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Patterns, Predictors, and Intercenter Variability in Empiric Gram-Negative Antibiotic Use Across 928 United States Hospitals

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Background. Empiric antibiotic use among hospitalized adults in the United States (US) is largely undescribed. Identifying factors associated with broad-spectrum empiric therapy may inform antibiotic stewardship interventions and facilitate benchmarking.

Methods. We performed a retrospective cohort study of adults discharged in 2019 from 928 hospitals in the Premier Healthcare Database. "Empiric" gram-negative antibiotics were defined by administration before day 3 of hospitalization. Multivariable logistic regression models with random effects by hospital were used to evaluate associations between patient and hospital characteristics and empiric receipt of broad-spectrum, compared to narrow-spectrum, gram-negative antibiotics.

Results. Of 8 017 740 hospitalized adults, 2 928 657 (37%) received empiric gram-negative antibiotics. Among 1 781 306 who received broad-spectrum therapy, 30% did not have a common infectious syndrome present on admission (pneumonia, urinary tract infection, sepsis, or bacteremia), surgery, or an intensive care unit stay in the empiric window. Holding other factors constant, males were 22% more likely (adjusted odds ratio [aOR], 1.22 [95% confidence interval, 1.22–1.23]), and all non-White racial groups 6%–13% less likely (aOR range, 0.87–0.94), to receive broad-spectrum therapy. There were significant prescribing differences by region, with the highest adjusted odds of broad-spectrum therapy in the US West South Central division. Even after model adjustment, there remained substantial interhospital variability: Among patients receiving empiric therapy, the probability of receiving broad-spectrum antibiotics varied as much as 34+ percentage points due solely to the admitting hospital (95% interval of probabilities: 43%–77%).

Conclusions. Empiric gram-negative antibiotic use is highly variable across US regions, and there is high, unexplained interhospital variability. Sex and racial disparities in the receipt of broad-spectrum therapy warrant further investigation.

Keywords. gram-negative antibiotics; empiric therapy; inpatient antibiotic utilization; antibiotic stewardship.

Antibiotic resistance in gram-negative bacteria is an urgent public health threat. The World Health Organization's highest-priority bacterial pathogens, and 3 of the 4 urgent bacterial threats designated by the United States (US) Centers for Disease Control and Prevention (CDC), are multidrug-resistant gram-negative organisms [1, 2]. To reduce further resistance emergence, regulatory agencies and professional organizations encourage providers to use antibiotics only where necessary and, where antibiotics are indicated, to select the most narrow-spectrum antibiotic(s) that remain safe and effective [3, 4]. However, a significant proportion of antibiotics are prescribed empirically, that is, before there are culture results to guide antibiotic selection and even before there is confirmation of a bacterial infection [5]. Therefore, empiric antibiotic prescribing presents continued clinical challenges: Providers must balance the more theoretical risk of exacerbating the resistance crisis by prescribing broad-spectrum therapy against the more tangible risk of poor clinical outcomes due to undertreatment from narrow-spectrum therapy (or no antibiotic therapy) [6–8].

Due to turnaround times for bacterial culture and antibiotic susceptibility testing (AST), the first several days of hospitalization often fall within an empiric window. Antibiotic prescribing during this empiric period may sum to substantial amounts of antibiotic use when aggregated across all admissions. However, national patterns of early empiric therapy in US hospitalized adults have not been previously described.

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Understanding how much and what types of early empiric antibiotic use are occurring in US hospitals can identify novel opportunities for standardizing empiric decision-making to reduce overuse of broad-spectrum gram-negative antibiotics and to optimize empiric prescribing to improve patient outcomes. The current study aimed to quantify empiric gram-negative antibiotic use, to identify patient and hospital predictors of receiving empiric broad-spectrum therapy, and to measure intercenter variability across a large national cohort of US hospitals.

METHODS

We conducted a retrospective observational cohort study of adult patients who were discharged in 2019 from hospitals in the Premier Healthcare Database ("Premier Database"), an all-payer database encompassing >120 million US hospitalizations [9]. This dataset has been used previously to address infectious disease questions, including by the CDC [10–17]. All adult encounters (age ≥18 years) with 2019 discharge dates were eligible for cohort inclusion, except hospice transfers (curative antibiotic treatment is frequently not the therapeutic goal). This study did not include protected health information and was exempt from institutional review board review.

Cohort, Definitions, and Collected Data

Our primary research objective was to identify predictors of receiving broad-spectrum, compared to narrow-spectrum, empiric gram-negative therapy. Therefore, we restricted the study (analysis) cohort to admissions that received at least 1 empiric gram-negative antibiotic. "Empiric" administration was defined as receipt within the first 2 days of hospital admission (hospital day ≤2). Gram-negative antibiotics were classified by spectrum of activity by a panel of infectious disease specialists (J. D. B., A. D. H., E. L. H., and P. D. T.) (Figure 1).

For each cohort admission, we extracted comprehensive hospital and admission characteristics, payer information, and sociodemographic data. For each admission's empiric window (hospital day ≤2), we also extracted patient location, medication charge data, and *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis and procedure codes. We mapped present-on-admission (POA) diagnosis codes to Elixhauser comorbidities using Agency for Healthcare Research and Quality methodology [15] and to 5 infectious syndromes selected for clinical relevance and diagnostic code availability (ventilator-associated pneumonia [VAP], non-VAP pneumonia, urinary tract infection [UTI], bacteremia, and sepsis) [18] (code sets are listed in Supplementary Appendix 1).

Statistical Methods

Using variables selected a priori through literature review and expert consensus, we built a multivariable logistic regression model with random effects by hospital to evaluate the relationship between patient and hospital characteristics with empiric receipt of broad-spectrum, compared to narrow-spectrum, gram-negative antibiotics. In a sensitivity analysis, we included variables capturing previous hospitalizations, intensive care unit (ICU) stays, and inpatient antibiotic use in the 3 months preceding admission (Premier Database patients can be tracked across admissions within a single hospital); the sensitivity analysis excluded patients admitted in quarter 1 of 2019, to ensure that all patients had equivalent, 3-month lookback periods. All tests were 2-tailed, and P values ≤ .05 were used for statistical significance testing. Analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

During the 2019 study period, there were 8 017 740 admissions across 928 US hospitals. Overall, 37% (2 928 657) of admissions received gram-negative antibiotics within the first 2 days of hospitalization (ie, empiric gram-negative therapy). Patient and hospital characteristics by spectrum of therapy are displayed in Table 1. A total of 1 781 306 admissions (22% of all admissions and 61% of admissions that received empiric gram-negative therapy) received broad-spectrum gram-negative antibiotics (Figure 2). Piperacillin-tazobactam and cefepime were the most frequently used broad-spectrum agents, representing 43% and 22% of all broad-spectrum empiric days of therapy (DOTs), respectively (Table 2). Of admissions that received empiric gram-negative therapy, 0.12% received extremely broad-spectrum gram-negative antibiotics, with tigecycline being the most common (Table 2). A further 1 147 351 admissions (39% of admissions that received empiric gram-negative therapy) only received narrow-spectrum agents (Figure 2). Table 2 reflects the empiric usage distribution for all gram-negative antibiotics. Figure 3 delineates the characteristics of patients who received broad-spectrum therapy by infectious syndrome, surgery, and ICU status.

Factors Associated With Receiving Broad-Spectrum Therapy

In adjusted analysis, all severity-of-illness markers were independent predictors for receipt of broad-spectrum therapy, compared to receipt of only narrow-spectrum therapy (adjusted odds ratio [aOR] range, 1.15–1.50; all $P < .001$) (Table 3). Bacteremia, sepsis, and/or VAP were also independent predictors for receipt of broad-spectrum therapy (aOR, 1.73, 2.87, and 9.38, respectively; all $P < .001$). In contrast, patients with pneumonia and UTI were significantly more likely to receive narrow-spectrum empiric therapy (aOR for pneumonia, 0.84 [95% confidence interval {CI}, .83–.84]; aOR for UTI, 0.49 [95% CI, .49–.50]; both $P < .001$) (Table 3).

Age demonstrated roughly parabolic effects, with the odds of receiving broad-spectrum therapy increasing until middle age

NARROW SPECTRUM		BROAD SPECTRUM	
Narrowest-Spectrum	**Narrower-Spectrum**	**Extended-Spectrum**	**Extremely Broad-Spectrum**
• 2nd-generation cephalosporins • Amoxicillin • Ampicillin • Metronidazole	• Ceftriaxone • Third-generation oral cephalosporins • Amoxicillin-clavulanate • Ampicillin-sulbactam	• Antipseudomonal penicillins • Fluoroquinolones • Aminoglycosides • Cefepime • Ceftazidime • Carbapenems • Aztreonam • Colistin • Ceftaroline	• Imipenem/cilastatin/relebactam • Meropenem-vaborbactam • Tigecycline • Ceftolozane-tazobactam • Ceftazidime-avibactam • Cefiderocol

Figure 1. Gram-negative antibiotic spectrum-of-activity categories, as classified by a panel of infectious disease clinicians and antimicrobial stewardship experts. Antibiotics were classified using an iterative, multistage process by infectious disease specialists. Because this study focused on gram-negative empiric therapy, the steps and goals were to (1) identify antibiotics with gram-negative activity; (2) refine this list to only those antibiotics that are primarily used for gram-negative, rather than gram-positive, infections (see asterisk below); and (3) classify those antibiotics that remained into broad- vs narrow-spectrum categories based upon activity against gram-negative organisms. Following an antibiotic literature review (by K. E. G., A. D. H., and J. D. B.), steps 1–3 were performed independently by A. D. H. and J. D. B., followed by discussion to adjudicate discrepancies. The proposed classifications were subsequently provided to P. D. T. for review, comment, and proposal of changes. In round 2, A. D. H. and J. D. B. reconvened to discuss P. D. T.'s feedback and to implement agreed-upon modifications, with further outreach to E. L. H. and P. D. T. where necessary to reach consensus. Narrowest-spectrum and narrower-spectrum antibiotics were collectively designated as "narrow-spectrum" gram-negative antibiotics; extended-spectrum and extremely broad-spectrum antibiotics were classified as "broad-spectrum" gram-negative antibiotics. *The following antibiotics with gram-negative activity were excluded from classification, because they are primarily used for gram-positive infections: first-generation cephalosporins, oxacillin, cloxacillin, didoxacillin, trimethoprim-sulfamethoxazole, doxycycline, nafcillin, and penicillins.

(40–49 years), and then declining with each decade after age 59 (Table 3). Male sex was associated with 22% higher adjusted odds of receiving broad-spectrum empiric therapy compared to female sex (aOR, 1.22 [95% CI, 1.22–1.23]; $P < .001$). We performed 2 sensitivity analyses to further probe this finding. An unadjusted analysis restricting to patients with sepsis or bacteremia demonstrated that, in both instances, males received broad-spectrum empiric therapy at significantly higher rates than females (80% vs 75% for sepsis, and 71% vs 66% for bacteremia; both χ^2 $P < .001$). Although our multivariable model controlled for infection type, these results provided further confirmation that a single infection type such as UTI, which is more common among women and more commonly treated with narrow-spectrum agents, had not skewed observed associations. A second analysis executing the full multivariable model on a cohort that excluded female admissions for labor and delivery, which we hypothesized would disproportionately involve narrow-spectrum agents and could therefore bias sex-based associations, also did not meaningfully change the primary model finding (aOR from cohort excluding labor/delivery admissions, 1.17 [95% CI, 1.16–1.18]; $P < .001$).

All non-White patient racial groups were less likely to receive broad-spectrum therapy (aOR range, 0.87–0.94; all $P < .001$). Patient insurance status was not associated with receipt of broad-spectrum empiric therapy (aOR, 1.00; $P = .52$). The Elixhauser comorbidities associated with the highest odds of receiving broad-spectrum therapy were oncologic comorbidities (lymphoma, metastatic cancer, or solid tumor; aOR range, 1.32–1.82; all $P < .001$) and paralysis (aOR, 1.53 [95% CI, 1.50–1.55]; $P < .001$) (Table 3). In a sensitivity analysis incorporating information from patients' previous hospitalizations, the odds of receiving empiric broad-spectrum therapy doubled for each prior hospitalization in which a patient had received broad-spectrum gram-negative antibiotics (aOR, 2.02 [95% CI, 2.00–2.05]; $P < .001$) (Supplementary Table 1).

Regarding hospital characteristics, in adjusted analysis admission to a teaching hospital was associated with 12% lower odds of receiving broad-spectrum empiric therapy (aOR, 0.88 [95% CI, .81–.96]; $P < .001$). There were significant differences by US census division, with the highest adjusted odds of broad-spectrum therapy in the West South Central division (Arkansas, Louisiana, Oklahoma, Texas). Relative to the South Atlantic division (chosen as the reference category because it had the largest cohort representation), the adjusted odds of receiving broad-spectrum therapy were 43%, 34%, 27%, and 18% lower in the New England, Pacific, Mountain, and East North Central divisions, respectively (all $P < .001$) (Table 3).

Variability Across Hospitals

After model adjustment for patient and hospital characteristics, there remained substantial variability (ie, unexplained variance) between hospitals, as reflected in the distribution of the hospital-specific random intercepts. If 2 otherwise equal

Table 1. Select Patient and Hospital Characteristics in a Cohort of 2 928 657 Inpatients Who Received Empiric Gram-Negative Antibiotics Across 928 US Hospitals in 2019, by Spectrum of Therapy

Characteristic	Total Empiric Therapy Cohort (N = 2 928 657)	Received Empiric Broad-Spectrum Gram-Negative Antibiotics		*P* Value
		No[*a] (n = 1 147 351 [39%])	Yes (n = 1 781 306 [61%])	
Patient and admission characteristics				
Age group, y				<.001*
18–29	203 096 (6.9)	102 992 (9.0)	100 104 (5.6)	
30–39	235 239 (8.0)	102 820 (9.0)	132 419 (7.4)	
40–49	260 042 (8.9)	93 250 (8.1)	166 792 (9.4)	
50–59	437 863 (15.0)	152 351 (13.3)	285 512 (16.0)	
60–69	597 069 (20.4)	209 425 (18.3)	387 644 (21.8)	
70–79	603 871 (20.6)	228 437 (19.9)	375 434 (21.1)	
≥80	591 477 (20.2)	258 076 (22.5)	333 401 (18.7)	
Male sex	1 321 892 (45.1)	455 856 (39.7)	866 036 (48.6)	<.001*
Publicly insured	2 137 044 (73.0)	837 769 (73.0)	1 299 275 (72.9)	.141*
Hispanic ethnicity	264 667 (9.0)	101 218 (8.8)	163 449 (9.2)	<.001*
Race				<.001*
Asian	56 966 (1.9)	23 192 (2.0)	33 774 (1.9)	
Black	383 478 (13.1)	151 839 (13.2)	231 639 (13.0)	
Other/unknown	308 232 (10.5)	125 211 (10.9)	183 021 (10.3)	
White	2 179 981 (74.4)	847 109 (73.8)	1 332 872 (74.8)	
Admission type[b]				<.001*
Emergency	2 155 741 (73.6)	805 234 (70.2)	1 350 507 (75.8)	
Urgent	385 176 (13.2)	156 072 (13.6)	229 104 (12.9)	
Elective	345 954 (11.8)	166 138 (14.5)	179 816 (10.1)	
Trauma center	16 458 (0.6)	7821 (0.7)	8637 (0.5)	
Information unavailable	25 328 (0.9)	12 086 (1.1)	13 242 (0.7)	
Source of hospital admission (point-of-origin)[b]				<.001*
Non–healthcare facility[c]	2 365 626 (80.8)	937 242 (81.7)	1 428 384 (80.2)	
Clinic	269 971 (9.2)	112 069 (9.8)	157 902 (8.9)	
Transfer from an outside hospital	182 182 (6.2)	62 447 (5.4)	119 735 (6.7)	
Transfer from skilled nursing facility or intermediate care facility	66 771 (2.3)	19 020 (1.7)	47 751 (2.7)	
Transfer from healthcare facility or ambulatory surgery center	31 420 (1.1)	11 721 (1.0)	19 699 (1.1)	
Court/law enforcement	2884 (0.1)	1073 (0.1)	1811 (0.1)	
Information unavailable	9803 (0.3)	3779 (0.3)	6024 (0.3)	
Total Elixhauser score, POA, mean (SD)	3.64 (2.28)	3.36 (2.23)	3.82 (2.29)	<.001
Severity-of-illness markers in day ≤2 of hospital admission	972 411 (33.2)	326 842 (28.5)	645 569 (36.2)	<.001*
Mechanical ventilation	146 106 (5.0)	29 754 (2.6)	116 352 (6.5)	<.001*
Major surgery[d]	523 932 (17.9)	205 818 (17.9)	318 114 (17.9)	.081*
ICU admission	491 596 (16.8)	137 739 (12.0)	353 857 (19.9)	<.001*
Vasopressor receipt	382 784 (13.1)	109 772 (9.6)	273 012 (15.3)	<.001*
Infectious syndromes POA				
Pneumonia[e]	562 467 (19.2)	203 756 (17.8)	358 711 (20.1)	<.001*
Ventilator-associated pneumonia	1611 (0.1)	50 (0.0)	1561 (0.1)	<.001*
Urinary tract infection	663 908 (22.7)	313 614 (27.3)	350 294 (19.7)	<.001*
Sepsis	677 656 (23.1)	153 501 (13.4)	524 155 (29.4)	<.001*
Bacteremia	41 008 (1.4)	12 853 (1.1)	28 155 (1.6)	<.001*
Hospital characteristics				
Urban[f]	2 540 669 (86.8)	992 102 (86.5)	1 548 567 (86.9)	<.001*
Teaching hospital	1 315 323 (44.9)	516 123 (45.0)	799 200 (44.9)	.048*
Bed size				<.001*
0–99	189 385 (6.5)	78 649 (6.9)	110 736 (6.2)	
100–199	454 285 (15.5)	183 057 (16.0)	271 228 (15.2)	
200–299	525 687 (17.9)	203 707 (17.8)	321 980 (18.1)	
300–399	539 235 (18.4)	212 624 (18.5)	326 611 (18.3)	
400–499	329 232 (11.2)	137 768 (12.0)	191 464 (10.7)	
≥500	890 833 (30.4)	331 546 (28.9)	559 287 (31.4)	

Table 1. Continued

Characteristic	Total Empiric Therapy Cohort (N = 2 928 657)	Received Empiric Broad-Spectrum Gram-Negative Antibiotics		*P* Value
		No[*a] (n = 1 147 351 [39%])	Yes (n = 1 781 306 [61%])	
US census region and division[g]				<.001*
South				
South Atlantic	771 481 (26.3)	290 188 (25.3)	481 293 (27.0)	
West South Central	375 843 (12.8)	125 576 (10.9)	250 267 (14.0)	
East South Central	241 618 (8.3)	90 372 (7.9)	151 246 (8.5)	
Northeast				
Middle Atlantic	425 404 (14.5)	169 331 (14.8)	256 073 (14.4)	
New England	55 155 (1.9)	28 161 (2.5)	26 994 (1.5)	
Midwest				
East North Central	482 356 (16.5)	201 826 (17.6)	280 530 (15.7)	
West North Central	154 389 (5.3)	63 705 (5.6)	90 684 (5.1)	
West				
Mountain	149 430 (5.1)	55 627 (4.8)	93 803 (5.3)	
Pacific	272 981 (9.3)	122 565 (10.7)	150 416 (8.4)	

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

Abbreviations: ICU, intensive care unit; POA, present on admission; SD, standard deviation; US, United States.

[a]All cohort patients received empiric gram-negative therapy, and patients who did not receive any broad-spectrum gram-negative antibiotics received narrow-spectrum gram-negative antibiotics. This table does not include information on the 2019 admissions in the Premier Healthcare Database that did not receive empiric gram-negative antibiotics, which represent a mixture of patients who did not receive any empiric antibiotics and patients who received only empiric gram-positive antibiotics. These patients were not analyzed in this study.

[b]Designated using the Uniform Billing form UB-40 (Centers for Medicare and Medicaid Services Form 1450).

[c]Represents patients presenting from home, a physician's office, or workplace upon physician referral, as well as patients who were admitted through the emergency department.

[d]Designated using Agency for Healthcare Research and Quality definitions of "major therapeutic" and "major diagnostic" procedures. Major procedures are considered operating room procedures. Further information and mapping code are available at: https://www.hcup-us.ahrq.gov/toolssoftware/procedureicd10/procedure_icd10.jsp.

[e]Excluding ventilator-associated pneumonia.

[f]Designation provided by Premier, based upon American Hospital Association Annual Survey response.

[g]US census divisions comprise 4 US census regions: Northeast (Middle Atlantic, New England), South (South Atlantic, East South Central, West South Central), Midwest (East North Central, West North Central), and West (Mountain, Pacific). States in each US census division are as follows: New England Division: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont. Middle Atlantic Division: New Jersey, New York, Pennsylvania. East North Central Division: Illinois, Indiana, Michigan, Ohio, Wisconsin. West North Central Division: Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota. South Atlantic Division: Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia. East South Central Division: Alabama, Kentucky, Mississippi, Tennessee. West South Central Division: Arkansas, Louisiana, Oklahoma, Texas. Mountain Division: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming. Pacific Division: Alaska, California, Hawaii, Oregon, Washington.

*χ^2 test.

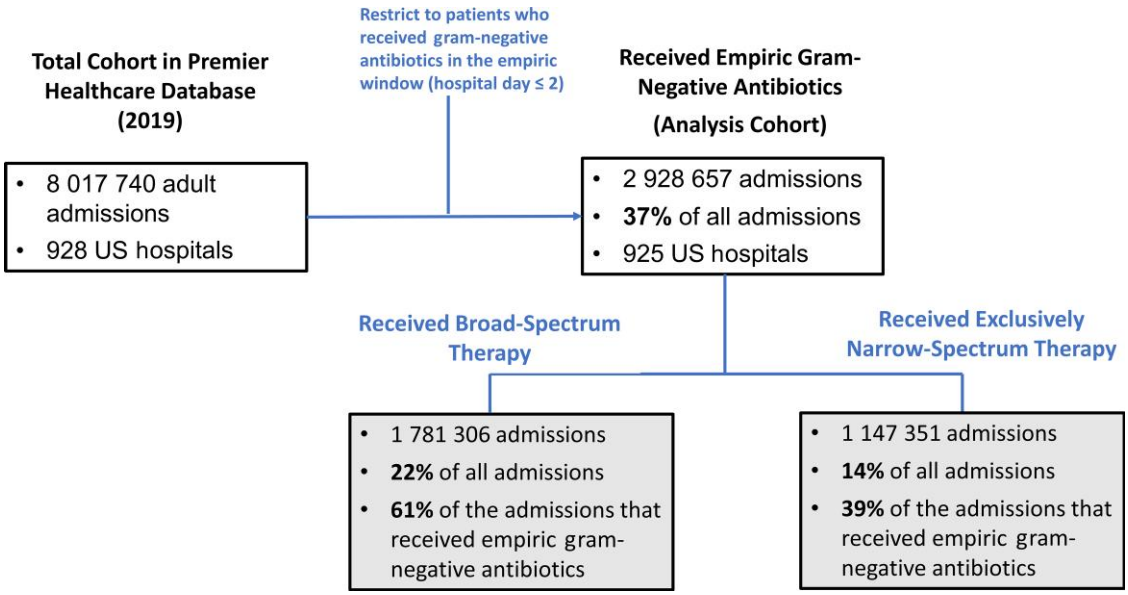


Figure 2. Cohort of hospitalized patients who received empiric gram-negative antibiotics across 928 United States (US) hospitals (2019).

Table 2. Distribution of Empiric Gram-Negative Antibiotic Use by Days of Therapy (Hospital Day ≤ 2)

Narrow-Spectrum Gram-Negative Antibiotics*	Total Empiric Days of Therapy (DOTs) in Cohort (n, % of total empiric DOTs)[a]	Broad-Spectrum Gram-Negative Antibiotics**	Total Empiric Days of Therapy (DOTs) in Cohort (n, % of total empiric DOTs)[a]	Extremely Broad-Spectrum Gram-Negative Antibiotics***	Total Empiric Days of Therapy (DOTs) in Cohort (n, % of total empiric DOTs)[a]
Ceftriaxone	1 883 838 (60.1%)	Piperacillin-tazobactam	1 495 491 (43.0%)	Tigecycline	2268 (40.0%)
Metronidazole	654 142 (20.9%)	Cefepime	778 853 (22.4%)	Ceftolozane/tazobactam	1690 (29.8%)
Ampicillin/sulbactam	172 720 (5.5%)	Levofloxacin	419 586 (12.1%)	Ceftazidime/avibactam	1432 (25.8%)
Ampicillin	166 724 (5.3%)	Ciprofloxacin	211 415 (6.1%)	Meropenem/vaborbactam	252 (4.4%)
Cefoxitin	79 590 (2.5%)	Meropenem	207 012 (6.0%)		
Amoxicillin-clavulanate	65 718 (2.1%)	Gentamicin	134 444 (3.9%)		
Cefuroxime	48 703 (1.6%)	Aztreonam	72 326 (2.1%)		
Cefotetan	19 863 (0.6%)	Ertapenem	63 768 (1.8%)		
Amoxicillin	19 548 (0.6%)	Tobramycin	31 963 (0.9%)		
Cefdinir	17 773 (0.6%)	Ceftazidime	26 546 (0.8%)		
Cefpodoxime	5288 (0.2%)	Moxifloxacin	9401 (0.3%)		
		Ceftaroline	7382 (0.2%)		
		Imipenem-cilastatin	5471 (0.2%)		
		Amikacin	4172 (0.1%)		

*The following antibiotics with ≤0.1% frequency were excluded from this column: cefixime, cefprozil, and cefaclor.

**The following antibiotics with ≤0.1% frequency were excluded from this column: colistin, delafloxacin, plazomicin, and kanamycin.

***The following antibiotics with ≤0.1% frequency were excluded from this column: cefiderocol. In statistical analyses, broad and extremely broad-spectrum antibiotics were combined into a single "broad-spectrum" category.

[a]Empiric DOTs represent only the DOTs received on or before Hospital Day 2. If a patient was continued on the same antibiotic(s) after Day 2, when use may have no longer been empiric, those DOTs are not captured in this table.

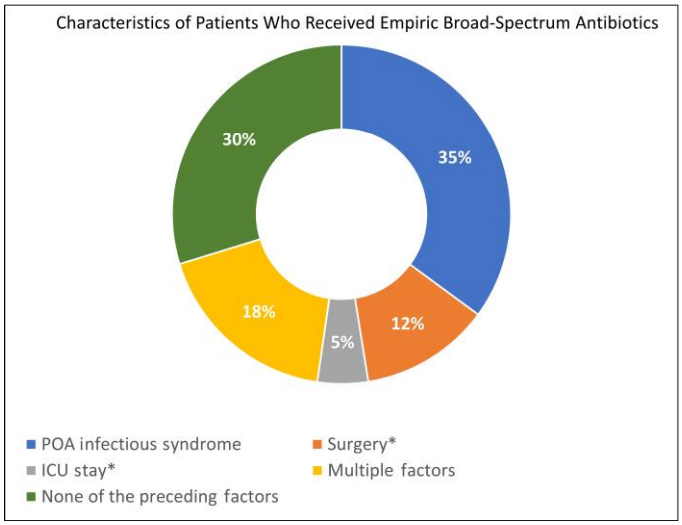
patients were admitted to 2 otherwise equal hospitals (ie, equivalence on every patient, hospital, and geographic characteristic included in the multivariable model, Table 3), and they both received empiric antibiotics, the 2 patients could still have their probabilities of receiving broad-spectrum therapy differ by as much as 34+ percentage points due solely to their admitting hospital (95% interval of probabilities, 43%–77%); this high variability was present within every geographic region (Figure 4*A*). When accounting for each hospital's fixed-effect characteristics (eg, teaching status, urban/rural location), in addition to each hospital's random effect, interhospital differences became even more extreme (Figure 4*B*). For example, our cohort included 41 urban teaching hospitals in the South Atlantic division. Among these 41 hospitals, a patient's starting or "baseline" probability of receiving broad-spectrum therapy (ie, before considering any characteristics about the individual patient) ranged from a low of 38% to a high of 82%.

DISCUSSION

To our knowledge, this is the largest study to date of empiric gram-negative antibiotic use in US hospitalized adults. Across a large and diverse cohort of 928 US hospitals, and >8 million discharges in 2019, we found that 37% of hospitalized patients received gram-negative antibiotics within the first 2 days of hospitalization. Moreover, 1 of every 5 hospitalized patients received broad-spectrum empiric gram-negative antibiotics specifically. Not surprisingly, we found that all patient severity-of-illness markers were independent predictors of receipt of broad-spectrum empiric therapy, as were invasive infections at admission and receipt of broad-spectrum gram-negative antibiotics in the 3 months preceding admission.

Nearly one-third (30%) of patients who received broad-spectrum empiric therapy were not admitted to the ICU, did not have surgery, or did not have one of the common infectious syndromes defined in this study (pneumonia, UTI, sepsis, bacteremia) within the empiric window, suggesting that a subset of these patients may have been exposed unnecessarily to broad-spectrum empiric therapy and its associated downstream consequences. A common perception is that a few days of antibiotic exposure will not cause harm. However, data indicate that each day of therapy increases the risk of adverse events [19–21]. For example, even 3 days of antibiotics for surgical prophylaxis increase the risks of acute kidney injury and *Clostridioides difficile* infection, and these risks increase with each additional DOT [20]. Given that antibiotics for surgical prophylaxis are typically narrow-spectrum, the risks from each DOT are likely even more pronounced for broad-spectrum therapy, making efforts to reduce unnecessary empiric broad-spectrum use especially important.

Although the potential overuse of broad-spectrum therapy when not indicated is problematic, the potential *underuse* of



Patients With Invasive Infections Who Received Empiric Gram-Negative Antibiotics

	Sepsis	Bacteremia
% that did not receive BS empiric therapy	23%	31%
Of patients with sepsis or bacteremia who also had ICU, MV, or vasopressor receipt in the empiric window, the % that did not receive BS therapy	12%	25%
Of patients with sepsis or bacteremia who also had inpatient BS gram-negative antibiotic exposure in the prior 3 months, the % that did not receive BS therapy	10%	21%
Of patients with sepsis or bacteremia who received only NS therapy, the % that received an antibiotic other than ceftriaxone	6%	10%

Figure 3. Characteristics of patients who received broad-spectrum empiric gram-negative therapy (n = 1 781 306) or with invasive infections who received any type of empiric gram-negative therapy (n = 717 217). Infectious syndromes were pneumonia, urinary tract infection, sepsis, and bacteremia. Invasive infection was defined as sepsis or bacteremia. *In the empiric window. Abbreviations: BS, broad-spectrum; ICU, intensive care unit; MV, mechanical ventilation; NS, narrow-spectrum; POA, present on admission.

broad-spectrum therapy when it is indicated may be even more concerning. In our cohort, 23% of patients with sepsis did not receive broad-spectrum empiric gram-negative therapy. Although ceftriaxone is a reasonable therapeutic option for many septic patients [22] depending upon their individual risk factors and presumed infection source, 6% of septic patients received narrow-spectrum antibiotics other than ceftriaxone. Moreover, patients with additional resistance risk factors [23, 24] or, depending upon institutional antimicrobial resistance patterns, with more severe clinical presentations should ideally receive broader-spectrum therapy with antipseudomonal coverage [25]. Yet, 10% of septic patients did not receive broad-spectrum therapy even though they had already received inpatient broad-spectrum gram-negative antibiotics in the previous 3 months, nor did 12% of septic patients who were in the ICU, mechanically ventilated, and/or who received vasopressors while receiving empiric therapy—together representing >32 000 patients. This is particularly concerning, because we identified patients with sepsis using a set of explicit diagnosis codes, which tend to select for the most severe cases [26] and have a high sensitivity for identifying patients with septic shock [27]. Thus, the sepsis patients in our cohort likely comprise a severely ill subpopulation, for whom each additional hour of inadequate antibiotic therapy can increase mortality [28–31]. Taken together, both the potential overtreating of patients without clear risk factors and the potential undertreating of patients with invasive infections underscores the need for more standardized guidelines, and ideally the development of validated risk-assessment tools, to inform empiric therapy selection.

Unexpectedly, we found that both male sex and White race were independently associated with higher odds of receiving broad-spectrum empiric gram-negative therapy. Holding other factors constant, men were 22% more likely than women to receive broad-spectrum empiric therapy, and this finding persisted across multiple sensitivity analyses. Moreover, Black, Asian, and other/unknown race patients were 13%, 10%, and 6% less likely, respectively, to receive broad-spectrum therapy compared to White patients. These associations were not explained by differences in insurance status. It is possible that there were additional residual confounding factors that our models did not include. For example, data suggest that men present to medical care later than women for both infectious and noninfectious processes [32–35], and perhaps delayed care-seeking necessitated the use of more aggressive empiric therapy in male patients. However, it is also possible that the sex- and race-based disparities we observed result from implicit provider bias. Prior investigations have identified similar antibiotic prescribing disparities in other settings and populations, including a higher likelihood of prescribing broad-spectrum agents to men, compared to women, in outpatient settings in Belgium [36] and to White children, compared to Black children, in outpatient pediatric settings in the US [37, 38]. There is also extensive literature identifying sex and racial biases in other US medical contexts [39–42] (eg, undertreatment of cardiovascular disease and myocardial infarction in women [43–46] and Black patients [47]). Our findings suggest that nonclinical factors influence empiric prescribing decisions, and that these effects are systemic and pervasive across US hospitals. Evaluating whether disparities in empiric broad-

Table 3. Association Between Patient, Hospital, and Geographic Characteristics and Receipt of Empiric Broad-Spectrum Gram-Negative Antibiotics Among United States Inpatients in a Multivariable Model

Characteristic	Adjusted OR (95% CI) for Empiric Receipt of Broad-Spectrum, Compared to Narrow-Spectrum, Gram-Negative Antibiotics (N = 2 928 657)	*P* Value
Patient and encounter characteristics		
Age group, y[a]		
18–29	0.67 (.67–.68)	<.001
30–39	0.83 (.82–.84)	<.001
40–49	1.01 (1.00–1.02)	.10
50–59	Ref	
60–69	0.96 (.95–.97)	<.001
70–79	0.85 (.84–.86)	<.001
≥80	0.73 (.72–.73)	<.001
Publicly insured	1.00 (1.00–1.01)	.52
Male sex	1.22 (1.22–1.23)	<.001
Hispanic ethnicity	0.97 (.96–.98)	<.001
Race		
White	Ref	
Asian	0.90 (.89–.92)	<.001
Black	0.87 (.86–.88)	<.001
Other/unknown	0.94 (.93–.95)	<.001
Admission type[b]		
Emergency	Ref	
Urgent	0.89 (.88–.90)	<.001
Elective	0.60 (.59–.60)	<.001
Trauma center	0.61 (.59–.63)	<.001
Information unavailable	0.59 (.57–.61)	<.001
Source of hospital admission (point-of-origin)[b]		
Nonhealthcare facility	Ref	
Clinic	1.02 (1.01–1.03)	<.001
Transfer from an outside hospital	1.17 (1.15–1.18)	<.001
Transfer from skilled nursing facility or intermediate care facility	1.70 (1.67–1.74)	<.001
Transfer from healthcare facility or ambulatory surgery center	1.15 (1.13–1.18)	<.001
Court/law enforcement	1.07 (.99–1.16)	.10
Information unavailable	1.09 (1.03–1.14)	<.001
Fall/winter admission month	0.96 (.96–.97)	<.001
Elixhauser comorbidities POA		
Congestive heart failure	0.97 (.96–.98)	<.001
Valvular disease	0.90 (.89–.91)	<.001
Pulmonary circulation disorders	1.21 (1.18–1.24)	<.001
Peripheral vascular disease	1.20 (1.18–1.21)	<.001
Uncomplicated hypertension	1.05 (1.04–1.05)	<.001
Hypertension with chronic complications	1.05 (1.04–1.05)	<.001
Paralysis	1.53 (1.50–1.55)	<.001
Other neurological disorders	1.00 (.99–1.01)	.93
Chronic pulmonary disease	0.99 (.98–1.00)	<.001
Uncomplicated diabetes	1.01 (1.00–1.02)	<.001
Diabetes with chronic complications	1.22 (1.21–1.22)	<.001
Hypothyroidism	1.05 (1.04–1.06)	<.001
Renal failure	1.02 (1.01–1.03)	<.001
Liver disease	0.85 (.84–.86)	<.001
Chronic peptic ulcer disease	0.95 (.93–.97)	<.001
AIDS	1.34 (1.28–1.40)	<.001
Lymphoma	1.82 (1.78–1.87)	<.001
Metastatic cancer	1.42 (1.40–1.44)	<.001
Solid tumor without metastasis	1.32 (1.30–1.33)	<.001
Rheumatoid arthritis/collagen vascular diseases	1.19 (1.17–1.20)	<.001
Coagulopathy	1.02 (1.01–1.03)	<.001
Obesity	1.06 (1.05–1.06)	<.001
Weight loss	1.27 (1.26–1.28)	<.001
Fluid and electrolyte disorders	1.04 (1.04–1.05)	<.001
Chronic blood loss anemia	0.79 (.77–.80)	<.001
Deficiency anemias	1.26 (1.25–1.27)	<.001
Alcohol abuse	0.72 (.71–.73)	<.001
Drug abuse	1.06 (1.05–1.07)	<.001
Psychoses	0.99 (.98–1.00)	.22
Depression	1.05 (1.04–1.06)	<.001
Infectious syndromes POA		
Pneumonia[c]	0.84 (.83–.84)	<.001
Ventilator-associated pneumonia[d]	9.38 (7.05–12.49)	<.001
Urinary tract infection	0.49 (.49–.50)	<.001
Sepsis	2.87 (2.85–2.89)	<.001
Bacteremia	1.73 (1.70–1.77)	<.001
Additional empiric receipt of antibiotics with gram-negative activity that are primarily used for gram-positive infections	0.76 (.76–.77)	<.001
Severity-of-illness markers in days ≤2 of hospital admission		
Major surgery[e]	1.37 (1.36–1.38)	<.001
ICU admission	1.39 (1.38–1.41)	<.001
Vasopressor receipt	1.15 (1.14–1.16)	<.001
Mechanical ventilation[d]	1.50 (1.48–1.53)	<.001
Hospital characteristics		
Hospital case-mix characteristics		
Average surgical volume[f]	1.26 (.98–1.62)	.07
Case-mix index[g]	1.26 (1.04–1.52)	.02
Percentage of publicly insured patients	1.00 (1.00–1.00)	.64
Urban location[h]	0.96 (.88–1.05)	.37
Teaching hospital	0.88 (.81–.96)	<.001
Bed size		
0–99	0.91 (.80–1.05)	.20
100–199	0.96 (.85–1.09)	.53
200–299	1.03 (.90–1.17)	.68
300–399	0.98 (.86–1.13)	.82
400–499	0.85 (.73–.99)	.04
≥500	Ref	
US census region and division[i]		
South		
South Atlantic	Ref	
West South Central	1.17 (1.04–1.31)	.01

Table 3. Continued

Characteristic	Adjusted OR (95% CI) for Empiric Receipt of Broad-Spectrum, Compared to Narrow-Spectrum, Gram-Negative Antibiotics (N = 2 928 657)	*P* Value
East South Central	1.07 (.94–1.21)	.29
Northeast		
Middle Atlantic	0.97 (.87–1.09)	.64
New England	0.57 (.44–.74)	<.001
Midwest		
East North Central	0.82 (.74–.91)	<.001
West North Central	0.95 (.83–1.09)	.48
West		
Mountain	0.73 (.62–.87)	<.001
Pacific	0.66 (.59–.74)	<.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; POA, present on admission; Ref, reference category; US, United States.

This model identifies factors associated with receiving empiric broad-spectrum gram-negative therapy, compared to receiving only empiric narrow-spectrum gram-negative therapy. The cohort used to fit this model restricted to patients who received at least 1 empiric gram-negative antibiotic. This decision was made to reduce the potential for residual confounding, on the assumption that patients who receive any type of empiric gram-negative therapy are likely to be more similar to each other in other, unmeasured ways than they are to patients who receive no empiric gram-negative therapy. This model and its effect estimates do not inform which factors are associated with receiving empiric gram-negative therapy compared to no empiric gram-negative therapy or to no empiric antibiotic therapy generally (either gram-negative or gram-positive).

[a]Continuous variables were examined for log-linearity with the outcome (receipt of broad-spectrum therapy); based upon the non-linear relationships identified, age was modeled categorically.

[b]Designated using the Uniform Billing form UB-40 (Centers for Medicare and Medicaid Services Form 1450).

[c]Excluding ventilator-associated pneumonia.

[d]Collinearity effects were tested, but not identified, between POA ventilator-associated pneumonia and receipt of mechanical ventilation in the empiric window (correlation <0.8 and variance inflation factor <3).

[e]Designated using Agency for Healthcare Research and Quality definitions of "major therapeutic" and "major diagnostic" procedures. Major procedures are considered operating room procedures. Further information and mapping code are available at: https://www.hcup-us.ahrq.gov/toolssoftware/procedureicd10/procedure_icd10.jsp.

[f]Calculated for each hospital as its total number of major surgeries performed during the study period divided by its total number of inpatient encounters during the study period.

[g]Calculated using fiscal year 2019 Medicare Severity–Diagnosis Related Group weights, available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2019-IPPS-Final-Rule-Home-Page-Items/FY2019-IPPS-Final-Rule-Tables.

[h]Designation provided by Premier, based upon American Hospital Association Annual Survey response.

[i]US census divisions comprise 4 US census regions: Northeast (Middle Atlantic, New England), South (South Atlantic, East South Central, West South Central), Midwest (East North Central, West North Central), and West (Mountain, Pacific). States in each US census division are as follows: New England Division: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont. Middle Atlantic Division: New Jersey, New York, Pennsylvania. East North Central Division: Illinois, Indiana, Michigan, Ohio, Wisconsin. West North Central Division: Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota. South Atlantic Division: Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia. East South Central Division: Alabama, Kentucky, Mississippi, Tennessee. West South Central Division: Arkansas, Louisiana, Oklahoma, Texas. Mountain Division: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming. Pacific Division: Alaska, California, Hawaii, Oregon, Washington.

spectrum antibiotic prescribing lead to differences in clinical outcomes between men and women, and White and minority patients, are important areas of future research.

Empiric therapy decision making relies heavily on clinical judgment, and some variance in broad-spectrum empiric prescribing is therefore expected. However, we were surprised by the high variability across regions and individual hospitals. In adjusted analysis, there were significant differences between many geographic census regions, with the highest odds of broad-spectrum therapy in the West South Central division (Arkansas, Louisiana, Oklahoma, and Texas). Interestingly, the West South Central division also has some of the highest inpatient usage rates of carbapenems, antipseudomonal agents, and total antibiotics [14]. Because many patients initiated on empiric therapy are not de-escalated even when cultures are negative [48], it is logical that high empiric usage of broad-spectrum antibiotics would correlate with high overall usage rates for broad-spectrum and total antibiotics, lending outsized importance to empiric prescribing decisions. Moreover, even after controlling for region and many other patient and hospital characteristics, we found that a patient's probability of receiving broad-spectrum empiric therapy could still be twice that of an otherwise equal patient, due solely to their different admitting hospitals. High, unexplained interhospital variability has also been documented for empiric therapy [49], broad-spectrum therapy [50], and total antibiotic usage [51] across US pediatric hospitals. Taken together, these findings—empiric antibiotic usage as a possible correlate of total antibiotic usage and existing high random variability—suggest that the empiric window is an underexploited but potentially "high-yield" target for antibiotic stewardship efforts.

This study is subject to several limitations. First, because we did not have microbiological data, we could not adjust for hospitals' local susceptibility patterns, which may influence empiric prescribing [6, 52]. Instead, our models included hospital-specific random effects. Therefore, while local AST patterns would not affect fixed-effect (ie, patient and hospital characteristic) estimates, they could contribute to some of the unexplained variance between hospitals that we identified. However, we do not believe that AST patterns completely explain our interhospital variability findings, because AST patterns should partly correlate with other hospital characteristics that our models included (eg, case-mix index [53, 54]). Second, our study used diagnostic claims codes to identify POA infections, and we did not have laboratory or vital signs data. Because diagnostic codes and POA designations are retroactively assigned at discharge, some patients may not have presented with signs and symptoms even though POA infections were subsequently confirmed. To mitigate against this possibility, we restricted our analysis to patients who received empiric gram-negative antibiotics, that is, patients who were presumably sick enough to trigger empiric therapy. Nevertheless, depending upon clinical presentation, some proportion of narrow-spectrum empiric therapy in patients with invasive infections may have been clinically justified. Third and similarly, to increase internal validity we used validated code sets for infectious syndromes that synchronize with other infectious disease studies [18, 55, 56]. While we included the most common inpatient infectious syndromes [57], this

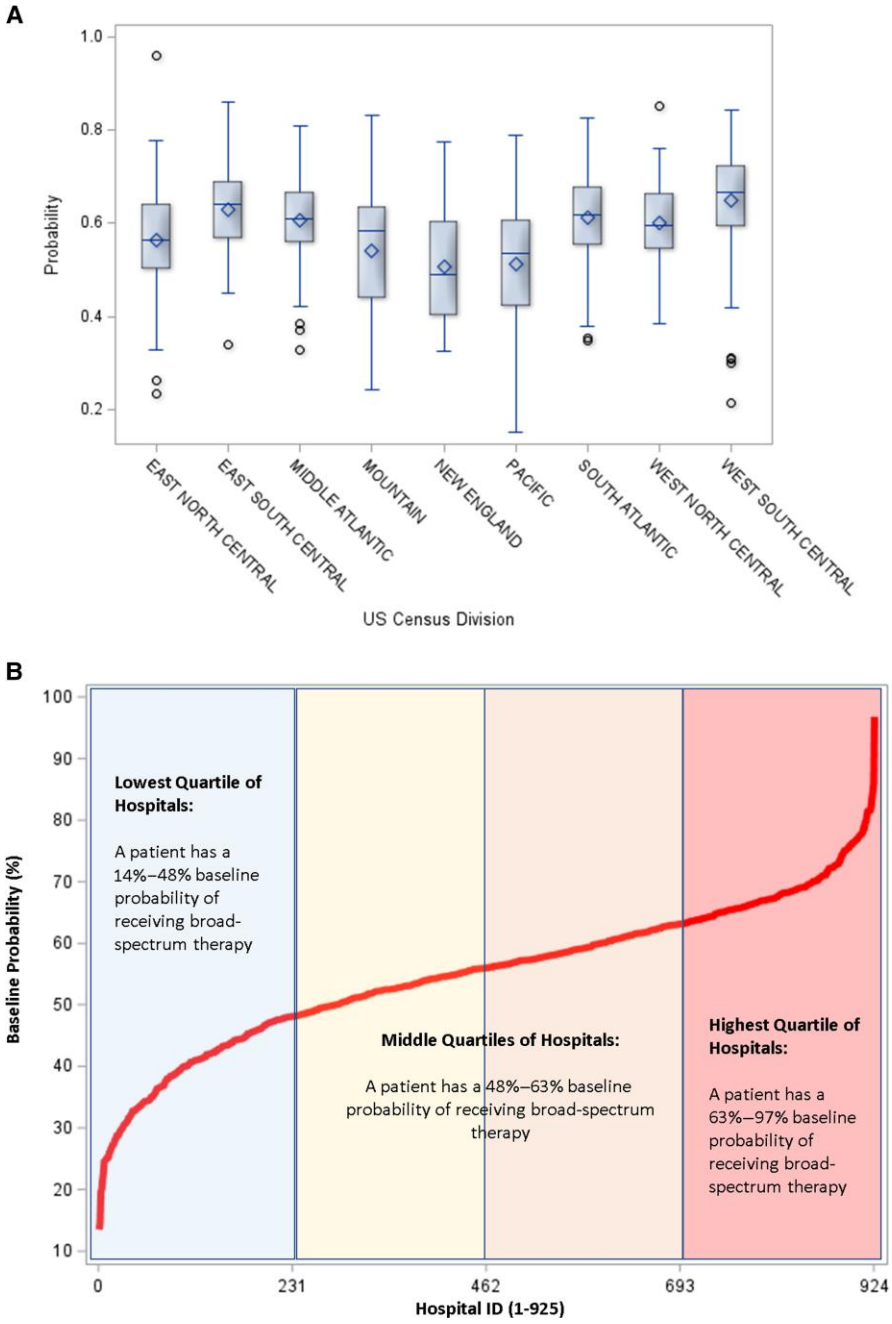


Figure 4. *A*, Distribution of the estimated hospital-specific probabilities of receiving broad-spectrum therapy among patients receiving empiric gram-negative antibiotics, stratified by United States (US) census division, controlling for patient and hospital characteristics. The boxes represent the 25th–75th percentile interquartile range (IQR); the horizontal line in each box reflects the median; the diamond reflects the mean; the whiskers reflect ± 1.5 IQR; and the circles reflect outliers. The estimated probabilities are derived from each hospital's random intercept from the mixed-effects regression model (ie, empirical Bayes estimates) and are interpretable as the probabilities in each hospital at the reference value of all variables (fixed-effects) in the regression model. As such, the interhospital variability estimate is not influenced by each hospital's sample size, which could inflate interhospital variability due to chance. There was high interhospital variability within each geographic division, with the widest IQR in the Mountain (IQR, 44%–64%; hospital n = 41), New England (IQR, 40%–60%; hospital n = 15), and Pacific (IQR, 42%–61%; hospital n = 117) divisions. The narrowest interquartile ranges were in the West North Central (IQR, 54%–66%; hospital n = 72) and the Middle Atlantic (IQR, 56%–67%; hospital n = 113) divisions. *B*, "Baseline" (ie, starting) estimated probability of receiving broad-spectrum therapy for each hospital in the cohort, among patients who received empiric gram-negative antibiotics in 925 US hospitals. The probability is plotted as a red dot that, due to the large sample size, displays as a continuous red line. These starting probabilities for each hospital are calculated from the hospital's random-effects as well as its fixed-effects coefficient estimates for the 7 hospital characteristics included in the multivariable model (eg, teaching status, case-mix index) and are interpretable as the probabilities in that hospital for a patient with reference category values for each patient characteristic included in the multivariable model (see Table 3). At each hospital, a patient's probability of receiving broad-spectrum therapy could move up or down from this starting point based upon their specific patient characteristics, as governed by the effect estimates for these characteristics in the multivariable model. We have divided the graph into 4 shaded boxes, each representing a quartile of hospitals, progressing from lowest (left) to highest (right) based upon the hospital's starting probability. In this cohort, a hospital's starting probability of a patient receiving broad-spectrum therapy was as low as 14% or as high as 97%.

restriction meant that we did not include all infection types (eg, intra-abdominal infection, meningitis), and some patients without explanatory risk factors for empiric therapy may have had unmeasured infections. Fourth, our study did not evaluate clinical outcomes. To conduct rigorous outcomes studies would require stratifying by infection types, using additional variables and adjustment techniques such as propensity scoring. Thus, although examining associations between empiric gram-negative antibiotic prescribing and clinical outcomes is outside the scope of the present study, we hope to pursue these analyses in future research. Fifth, this study investigated empiric prescribing early in hospitalization and restricted to patients who received at least 1 empiric gram-negative antibiotic. Findings may not be representative of empiric therapy initiated later in the hospital stay, and the predictors of broad-spectrum therapy that we identified should not be interpreted as predictors of receiving empiric therapy vs no antibiotic therapy (which is a different empiric prescribing research question that this study did not address). Finally, a small percentage (<10%) of cohort patients were transfers from other healthcare or skilled nursing facilities, some of whom may have received definitive therapy based upon microbiological results obtained prior to admission. On balance, we elected to include transferred patients to maintain study generalizability and controlled for source of hospital admission to limit possible confounding. However, due to potential therapeutic misclassification in this subset, the true number of inpatients who received empiric gram-negative therapy may be marginally lower than the study estimate.

Overall, our study found that >1 of every 5 US hospitalized patients received broad-spectrum gram-negative antibiotics in the first 2 days of hospitalization. There was high variability in the receipt of broad-spectrum therapy across geographic regions and high unexplained variance between individual hospitals. Moreover, there were significant disparities in the receipt of broad-spectrum therapy by patient sex and race, which suggests that nonclinical factors influence inpatient empiric prescribing and that these patterns are systemic across US hospitals. And while this study was not specifically designed to evaluate antibiotic appropriateness, we identified signals of both overuse and underuse of broad-spectrum empiric therapy that warrant further investigation. Taken together, our findings underscore the need for greater standardization of empiric antibiotic prescribing in US inpatients, which may require multistakeholder initiatives between medical and surgical organizations and infectious disease societies. In parallel, we encourage qualitative research studies to better understand the factors that influence provider prescribing decisions and whether they vary by provider attribute (eg, specialty) and geographic region. These data could uncover reasons for the large variance in empiric broad-spectrum antibiotic prescribing across US hospitals.

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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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.

References

1. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed. **2017**. Available at: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed. Accessed 25 January 2022.
2. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. **2019**. Available at: https://www.cdc.gov/drugresistance/biggest-threats.html. (Last accessed 29 June 2022).
3. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis **2016**; 62:e51–77.
4. Centers for Disease Control and Prevention. Core elements of hospital antibiotic stewardship programs. **2019**. Available at: https://www.cdc.gov/antibiotic-use/core-elements/hospital.html. Last accessed 29 June 2022.
5. Tamma PD, Avdic E, Keenan JF, et al. What is the more effective antibiotic stewardship intervention: preprescription authorization or postprescription review with feedback? Clin Infect Dis **2017**; 64:537–43.
6. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-*P. aeruginosa*). Clin Infect Dis **2021**; 72:1109–16.
7. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America guidance on the treatment of AmpC β-lactamase-producing Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* infections. Clin Infect Dis **2022**; 74:2089–114.
8. Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. Mayo Clin Proc **2011**; 86:156–67.
9. Premier Applied Sciences. Premier Healthcare Database: data that informs and performs. **2018**. Available at: https://products.premierinc.com/downloads/PremierHealthcareDatabaseWhitepaper.pdf.
10. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. JAMA Netw Open **2020**; 3:e2029058.
11. Cunningham JW, Vaduganathan M, Claggett BL, et al. Clinical outcomes in young US adults hospitalized with COVID-19. JAMA Intern Med **2020**; 181:379–81.
12. Poeran J, Mazumdar M, Rasul R, et al. Antibiotic prophylaxis and risk of *Clostridium difficile* infection after coronary artery bypass graft surgery. J Thorac Cardiovasc Surg **2016**; 151:589–97.e2.
13. Lavery AM, Preston LE, Ko JY, et al. Characteristics of hospitalized COVID-19 patients discharged and experiencing same-hospital readmission—United States, March–August 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:1695–9.

14. Goodman KE, Cosgrove SE, Pineles L, et al. Significant regional differences in antibiotic use across 576 U.S. hospitals and 11 701 326 million adult admissions, 2016–2017. Clin Infect Dis **2021**; 73:213–22.
15. Goodman KE, Magder LS, Baghdadi JD, et al. Impact of sex and metabolic comorbidities on COVID-19 mortality risk across age groups: 66 646 inpatients across 613 U.S. hospitals. Clin Infect Dis **2021**; 73:e4113–23.
16. Baghdadi JD, Coffey KC, Adediran T, et al. Antibiotic use and bacterial infection among inpatients in the first wave of COVID-19: a retrospective cohort study of 64 691 patients. Antimicrob Agents Chemother **2021**; 65:e0134121.
17. Jackson SS, Leekha S, Magder LS, et al. The effect of adding comorbidities to current Centers for Disease Control and Prevention central-line–associated bloodstream infection risk-adjustment methodology. Infect Control Hosp Epidemiol **2017**; 38:1019–24.
18. Agency for Healthcare Research and Quality. Clinical classifications software refined (CCSR). **2022**. Available at: https://www.hcup-us.ahrq.gov/toolssoftware/ccsr/ccs_refined.jsp. Last accessed 1 June 2022.
19. Teshome BF, Vouri SM, Hampton N, Kollef MH, Micek ST. Duration of exposure to antipseudomonal β-lactam antibiotics in the critically ill and development of new resistance. Pharmacotherapy **2019**; 39:261–70.
20. Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of duration and type of surgical prophylaxis with antimicrobial-associated adverse events. JAMA Surg **2019**; 154:590–8.
21. Vaughn VM, Flanders SA, Snyder A, et al. Excess antibiotic treatment duration and adverse events in patients hospitalized with pneumonia: a multihospital cohort study. Ann Intern Med **2019**; 171:153–63.
22. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med **2017**; 45:486–552.
23. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis **2016**; 63:e61–111.
24. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Crit Care Med **2021**; 49:e1063.
25. Strich JR, Heil EL, Masur H. Considerations for empiric antimicrobial therapy in sepsis and septic shock in an era of antimicrobial resistance. J Infect Dis **2020**; 222: S119–31.
26. Whittaker S-A, Mikkelsen ME, Gaieski DF, Koshy S, Kean C, Fuchs BD. Severe sepsis cohorts derived from claims-based strategies appear to be biased toward a more severely ill patient population. Crit Care Med **2013**; 41:945–53.
27. Rhee C, Jentzsch MS, Kadri SS, et al. Variation in identifying sepsis and organ dysfunction using administrative versus electronic clinical data and impact on hospital outcome comparisons. Crit Care Med **2019**; 47:493–500.
28. Gaieski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med **2010**; 38: 1045–53.
29. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med **2006**; 34:1589–96.
30. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med **2014**; 42: 1749–55.
31. Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med **2017**; 45:623–9.
32. Lim MT, Lim YMF, Tong SF, Sivasampu S. Age, sex and primary care setting differences in patients' perception of community healthcare seeking behaviour towards health services. PLoS One **2019**; 14:e0224260.
33. Thompson AE, Anisimowicz Y, Miedema B, Hogg W, Wodchis WP, Aubrey-Bassler K. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Fam Pract **2016**; 17:38.
34. Geisler WM, Chyu L, Kusunoki Y, Upchurch DM, Hook EW. Health insurance coverage, health care-seeking behaviors, and genital chlamydial infection prevalence in sexually active young adults. Sex Transm Dis **2006**; 33:389–96.
35. Kojima N, Brobeck M, Slepnev V, Klausner JD. A national survey of early treatment seeking behavior among those with incident SARS-CoV-2 infection. medRxiv [Preprint]. Posted online 14 January **2022**. https://doi.org/10.1101/2022.01.13.22269022.
36. Blommaert A, Coenen S, Gielen B, Goossens H, Hens N, Beutels P. Patient and prescriber determinants for the choice between amoxicillin and broader-spectrum antibiotics: a nationwide prescription-level analysis. J Antimicrob Chemother **2013**; 68:2383–92.
37. Gerber JS, Prasad PA, Localio AR, et al. Racial differences in antibiotic prescribing by primary care pediatricians. Pediatrics **2013**; 131:677–84.
38. Kornblith AE, Fahimi J, Kanzaria HK, Wang RC. Predictors for underprescribing antibiotics in children with respiratory infections requiring antibiotics. Am J Emerg Med **2018**; 36:218–25.
39. Alspach JG. Is there gender bias in critical care? Critical Care Nurse **2012**; 32: 8–14.
40. Bertakis KD. The influence of gender on the doctor-patient interaction. Patient Educ Couns **2009**; 76:356–60.
41. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on Community-Based Solutions to Promote Health Equity in the United States; Baciu A, Negussie Y, Geller A, et al, eds. The state of health disparities in the United States. Washington, DC: National Academies Press, **2017**.
42. Himmelstein G, Bates D, Zhou L. Examination of stigmatizing language in the electronic health record. JAMA Network Open **2022**; 5:e2144967.
43. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women. Circulation **2016**; 133:916–47.
44. Maynard C, Litwin PE, Martin JS, Weaver WD. Gender differences in the treatment and outcome of acute myocardial infarction. Results from the Myocardial Infarction Triage and Intervention Registry. Arch Intern Med **1992**; 152:972–6.
45. Radovanovic D, Erne P, Urban P, et al. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20 290 patients from the AMIS Plus Registry. Heart **2007**; 93:1369–75.
46. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association guidelines) national quality improvement initiative. J Am Coll Cardiol **2005**; 45:832–7.
47. Arora S, Stouffer GA, Kucharska-Newton A, et al. Fifteen-year trends in management and outcomes of non–ST-segment–elevation myocardial infarction among black and white patients: the ARIC Community Surveillance Study, 2000–2014. J Am Heart Assoc **2018**; 7:e010203.
48. Liu P, Ohl C, Johnson J, Williamson J, Beardsley J, Luther V. Frequency of empiric antibiotic de-escalation in an acute care hospital with an established antimicrobial stewardship program. BMC Infect Dis **2016**; 16:751.
49. Chiotos K, D'Arinzo L, Kitt E, Ross R, Gerber JS. Quantifying empiric antibiotic use in US children's hospitals [manuscript published online ahead of print 1 December 2021]. Hosp Pediatr **2021**. https://doi.org/10.1542/hpeds.2021-005950.
50. Griffith HG, Dantuluri K, Thurm C, et al. Considerable variability in antibiotic use among United States children's hospitals in 2017–2018. Infect Control Hosp Epidemiol **2020**; 41:571–8.
51. Gerber JS, Newland JG, Coffin SE, et al. Variability in antibiotic use at children's hospitals. Pediatrics **2010**; 126:1067–73.
52. Tallman GB, Vilches-Tran RA, Elman MR, et al. Empiric antibiotic prescribing decisions among medical residents: the role of the antibiogram. Infect Control Hosp Epid **2018**; 39:578–83.
53. Kuster SP, Ruef C, Bollinger AK, et al. Correlation between case mix index and antibiotic use in hospitals. J Antimicrob Chemother **2008**; 62:837–42.
54. Mendez CM, Harrington DW, Christenson P, Spellberg B. Impact of hospital variables on case mix index as a marker of disease severity. Popul Health Manag **2014**; 17:28–34.
55. Courchia B, Ramirez D, Rauch DA. Changes in urinary tract infection hospitalizations post 2011 revised American Academy Pediatrics Guidelines. Clin Pediatr (Phila) **2018**; 57:1409–13.
56. Goodman KE, Pineles L, Magder LS, et al. Electronically available patient claims data improve models for comparing antibiotic use across hospitals: results from 576 U.S. facilities. Clin Infect Dis **2020**; 73:e4484–92.
57. Christensen KLY, Holman RC, Steiner CA, Sejvar JJ, Stoll BJ, Schonberger LB. Infectious disease hospitalizations in the United States. Clin Infect Dis **2009**; 49:1025–35.