therapy duration
Merrer 2000[21]	France	Prospective cohort	ICU (12 beds)	MRSA	Nares, axilla, perineum, and clinical samples	Proportion of MRSA-positive patient-days per total patient-days in the unit for the week	Surveillance (admission, weekly) clinical culture	OR not reported; CP significant in multivariable analysis (P = .002)	
Bonten 1998[2]	United States	Prospective cohort	ICU (16 beds)	VRE	Rectum	Average daily pro-portion of VRE-positive patients in the ICU until VRE acquisition or discharge	Surveillance (admission and daily thereafter)	HR = 1.03 (95% CI, 1.01–1.05)	Enteral feeding, proportion of patient-days with cephalosporin use

NOTE. 1G, first-generation; 3G, third-generation; 4G, fourth-generation; CCP, *C. difficile* colonization pressure; CDAD, *C. difficile*–associated disease; CMI, Charlson comorbidity index; CP, colonization pressure; FQ, fluoroquinolone; H2, histamine-2; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; OR, odds ratio; PPI, proton pump inhibitor; SAPS II, simplified Acute Physiology Score; VRE, vancomycin-resistant enterococci.

[a] Measure of effect for colonization pressure. An odds ratio of 1.02 for colonization pressure indicates that for each 1% increase in colonization pressure, the odds of acquiring the antibiotic-resistant bacteria increased by 2%. A hazard ratio of 1.4 for colonization pressure indicates that for each 1% increase in colonization pressure, the risk of acquiring the antibiotic-resistant bacteria increased by 40%.

[b] Other factors associated with MRSA, VRE, and/or *C. difficile* acquisition after adjustment for colonization pressure.