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MAJOR ARTICLE

Potential Adverse Effects of Broad-Spectrum Antimicrobial Exposure in the Intensive Care Unit

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Background. The potential adverse effects of empiric broad-spectrum antimicrobial use among patients with suspected but subsequently excluded infection have not been fully characterized. We sought novel methods to quantify the risk of adverse effects of broad-spectrum antimicrobial exposure among patients admitted to an intensive care unit (ICU).

Methods. Among all adult patients admitted to ICUs at a single institution, we selected patients with negative blood cultures who also received ≥1 broad-spectrum antimicrobials. Broad-spectrum antimicrobials were categorized in ≥1 of 5 categories based on their spectrum of activity against potential pathogens. We performed, in serial, 5 cohort studies to measure the effect of each broad-spectrum category on patient outcomes. Exposed patients were defined as those receiving a specific category of broad-spectrum antimicrobial; nonexposed were all other patients in the cohort. The primary outcome was 30-day mortality. Secondary outcomes included length of hospital and ICU stay and nosocomial acquisition of antimicrobial-resistant bacteria (ARB) or *Clostridium difficile* within 30 days of admission.

Results. Among the study cohort of 1918 patients, 316 (16.5%) died within 30 days, 821 (42.8%) had either a length of hospital stay >7 days or an ICU length of stay >3 days, and 106 (5.5%) acquired either a nosocomial ARB or *C. difficile*. The short-term use of broad-spectrum antimicrobials in any of the defined broad-spectrum categories was not significantly associated with either primary or secondary outcomes.

Conclusions. The prompt and brief empiric use of defined categories of broad-spectrum antimicrobials could not be associated with additional patient harm.

Keywords. antibiotic stewardship; antimicrobials; broad-spectrum; intensive care unit; nosocomial.

Multiple studies have demonstrated improved outcomes with the use of prompt empiric antimicrobial therapy—including the use of broad-spectrum antimicrobial coverage—among patients with a serious infection [1–8]. In patients where an infection is eventually excluded, however, the effect of empiric short-term broad-spectrum antimicrobial therapy is not as well understood.

Antimicrobials are also associated with adverse clinical effects including, but not limited to, an increased frequency of colonization and/or infection with multidrug-resistant bacteria and *Clostridium difficile* and end-organ dysfunction, both of which may increase mortality risk [9–13]. There are data to suggest that reducing antimicrobial exposure may be associated with similar or improved clinical outcomes and reduced harm [14–19]. De-escalation of antimicrobial therapy is recognized as an important stewardship intervention. However, in published studies of treatment for culture-confirmed sepsis, de-escalation has demonstrated a variable effect on patient- and population-centered outcomes, with 1 randomized clinical trial awaiting publication (https://clinicaltrials.gov/ct2/show/NCT01626612) [20–24].

In the context of these complex factors, and because spectrum of activity may be more readily modified in situations where antimicrobials are by common practice indicated, this study focuses specifically on the effect of empiric broad-spectrum (vs narrow-spectrum) antimicrobial treatment. We hypothesize that within a population of patients for whom infection was initially suspected but subsequently excluded, the spectrum of activity of the antimicrobials selected for empiric coverage of infection may correlate with patient-centered outcomes. Using a rigorous study design, we sought to characterize the potential adverse effects of broad-spectrum antimicrobial use among patients admitted to the ICU without bacteremia, for whom infection was eventually excluded.

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METHODS

DATA Collection

Data were extracted from the Medical Information Mart for Intensive Care (MIMIC) database, which has been previously described [25]. Briefly, the publicly available database comprises all patients admitted to ICUs at Beth Israel Deaconess Medical Center (BIDMC) during the period 2001–2012, divided into 2 database cohorts (2001–2007 and 2008–2012) by database structure due to a change in the proprietary source ICU information system. Data included in the MIMIC database are extracted from clinical databases (eg, hospital, pharmacy, and microbiology databases) as well as physiological databases (eg, measurements of vital signs from bedside monitors). These data are then organized and processed, which includes formatting, calculation of composite metrics, and de-identification, in compliance with Health Insurance Portability and Accountability Act standards. Further details regarding the database can be found at http://mimic.physionet.org/.

Study Population

BIDMC is a 672-bed tertiary care medical center and level 1 trauma center with 77 adult critical care beds (including medical, surgical, coronary, and cardiac surgery units) in Boston, Massachusetts. The study cohort excluded all patients admitted to the hospital from sources other than the emergency department or outpatient setting. We excluded patients transferred from another facility or who had no data on the admission source. In order to minimize the likelihood of current or recent treatment for infection, receipt of antimicrobials, or recent acquisition of antimicrobial-resistant bacteria (ARB) or *C. difficile*, we excluded patients who were admitted directly from another hospital or a long-term care nursing facility, or who had a prior admission to an ICU at BIDMC in the preceding 30 days. Additional inclusion criteria comprised at least 2 blood cultures drawn within the first 12 hours of ICU admission (and/or during the emergency department visit immediately preceding admission to the ICU or during the preceding non-ICU component of the admission for patients transferred from a non-ICU ward) and no positive blood cultures within the first 48 hours of and immediately prior to ICU admission. The study cohort was then characterized by the antimicrobial administered. We excluded patients who received antimicrobials during the hospital admission leading up to ICU admission, who did not receive at least 1 antimicrobial in at least 1 of the defined broad-spectrum antimicrobial categories within 24 hours of ICU admission, or who continued receiving an antimicrobial for at least 96 hours from the time of ICU admission. The study population and inclusion criteria are summarized in Supplementary Figure E1.

Definitions and Outcomes

Broad-spectrum antimicrobials were classified into 1 or more of the 5 spectrum-of-activity categories based on expert opinion (G.S., M.M.), including:

- 2 antimicrobial agents active against Gram-negative bacilli ("double Gram-negative");
- antimicrobials with activity against *Pseudomonas aeruginosa*;
- antimicrobials with activity against anaerobic bacteria;
- antimicrobials with activity against methicillin-resistant *Staphylococcus aureus* (MRSA);
- antimicrobials with activity against "atypical" bacteria (eg, *Mycoplasma pneumoniae*).

The classifications of individual antimicrobials are included in Supplementary Table E1.

For each cohort analysis, we defined patients with the exposure as those receiving antimicrobials in the category of interest and the remaining patients in the cohort as the comparison group (ie, those receiving an antimicrobial, but not one in the broad-spectrum category of interest). The exposed and unexposed groups were redefined for each of the 5 analyses. A schematic of the characterization of exposed and unexposed patients is shown in Supplementary Figure E2.

The primary outcome was death within 30 days of ICU admission. A priori, we defined 2 secondary outcomes: 1) ICU and hospital length of stay and 2) acquisition of an ARB or *C. difficile*. We defined the length of stay outcome as a composite outcome that was met if patients had an ICU length of stay >3 days *or* a hospital length of stay >7 days, starting from the time of admission to the ICU. Patients who died after ICU admission but prior to these time points, while still inpatients, were considered to have met the outcome. We defined the ARB outcome as a composite of nosocomial acquisition of 1 or more ARB or *C. difficile*. An ARB was defined as MRSA, vancomycin-resistant enterococci (VRE), or a Gram-negative bacteria resistant or intermediate on routine drug-susceptibility testing to 3 or more drug classes (β-lactam/β-lactamase inhibitors [ampicillin/sulbactam, piperacillin/tazobactam], third- or fourth-generation cephalosporins [ceftriaxone, cefepime, ceftazidime], fluoroquinolones [ciprofloxacin, levofloxacin], aminoglycosides [gentamicin, tobramycin]), or resistance to a carbapenem (meropenem, ertapenem, imipenem) [26]. For *P. aeruginosa*, the definition of ARB excluded ampicillin/sulbactam, ertapenem, and ceftriaxone. We classified *Acinetobacter* spp. as ARB if there was resistance to all antimicrobials tested or if there was susceptibility only to imipenem. We classified *Stenotrophomonas* spp. as ARB if there was resistance to trimethoprim-sulfamethoxazole. Patients who developed a positive culture with ≥1 of these ARB ≥48 hours but no more than 30 days after ICU admission met the ARB component of the composite outcome. (Data on frequency of ARB identified for this secondary outcome are included Supplementary Table E2.) Breakpoints to define antimicrobial resistance were defined using Clinical and Laboratory Standards Institute breakpoints contemporary to the time the organism was identified. Patients met the *C. difficile* component

of the outcome criteria if they demonstrated a positive cytotoxic culture, toxin assay, or polymerase chain reaction test ≥48 hours but no more than 30 days after ICU admission. Patients who acquired ≥1 ARB in the 12 months preceding ICU admission (6 months for *C. difficile*) or <48 hours after ICU admission were excluded from the ARB composite outcome [27–30].

Statistical Analysis

Because the study population consists of 2 separate cohorts as a result of a change in the information system in the ICU pertaining to different time periods during which there were changes in clinical management (eg, reduction in the use of sedation, mechanical ventilation, and vasopressor therapy; data not shown) and antimicrobial stewardship (including introduction of a formal stewardship program in 2007 that subsequently enhanced antimicrobial restriction, prospective review of prescribed antimicrobials, and condition-specific protocols, among other interventions), we chose to keep the cohorts separate in our analysis. To control for baseline covariates, we conducted a propensity score analysis based on 85 baseline variables for each patient admission (listed in Supplementary Table E3) [31]. Using L1-regularized logistic regression, we built propensity models for each of the 5 case-control studies. For each patient, we computed 5 different propensity scores, 1 corresponding to each broad-spectrum antimicrobial category. The corresponding areas under the curve (AUROCs) of these propensity scores for the entire cohorts are available in Supplementary Table E4.

Stratification matching based on these propensity scores was repeated for all 5 cohort analyses (corresponding with each broad-spectrum antimicrobial category). We stratified patients into quintiles based on the estimated propensity score from the combined group [31, 32]. For each cohort analysis, we measured the number of exposed and unexposed patients in each quintile that had the primary and secondary outcomes. In addition, we calculated all corresponding odds ratios (ORs) [33]. To correct for multiple hypothesis testing, we used a Bonferroni correction against a desired type 1 error limit of .05 [34]. Our study generated 75 effect estimates. Thus we calculated 99.9% confidence intervals for each OR. For each case-control study, we also estimated the pooled odds ratio across all strata using the Mantel-Haenszel method. All computation was done in MATLAB.

To explore the possibility that receipt of >1 category of broad-spectrum antimicrobial confers additive or multiplicative risk, we additionally performed analyses comparing patients receiving 1 vs 5, and ≥4 vs ≤3 categories of broad-spectrum antimicrobials.

RESULTS

Study Population

The study flow diagram is presented in Supplementary Figure E1. The source population comprised 54 571 unique patients including 36 244 in Cohort 1 (2001–2007) and 18 327 in Cohort 2 (2008–2012), from which 895 (2.5%) and 1023 (5.6%) met the study criteria, respectively, and were included in the analysis. Table 1 provides descriptive data for the source and study populations. Patients in Cohort 1 and Cohort 2 had a median of 2 (range, 2–6) and 2 (range, 2–13) blood cultures drawn within 48 hours of admission, respectively. The median ICU length of stay was 1.80 days (interquartile range [IQR], 1.09–2.66) and 1.62 days (IQR, 1.03–2.30) for Cohorts 1 and 2, respectively.

Antimicrobial Administration

The 1918 patients in the study were ordered a total of 9370 unique antimicrobials classified as at least 1 of the 5 broad-spectrum categories. In Cohort 1, the median number of unique antimicrobials per patient was 4 (IQR, 3–6). In Cohort 2, the median number of unique antimicrobials per patient was 4 (IQR, 2–7). Among antimicrobials classified as broad-spectrum in 1 or more of the 5 broad-spectrum categories, 32% were classified as offering Gram-negative activity, 23% pseudomonal activity, 17% MRSA activity, 16% anaerobic activity, and 11% atypical activity. Most patients in the study received antimicrobials representing either 3 or 4 of the 5 broad-spectrum antimicrobial categories (Figure 1). Figure 2 shows the distribution of broad-spectrum antimicrobial receipt in the study population in the first 96 hours for both Cohort 1 and Cohort 2.

Table 1. Descriptive Characteristics of the Source Population and Final Study Population

	Source Population (n = 54 571)	Cohort 1 (n = 895)	Cohort 2 (n = 1023)
Age, median (range),[a] y	59.4 (0–90+)	67.5 (18.7–90+)	67.8 (18.0–90+)
Male gender, %	55.8	50.28	52.88
Initial SOFA score, median (IQR)	3 (1–7)	5 (2–8)	1 (1–6)
Initial SAPS I, median (IQR)	12 (7–16)	12 (9–16)	13 (9–17)
Hospital admission source, No. (%)			
Emergency department	21 619	847 (94.6)	432 (42.2)
Physician referral	13 832	30 (3.4)	12 (1.2)
Clinic referral	10 588	18 (2.0)	579 (56.6)
Other[b]	8532		

Abbreviations: IQR, interquartile range; SAPS I, Simplified Acute Physiology Score I [35]; SOFA, Sequential Organ Failure Assessment [36].

[a]For de-identification purposes, the age for individuals aged >90 years is replaced with the value 90 years, and all individuals aged <18 years are removed.

[b]"Other" includes transfer from skilled nursing facility, transfer from other health care facilities, transfer information not available, and health maintenance organization referral.

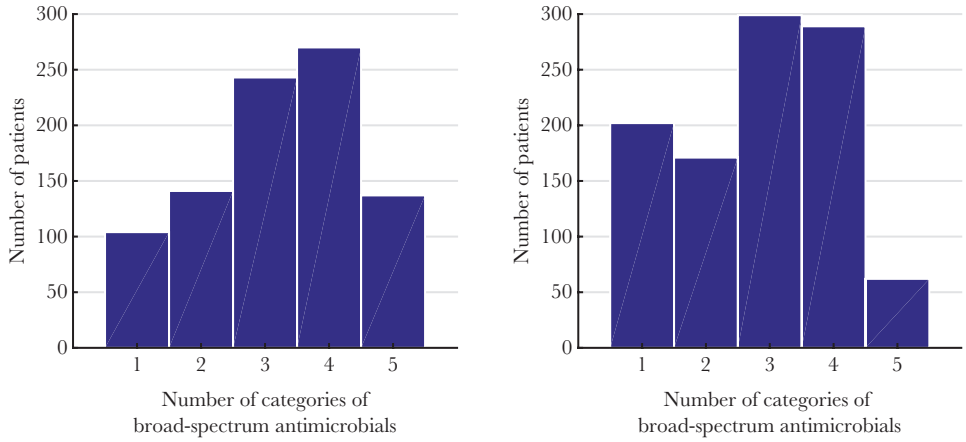

Figure 1. The number of patients among the study population who received ≥1 antimicrobials in 1, 2, 3, 4, or 5 categories of broad-spectrum antimicrobial.

Cohort Analyses

Table 2 presents the frequency of the primary outcome and secondary composite outcomes among exposed and unexposed patients in each of the 5 cohort analyses. Before adjusting for baseline covariates, there was a significant difference between exposed and unexposed patients for the primary outcome in both Cohorts 1 and 2, except for the atypical spectrum of activity case-control study. Length-of-stay and ARB outcomes were generally more common among exposed than unexposed patients, before adjustment. Table 3 presents the ORs for the primary outcome among exposed and unexposed patients, after stratifying patients based on the propensity score. Among the 5 analyses in Cohort 1 and Cohort 2, no strata in any of the 5 analysis groups demonstrated an OR significantly different than the null hypothesis. Among the analyses of the relationship between broad-spectrum antimicrobial receipt and secondary composite outcomes of length of stay and acquisition of ARB, there was no statistically significant OR for any analysis group in either Cohort 1 or Cohort 2 (Supplementary Tables E5A through E6B). No statistically significant ORs were obtained when comparing the primary and secondary outcomes of patients receiving 1 category of broad-spectrum antimicrobial with patients receiving all 5 categories of broad-spectrum antimicrobial, nor when comparing patients receiving 4 or 5 categories of broad-spectrum antimicrobial with patients receiving 3 or fewer categories of broad-spectrum antimicrobial (Supplementary Tables E7A and E7B).

DISCUSSION

In this study, we characterized the potential adverse effects of broad-spectrum antimicrobial exposure among patients for whom infection was eventually excluded. From 2 large databases of patients admitted to an ICU, we studied a cohort of patients who, on admission, received broad-spectrum antimicrobials for a short duration (<96 hours) but had negative blood cultures. After controlling for potential confounders by stratifying patients based on their propensity to receive each category of broad-spectrum antimicrobial, we found no

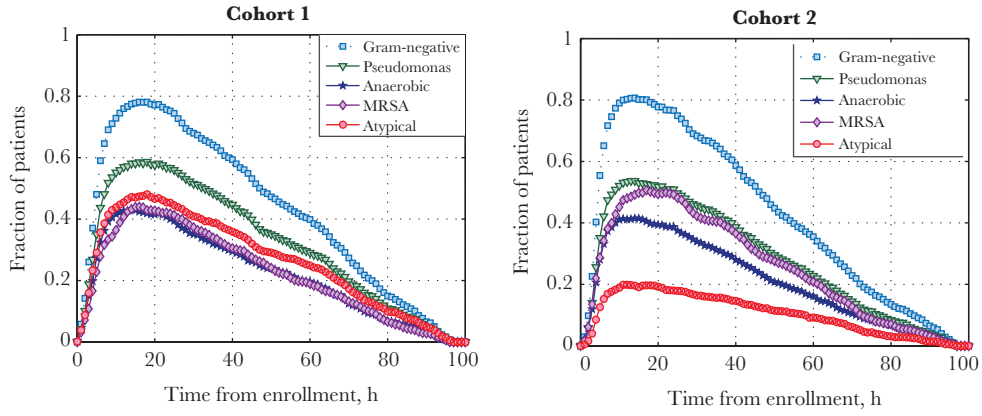

Figure 2. Distribution of antimicrobials by spectrum of activity category over time. The plot indicates the fraction of the study population receiving at least 1 antimicrobial with the defined spectrum of coverage at anytime during the first 4 days after enrollment. In the case of Gram-negative agents, data represented are for the fraction of patients receiving 1 or more antimicrobials with activity against Gram-negative bacteria. Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

statistically significant association between short-term exposure to broad-spectrum antimicrobials in each of 5 specific categories of broad-spectrum antimicrobial and either the primary outcome (30-day mortality) or the secondary outcomes (composite measures of prolonged length of stay and acquisition of ARB). Furthermore, we did not identify an additive or multiplicative risk among patients receiving multiple categories of broad-spectrum antimicrobial compared with patients receiving few categories or only 1 category of broad-spectrum antimicrobial agents.

In a clinical setting where infection is suspected and prompt treatment with broad-spectrum antimicrobial therapy may provide benefit, the additional theoretical harm from antimicrobials may be minimal, on average, to the individual patient. It is important to note that we have selected a population for which antimicrobials were stopped in the absence of infection, an important antimicrobial stewardship intervention that almost certainly mitigates potential harm. There are 2 other possible explanations for our findings. First, the risk of harm of unnecessary short-term exposure to broad-spectrum antimicrobials exists, but the study was not powered to detect such harm. Second, the risk is not uniform across ICU patient subsets, and there are subgroups with adverse outcomes from unnecessary short-term exposure to broad-spectrum antimicrobials. A much larger database would be required to exclude these possibilities.

While to our knowledge no prior study has investigated the effect of short-term broad-spectrum antimicrobials on patient outcome among patients admitted to the ICU where infection was eventually excluded, previous studies including meta-analyses have found discordant results when comparing mortality among patients receiving monotherapy vs combination therapy, potentially dependent on risk of adverse events, specific antimicrobial combinations, and adequacy of antibacterial or antifungal therapy [5, 6, 37, 38]. The results of our study are complementary to these data, as we studied a population of patients in a distinct category: patients who receive antimicrobials but who were ultimately deemed to be uninfected or who had a limited degree of infection, as all blood cultures were negative at the time of admission and all antimicrobials (including broad-spectrum) were discontinued within 96 hours of ICU admission.

An important implication of our findings relates to antimicrobial stewardship. It is notable that in this study, approximately 80% of broad-spectrum antimicrobials were discontinued within 96 hours in the setting of a clinical infection eventually being excluded. However, even with the strength of a large database with numerous clinical variables, our ability to predict which patients will receive certain categories of broad-spectrum antimicrobials was limited. This suggests that clinicians are using additional data (beyond the clinical variables captured in MIMIC) when deciding who should receive broad-spectrum antimicrobials (defined 5 ways), or there is an element of randomness in the selection of empiric antibiotic coverage. Therefore, while prompt de-escalation does not appear to lead to detrimental adverse effects, further study may be warranted to understand these clinical decision-making processes.

Prior data have demonstrated that even minimal antimicrobial exposure may promote the development of resistant organisms, particularly *C. difficile,* but also fluoroquinolone- and carbapenem-resistant Gram-negative bacteria and other pathogens [39, 40]. Our study suggests that in a pragmatic setting, there is no significant association between short-term distinct types of broad-spectrum antimicrobial exposure and acquisition

Table 2. Frequency of Primary and Secondary Outcomes Among Patients Exposed and Unexposed to Each of 5 Broad-Spectrum Antimicrobial Categories in Cohort 1 and Cohort 2

			Outcome Frequency, %					
	No. of Patients		Mortality, 30-d		LOS		ARB	
Treatment	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Cohort 1								
Double Gram-negative	330	565	98 (30)	116 (21)	173 (52)	253 (45)	23 (7)	26 (5)
Pseudomonas	625	270	177 (28)	37 (14)	306 (49)	120 (44)	35 (6)	14 (5)
Anaerobic	459	436	156 (34)	58 (13)	248 (54)	178 (41)	28 (6)	21 (5)
MRSA	476	419	131 (28)	83 (20)	253 (53)	173 (41)	31 (7)	18 (4)
Atypical	526	369	127 (24)	87 (24)	233 (44)	193 (52)	25 (5)	24 (7)
Cohort 2								
Double Gram-negative	526	497	56 (11)	46 (9)	216 (41)	179 (36)	23 (4)	34 (7)
Pseudomonas	626	397	72 (12)	30 (8)	254 (41)	141 (36)	28 (4)	29 (7)
Anaerobic	477	546	57 (12)	45 (8)	197 (41)	198 (36)	20 (4)	37 (7)
MRSA	610	413	65 (11)	37 (9)	242 (40)	153 (37)	37 (6)	20 (5)
Atypical	263	760	24 (9)	78 (10)	103 (39)	292 (38)	18 (7)	39 (5)

Abbreviations: ARB, antimicrobial-resistant bacteria, referring to patients who met the ARB composite outcome including acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, multidrug-resistant Gram-negative bacteria, or *Clostridium difficile*; LOS, length of stay, referring to patients who met the length of stay composite outcome including either intensive care unit length of stay greater than 3 days or hospital length of stay greater than 7 days.

Table 3. Relationship Between Broad-Spectrum Antimicrobial Receipt—Defined for 5 Different Categories of Broad-Spectrum Antimicrobial—and 30-Day Mortality Among Patients in Cohort 1 (2001–2007) and Cohort 2 (2008–2012) Admitted to an Intensive Care Unit, Stratified by Propensity to Receive Broad-Spectrum Antimicrobial

		Cohort 1						Cohort 2					
		No. of Patients		30-d Mortality				No. of Patients		30-d Mortality			
Analysis Group	PS Quintile	Exposed	Unexposed	Exposed	Unexposed	OR	(95% CI)	Exposed	Unexposed	Exposed	Unexposed	OR	(95% CI)
Double Gram-negative	1	36	143	6	17	1.48	(0.27–8.15)	78	128	4	5	1.33	(0.14–12.82)
	2	56	125	8	20	0.88	(0.20–3.90)	82	121	9	16	0.81	(0.19–3.50)
	3	62	115	16	16	2.15	(0.58–7.95)	117	88	9	9	0.73	(0.14–3.74)
	4	72	107	22	31	1.08	(0.36–3.24)	109	101	12	11	1.01	(0.24–4.36)
	5	104	75	46	32	1.07	(0.39–2.92)	140	59	22	5	2.01	(0.36–11.27)
Pseudomonas	1	98	81	15	7	1.91	(0.39–9.46)	84	121	6	5	1.78	(0.23–13.94)
	2	106	73	22	8	2.13	(0.49–9.23)	109	95	14	7	1.85	(0.37–9.21)
	3	128	51	34	7	2.27	(0.51–10.15)	140	65	20	3	3.44	(0.42–28.34)
	4	135	44	37	9	1.47	(0.37–5.88)	139	65	7	8	0.38	(0.06–2.25)
	5	158	21	69	6	1.94	(0.36–10.40)	154	51	25	7	1.22	(0.27–5.59)
Anaerobic	1	47	132	7	9	2.39	(0.41–14.02)	62	143	5	6	2.00	(0.25–15.79)
	2	76	103	13	11	1.73	(0.40–7.40)	75	129	11	7	3.00	(0.56–15.99)
	3	86	93	14	12	1.31	(0.32–5.34)	94	111	15	13	1.43	(0.37–5.50)
	4	100	79	29	17	1.49	(0.47–4.75)	107	98	17	13	1.24	(0.33–4.60)
	5	150	29	93	9	3.63	(0.86–15.24)	139	65	9	6	0.68	(0.11–4.18)
MRSA	1	60	122	8	11	1.55	(0.30–7.93)	86	119	7	11	0.87	(0.16–4.62)
	2	82	95	14	16	1.02	(0.27–3.83)	109	95	10	8	1.10	(0.21–5.66)
	3	94	84	22	15	1.41	(0.41–4.84)	114	91	12	11	0.86	(0.20–3.70)
	4	101	78	23	21	0.80	(0.25–2.53)	133	71	18	5	2.07	(0.36–11.82)
	5	139	40	64	20	0.85	(0.26–2.79)	168	37	18	2	2.10	(0.17–26.53)
Atypical	1	70	109	17	21	1.34	(0.40–4.55)	22	183	1	16	0.50	(0.02–16.24)
	2	91	88	27	18	1.64	(0.52–5.21)	43	161	7	15	1.89	(0.37–9.67)
	3	113	66	28	18	0.88	(0.27–2.81)	48	158	3	13	0.74	(0.08–6.63)
	4	127	52	25	14	0.67	(0.19–2.36)	60	145	3	19	0.35	(0.04–2.90)
	5	125	54	30	16	0.75	(0.23–2.50)	90	113	10	15	0.82	(0.19–3.43)

Abbreviations: CI, confidence interval; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; PS, propensity score.

of these organisms. However, as we did not include patients who received no antimicrobials or only narrow-spectrum antimicrobials in our study, we cannot exclude the possibility that the promotion of ARB acquisition is a universal and uniform effect of all broad-spectrum antimicrobial categories. Furthermore, our study was limited by the small number of positive ARB or *C. difficile* cases. Finally, this study does not address the potential impact on antimicrobial resistance among microbial flora constituting the ICU or hospital-wide ecosystem, as well as the potential delayed effects of alteration of the gut microbiome from unnecessary broad-spectrum antimicrobials.

There exist several limitations to our analysis. First, our study is based on an assumption that if all antimicrobials are stopped within 96 hours of admission to the ICU, then the patient did not have an infection. Further limitations derive from those inherent to the MIMIC data set. Antimicrobial use is recorded using prescribing rather than administration databases. In our analysis, we exclude patients who are transferred from long-term nursing facilities or other hospitals. However, patients from nursing homes who are admitted from the emergency department were not excluded. While the 30-day mortality outcome was validated against a Social Security database, the cause of death was not recorded. Thus, we could not assess differences in cause of death among exposed and unexposed patients. Because the assessment of ARB acquisition relies on the assumption that future cultures are obtained and documented at the same institution, we may have underestimated the frequency of this outcome, especially if it arose after hospital discharge. Adverse events directly attributable to the administration of antimicrobials—including allergic reactions and organ toxicities—and drug-drug interactions could not be specifically investigated with this data set. Finally, this study is limited to a single-center analysis. Validation in another data set would strengthen the results and conclusions and may also provide improved power to detect a difference in the primary or secondary outcomes. It is notable that in our study findings were robust through 2 similarly-sized noncontemporaneous cohorts; the 2 cohorts in this study were distinguished by time, further development of database structure and elements, and evolution of clinical practice and antimicrobial stewardship. Future prospective studies may also be designed to investigate the effect on microbial ecology of brief broad-spectrum antimicrobial use among blood culture–negative patients.

In conclusion, we have demonstrated in an ICU cohort of patients receiving 1 or more categories of broad-spectrum antimicrobial that the administration of each of 5 categories of broad-spectrum antimicrobial (compared with nonreceipt of that category of antimicrobial), or the receipt of multiple vs few categories of broad-spectrum antimicrobial, is not associated with 30-day mortality or secondary outcomes, including length of stay and acquisition of nosocomial bacterial pathogens. While these findings remain to be validated in other larger study populations, the prompt and brief use for suspected infection of defined categories of broad-spectrum antimicrobial use may not be associated with additional patient harm among patients receiving empiric broad-spectrum antimicrobials.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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Prior presentations. Preliminary data from this research have been published at the Critical Data Conference (Cambridge, MA) in 2014.

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