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MAJOR ARTICLE

Epidemiology of Gram-Negative Bloodstream Infections in the United States: Results From a Cohort of 24 Hospitals

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Background. To address knowledge gaps in management of Gram-negative bloodstream infection, the Antibiotic Stewardship Implementation Collaborative was established consisting of programs from 24 academic and community hospitals across the United States.

Methods. A retrospective cohort study was conducted of unique adult patients with Gram-negative bloodstream infection hospitalized at participating hospitals from January to December 2019. Patient level and microbiologic data were collected via electronic medical record review with a standardized data collection form and data dictionary. Data analysis was largely descriptive. The Pearson $\chi 2$ test to compare categorical variables and the Wilcoxon rank sum test for continuous variables were used.

Results. In total, 4851 bacterial isolates from 3710 eligible unique patients were included in the cohort. Most common source of infection was the urinary tract (47.9%). Source control was achieved in 84% of cases. Escherichia coli (2471, 51.0%) was the most common Gram-negative organism recovered. Antibiogram combining isolates from all participating centers with species-level susceptibilities and source specific antibiograms for isolates from urinary, respiratory, and intraabdominal source were created. Northeast sites contributed the most extended spectrum beta-lactamase (ESBL) producing organisms (73%), but West sites had the highest percentage of ESBL producers of total isolates (16%). A statistically significant difference in percentage of ESBL-producing organisms in Whites vs. non-Whites (14.6 % and 9.5 %, respectively, $P<0.01$) was observed.

Conclusions. While the present study was conducted pre-pandemic, it highlights the need for stewardship data collaboratives to enhance our understanding of the antimicrobial resistance patterns.

Keywords. antimicrobial resistance; antimicrobial stewardship; Gram-negative bacteremia.

Despite advances in the diagnosis and management of Gram-negative bloodstream infection (GN-BSI), notable gaps remain. Applicability of existing randomized controlled trials [1–3] to clinical practice may be limited by exclusion of patients at extremes of age; those with obesity, severe immunocompromise, or critical illness; those lacking appropriate source control; or those infected with highly drug-resistant bacteria.

To address ongoing knowledge gaps in the management of GN-BSI frequently encountered in clinical practice, the Antibiotic Stewardship Implementation Collaborative (ASIC) was formed in 2019 to develop a multicenter cohort of patients with these infections. ASIC membership includes physician and pharmacist antibiotic stewardship program leaders from 24 academic and community hospitals across the United States, whose goal is to identify important clinical questions and develop strategies to transform findings of studies into "expected practice" [4]. One objective of the collaborative was to establish a contemporary understanding of GN-BSI epidemiology in the United States to help inform empiric antibiotic selection. Herein, we describe the microbiology and antibiotic susceptibility patterns of GN-BSI isolates from ASIC sites across the United States.

METHODS

Setting, Participants, and Baseline Stewardship Program Characteristics

A retrospective cohort study was conducted of all unique consecutive patients aged ≥18 years with GN-BSI (Enterobacterales and glucose-nonfermenting organisms) who were hospitalized at any of the 24 participating US hospitals from January to December 2019. The 24 sites consisted of 16 academic medical centers, 4 community hospitals, and 4 Veterans Affairs hospitals (Table 1,

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Table 1. Hospitals Participating in the Antibiotic Stewardship Implementation Collaborative (24 Sites)

Hospital	State	US Census Region	Bed Size	Facility Type	Setting	No. of Unique Patients Contributing to Cohort
Bayview Medical Center	Maryland	NE	420	Academic	Urban	176
Beth Israel Deaconess Medical Center	Massachusetts	NE	743	Academic	Urban	183
Denver Health	Colorado	MoW	525	Academic	Urban	211
Highland Hospital	New York	NE	247	Community	Urban	247
Howard County General Hospital	Maryland	NE	225	Community	Urban	245
Johns Hopkins Hospital	Maryland	NE	1019	Academic	Urban	380
Montefiore Medical Center						
Moses Campus	New York	NE	726	Academic	Urban	456
Wakefield Campus	New York	NE	345	Academic	Urban	121
Weiler Campus	New York	NE	431	Academic	Urban	293
Sibley Memorial Hospital	Washington DC	NE	318	Community	Urban	142
Trinity Health St Joseph Mercy Ann Arbor	Michigan	MiW	537	Academic	Suburban	328
Strong Memorial Hospital	New York	NE	874	Academic	Urban	415
Suburban Hospital	Maryland	NE	228	Community	Suburban	227
University of California, San Francisco	California	We	800	Academic	Urban	146
University of Iowa	Iowa	MiW	602	Academic	Urban	283
University of Maryland	Maryland	NE	837	Academic	Urban	275
University of Michigan	Michigan	MW	1000	Academic	Urban	50
University of Nebraska	Nebraska	MiW	718	Academic	Urban	215
Presbyterian Hospital (UPMC)	Pennsylvania	NE	675	Academic	Urban	100
University of Utah	Utah	MoW	700	Academic	Urban	231
VA Ann Arbor	Michigan	MiW	146	VA	Suburban	53
VA Ann Baltimore	Maryland	NE	140	VA	Urban	34
VA Iowa City	Iowa	MiW	83	VA	Urban	19
VA Salt Lake City	Utah	MoW	120	VA	Urban	45

Abbreviations: MiW, Midwest; MoW, Mountain West; NE, Northeast; UPMC, University of Pittsburgh Medical Center; VA, Veterans Affairs; We, West.

Figure 1). Mean antibiotic stewardship program full-time equivalents in 2019 were 1.3 (pharmacy) and 0.6 (physician). In general, stewardship programs conducted active interventions and were available by pager during business hours. Additionally, 5 of 24 programs (20%) had stewardship staffing available by pager 24 hours per day, 7 days per week. None of the 24 antibiotic stewardship programs intervened on every positive blood culture result but did intervene as required to optimize patients' antibiotic regimens (eg, dose optimization, "bug-drug mismatch" [ie, inappropriate antibiotic therapy]).

Data Collection

Data collection across the 24 hospitals was performed by physicians, pharmacists, or postgraduate trainees under the supervision of ASIC leads. Demographic data, preexisting medical conditions, clinical signs and symptoms, microbiological data, antibiotic regimens, source control interventions, and outcome data were collected via electronic medical record review with a standardized data collection form and data dictionary. Only the first clinical isolate of an individual species from a unique patient was included within a 90-day time frame. Source control was defined as drainage of all infected collections and/or removal of all infected hardware. Repeat infection was defined as isolation of the same bacterial species from any site, including the bloodstream, within 30, 60, and 90 days (Table 2). All sites entered data into a secure REDCap database. The institutional review board of each participating site approved the study, with waivers of informed consent.

Microbiological Data

Local clinical microbiology laboratories oversaw organism identification and antimicrobial susceptibility testing. The following approaches were used for organism identification: Verigene (4 sites, 757 isolates), Filmarray (2 sites, 442 isolates), and GenMark ePlex (4 sites, 984 isolates). Of 24 sites (2692 isolates), 14 utilized matrix-assisted laser desorption ionization time-of-flight mass spectrometry for organism identification, either alone or in combination with other technology. The primary methodology for determining Gram-negative antimicrobial susceptibility testing included disc or broth microdilution (4 sites, 920 total isolates, 870 with Phoenix automated antimicrobial susceptibility testing), Vitek2 (8 sites, 1698 isolates), BD Phoenix (8 sites, 1585 isolates), Microscan (3 sites, 526 isolates), and Trek Sensititre (1 site, 146 isolates). The 2021 Clinical and Laboratory Standards Institute (CLSI) criteria were applied to all local minimum inhibitory concentration (MIC) results to determine if isolates were susceptible to specific antibiotics [6].

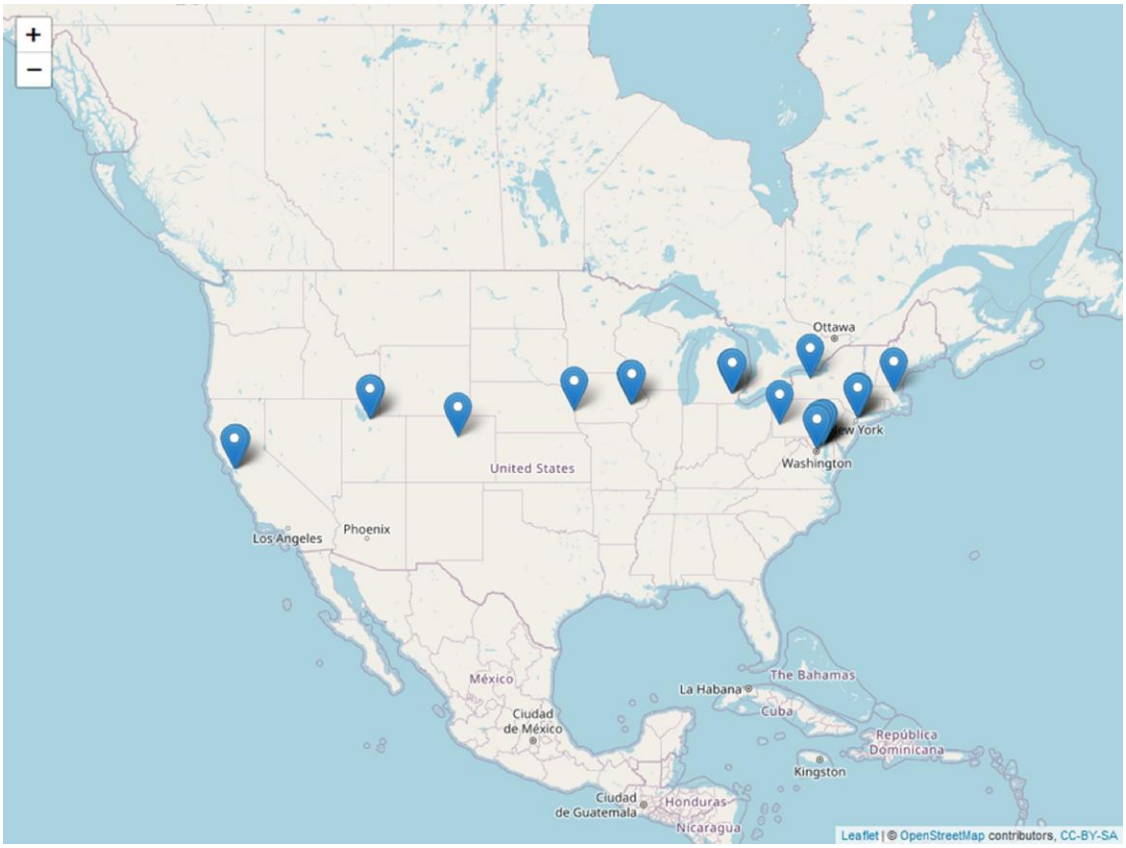

Figure 1. Geography of Antibiotic Stewardship Implementation Collaborative sites [5].

Isolates were characterized as extended-spectrum β-lactamase (ESBL) producing if they met any of the following criteria:

- $bla_{\text{CTX-M}}$ gene identified by a molecular platform (eg, Verigene Gram-negative blood culture nucleic acid test)
- ESBL phenotypic testing (eg, any *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* isolate with a ceftriaxone MIC ≥ 2 mcg/mL or a positive ESBL confirmatory phenotypic test result)
- Any *E coli*, *K pneumoniae*, or *K oxytoca* listed as intermediate/resistant to ceftriaxone (for organisms without ceftriaxone MICs provided)

Of the 24 participating sites, 8 performed confirmatory $bla_{\text{CTX-M}}$ gene testing for ESBL producers, and 12 used phenotypic methods. Carbapenem resistance was defined as resistance to at least 1 carbapenem antibiotic [7].

Statistical Analysis

Data analysis was largely descriptive. The Pearson χ^2 test was used to compare categorical variables and the Wilcoxon rank sum test for continuous variables. Statistical analysis was completed with Stata version 17.0 (StataCorp).

RESULTS

Patient Characteristics

In total, 4851 bacterial isolates from 3710 eligible unique patients were included in the cohort. The characteristics of the patients contributing isolates are described in Table 2. The median age was 67 years (IQR, 55–77). Overall, 946 (19.5%) patients had Pitt bacteremia scores ≥4, and 738 (15.2%) had a Charlson Comorbidity Index ≥5. Common sources of infection included urinary tract (47.9%), intra-abdominal (14.5%), and hepatobiliary (11.4%). Source control was achieved in 84% of cases. Median time from admission to collection of positive blood cultures was 0 days (IQR, 0–1).

Microbiology

In total, 4851 isolates were reported. *E coli* (n = 2471, 51.0%) was the most common Gram-negative organism recovered, followed by *K pneumoniae* (n = 841, 17.3%), *Pseudomonas aeruginosa* (n = 423, 8.7%), *Proteus mirabilis* (n = 235, 4.8%), *Enterobacter cloacae* complex (n = 227, 4.7%), *Serratia*

Table 2. Baseline Characteristics and Outcomes

Variable	No. (%)
Age, y	
18 to <50	872 (17.94)
50–59	743 (15.28)
60–69	1169 (24.05)
≥70	2077 (42.73)
Female gender	2303 (47.38)
Race/ethnicity	
White	2674 (55.01)
Black	1104 (22.71)
Asian	222 (4.57)
Hispanic	598 (12.30)
Other	263 (5.42)
Body mass index ≥30	1634 (33.61)
Charlson Comorbidity Index	
0	966 (19.87)
1–2	1899 (39.07)
3–4	1258 (25.88)
≥5	738 (15.18)
Moderate to severe immunocompromise[a]	1678 (34.52)
Patients in intensive care unit	1572 (32.34)
Patients with Pitt bacteremia scores of ≥4	946 (19.46)
Source of infection	
Bone or joint	82 (1.69)
Endocarditis/ICD/prosthetic valves	27 (0.56)
Hepatobiliary	550 (11.31)
Intra-abdominal	700 (14.40)
Meningitis/Infected ventricular shunt	6 (0.12)
Neutropenic fever with no other identification	119 (2.45)
Prostatitis	45 (0.93)
Respiratory	272 (5.60)
Skin or soft tissue	227 (4.67)
Urinary tract	2321 (47.75)
Vascular catheter	323 (6.64)
Vascular graft	18 (0.37)
Source control achieved[b]	3131 (84)
Outcomes	
Death after first positive blood culture	
Within 30 d	681 (14.01)
Within 60 d	839 (17.26)
Within 90 d	934 (19.21)
Repeat infection,[c] any source	
Within 30 d	247 (5.08)
Within 60 d	417 (8.58)
Within 90 d	501 (10.31)
Repeat bloodstream infection[c]	
Within 30 d	85 (1.75)
Within 60 d	147 (3.02)
Within 90 d	175 (3.60)
Time from admission to collection of positive blood culture, d, median (IQR)	0 (0–1)

Abbreviation: ICD, implantable cardiac device (implantable cardioverter/defibrillator or permanent pacemaker).

[a]Moderate to severe immunocompromise was defined by at least 1 of the following: (1) hematopoietic stem cell transplantation within the previous 12 months or active treatment for graft-versus-host disease, (2) active chemotherapy within the prior 6 months, (3) previous solid organ transplantation, (4) HIV infection with a CD4 count under 200 cells/mm3, (5) absolute neutrophil count under 500 cells/mm3 at the time of or within 7 days after blood culture collection, or (6) receipt of corticosteroids at a dose equivalent to 10 mg daily of prednisone for ≥14 days, or (7) receipt of other immunosuppressive therapy.

[b]Source control was defined as drainage of all infected collections and/or removal of all infected hardware.

[c]Repeat infection with the same bacterial strain.

marcescens (n = 158, 3.3%), *K oxytoca* (n = 112, 2.3%), *Klebsiella aerogenes* (n = 47, 1.0%). Table 3 displays the antibiogram combining isolates from all participating centers with species-level susceptibilities, and Table 4 displays the source-specific antibiogram for isolates from urinary, respiratory, and intra-abdominal sources. As ASIC sites have different formularies and their clinical microbiology laboratories may utilize cascading susceptibilities to varying degrees, the number of organisms tested for each reported antibiotic differed. Per CLSI standards, only organisms with at least 30 isolates tested for each listed antibiotic were displayed [6, 8].

β-Lactamase Resistance

Overall, 575 (15.7%) isolates—*E coli*, *K pneumoniae*, *K oxytoca*, and *P mirabilis*—met criteria for ESBL production and 47 of these were resistant to carbapenems. Of the 575 ESBL isolates, 73% (n = 421) were contributed by Northeast sites, 15% (n = 84) by Midwest, 8% (n = 46) by Mountain West, and 4% (n = 24) by Western. However, Western sites had the highest percentage of ESBL producers of total eligible isolates (16%), followed by Northeast (13%) and Midwest and Mountain West (9% each). Of the 310 isolates of *E cloacae*, *K aerogenes*, and *Citrobacter freundii*, organisms with a moderate to high likelihood of significant AmpC β-lactamase production, 75 (24.19%) had ceftriaxone MICs ≥2 μg/mL.

Ninety organisms were resistant to carbapenems. Of these 90 carbapenem-resistant organisms, 62% (n = 56) were contributed by Northeast sites, 18% each (n = 16) by Midwest and Mountain West and 2% (n = 2) by Western. Of the total number of isolates submitted per region, percentages of carbapenem-resistant organisms were not significantly different (2% each for Northeast and Midwest, 3% for Mountain West, 1% for Western). Regarding nonfermenting organisms, carbapenem resistance was identified in 36 (9%) *P aeruginosa* isolates and 7 (17%) *Acinetobacter baumannii* isolates. Of the 90 carbapenem-resistant organisms and 47 carbapenem-resistant Enterobacterales isolates, 14 (16%) and 13 (30%) were carbapenemase producing, respectively; however, carbapenemase testing was not be performed by all centers and the actual percentage may have been higher.

Of note, there was no statistical difference in the percentage of carbapenem-resistant organisms isolated in White vs non-White patients (1.9% vs 1.7%, respectively; $P = .6$); however, there was a statistically significant difference in the percentage of ESBL-producing organisms in White vs non-White patients (14.6% vs 9.5%, $P < .01$).

β-Lactam and Carbapenem Susceptibility

Among isolates tested, ceftriaxone susceptibility was 82% (n = 2123) for *E coli* and 84% for *K pneumoniae* (n = 732). Susceptibility decreased to 65% (n = 207) for the *E cloacae* complex. Cefepime susceptibility was 85% for *E coli* (n = 1937) and

Table 3. Antibiogram

Organisms	Isolates, No. (%)[b]	Susceptible, % (No. of Isolates Tested) [a]																			
		AMK	AMP	SAM	AMC	ATM	CFZ	FEP	CAZ	CRO	CIP	ETP	GEN	IPM/CS	LVX	MEM	TZP	TET	TGC	TOB	SXT
Enterobacterales																					
Citrobacter sp	83 (1.7)	100 (39)	0 (47)	54 (52)	…	83 (52)	28 (71)	95 (76)	78 (32)	81 (75)	91 (75)	84 (44)	95 (80)	…	…	99 (71)	90 (77)	…	…	94 (49)	78 (82)
Enterobacter																					
E cloacae complex	227 (4.7)	100 (139)	3 (158)	5 (122)	0 (31)	73 (153)	2 (176)	96 (222)	62 (101)	65 (207)	93 (190)	84 (127)	97 (223)	86 (51)	99 (77)	93 (213)	74 (225)	88 (43)	…	95 (155)	77 (215)
Other	33 (0.7)	…	…	…	…	…	…	…	…	…	…	…	97 (32)	…	…	…	65 (31)	…	…	…	60 (30)
Escherichia coli	2471 (50.9)	99 (1218)	45 (2328)	46 (2001)	82 (244)	801 (393)	46 (2209)	85 (1937)	87 (942)	82 (2123)	64 (1959)	871 (199)	87 (2440)	100 (625)	72 (606)	100 (1926)	90 (2051)	68 (260)	100 (250)	80 (1481)	61 (2421)
Klebsiella																					
K aerogenes	47 (1.0)	…	0 (30)	…	…	…	3 (40)	98 (45)	…	77 (44)	93 (41)	77 (30)	100 (46)	…	…	98 (47)	70 (47)	…	…	…	98 (46)
K pneumoniae	841 (17.3)	99 (484)	4- (656)	71 (736)	90 (63)	83 (486)	59 (731)	87 (703)	87 (354)	84 (732)	84 (706)	88 (417)	92 (833)	99 (207)	94 (232)	98 (699)	86 (717)	78 (129)	98 (126)	86 (516)	75 (823)
K oxytoca	112 (2.3)	100 (66)	2 (103)	55 (96)	…	92 (50)	30 (91)	94 (88)	89 (38)	93 (107)	92 ((83)	97 (78)	98 (108)	100 (46)	95 (42)	99 (94)	93 (104)	…	…	96 (73)	82 (106)
Other	31 (0.6)	…	…	90 (31)	…	…	…	…	…	…	…	…	100 (31)	…	…	…	…	…	…	…	94 (31)
Morganella morganii	43 (0.9)	…	0 (39)	10.81 (37)	…	87 (30)	0 (35)	93.75 (30)	…	83 (42)	68 (41)	…	90 (42)	…	…	100 (32)	93 (42)	…	…	…	67 (43)
Proteus mirabilis	235 (48.5)	98 (114)	74 (221)	84 (166)	…	96 (142)	11 (200)	96.86 (159)	97 (59)	96 (228)	69 (169)	99 (127)	89 (233)	…	75 (57)	99 (138)	98 (232)	…	…	861 (138)	73 (227)
Serratia marcescens	158 (3.3)	98 (97)	2 (100)	2 (92)	…	91 (107)	0 (125)	100 (155)	90 (71)	87 (153)	95 (125)	89 (91)	99 (156)	84 (37)	962 (49)	99 (153)	884 (141)	23 (31)	…	89 (97)	81 (104)
Nonfermenters																					
Acinetobacter																					
A baumannii	41 (0.9)	…	…	81 (37)	…	…	…	80 (35)	…	…	81 (36)	…	88 (40)	…	…	83 (30)	…	…	…	…	…
Other	31 (0.6)	…	…	97 (31)	…	…	…	93 (30)	…	…	…	…	100 (30)	…	…	…	…	…	…	…	…
Pseudomonas aeruginosa	423 (8.7)	99 (281)	…	…	…	73 (248)	…	88 (422)	87 (184)	…	80 (343)	…	94 (414)	76 (102)	82 (132)	89 (378)	82 (420)	…	…	98 (371)	…
Stenotrophomonas maltophilia	37 (0.8)	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	92 (37)

[a]AMK, amikacin; AMP, ampicillin; SAM, ampicillin-sulbactam; AMC, amoxicillin-clavulanate; ATM, aztreonam; CFZ, cefazolin; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; CIP, ciprofloxacin; ETP, ertapenem; GEN, gentamicin; IPM/CS, imipenem-cilastatin; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin-tazobactam; TET, tetracycline; TGC, tigecycline; TOB, tobramycin; SXT, trimethoprim-sulfamethoxazole.

[b]Number of isolates do not add to 4851 (ie, the total number of isolates reported), as strains with <30 isolates are not represented in the antibiogram.

Table 4. Source-Specific Antibiogram

Source: Organism	Isolates, No. (%)	Susceptible, % (No. of Isolates Tested) [a]																			
		AMK	AMP	SAM	AMC	ATM	CFZ	FEP	CAZ	CRO	CIP	ETP	GEN	IPM/CS	LVX	MEM	PTZ	TET	TGC	TOB	SXT
Urinary																					
Enterobacterales																					
Citrobacter sp	35 (0.7)	…	…	…	…	…	42 (31)	100 (31)	…	87 (30)	97 (31)	…	97 (32)	…	…	…	94 (32)	…	…	…	74 (35)
Enterobacter cloacae complex	45 (0.9)	…	3 (30)	…	…	…	3 (35)	96 (45)	…	67 (45)	95 (40)	…	98 (45)	…	…	100 (42)	76 (45)	…	…	97 (33)	79 (43)
Escherichia coli	1524 (31.4)	99 (736)	44 (1447)	43 (1228)	80 (168)	81 (894)	49 (1352)	85 (1211)	88 (566)	82 (1304)	54 (1197)	85 (731)	87 (1506)	100 (391)	75 (363)	100 (1175)	91 (1262)	72 (155)	100 (144)	80 (896)	59 (1507)
Klebsiella pneumoniae	322 (6.6)	100 (165)	3 (265)	68 (277)	89 (37)	81 (190)	60 (278)	85 (265)	88 (128)	83 (276)	74 (273)	88 (159)	92 (318)	100 (83)	91 (94)	99 (257)	84 (274)	…	…	86 (191)	73 (315)
Klebsiella oxytoca	35 (0.7)	…	3 (34)	52 (31)	…	…	…	93 (30)	…	91 (35)	…	…	94 (35)	…	…	100 (30)	91 (33)	75 (44)	97 (39)	…	82 (34)
Proteus mirabilis	145 (3.0)	99 (68)	71 (139)	84 (101)	…	95 (88)	13 (120)	96 (104)	95 (41)	959 (142)	63 (107)	100 (74)	90 (143)	…	76 (34)	100 (81)	98 (144)	…	…	89 (90)	70 (140)
Serratia marcescens	35 (0.7)	…	…	…	…	…	…	100 (34)	…	88 (33)	69 (32)	…	97 (34)	…	…	100 (35)	83 (30)	…	…	…	…
Nonfermenters																					
Pseudomonas aeruginosa	37 (0.8)	99 (72)	…	…	…	…	…	90 (116)	91 (56)	…	73 (97)	…	96 (113)	…	90 (30)	88 (104)	84 (116)	…	…	100 (108)	…
Respiratory																					
Enterobacterales																					
Escherichia coli	61 (1.3)	97 (32)	44 (57)	43 (53)	…	77 (31)	44 (57)	89 (44)	…	85 (53)	74 (46)	…	90 (59)	…	…	100 (45)	94 (49)	…	…	82 (33)	64 (59)
Klebsiella pneumoniae	59 (1.2))	100 (35)	2 944)	78 (49)	…	81 (37)	56 (55)	84 (49)	…	82 (51)	85 (48)	…	95 (58)	…	…	100 (48)	83 (48)	…	…	…	82 (57)
Nonfermenters																					
Pseudomonas aeruginosa	75 (15.5)	100 (45)	…	…	…	51 (39)	…	85 (75)	77 (31)	…	81 (53)	…	89 (73)	…	68 (31)	84 (61)	80 (74)	…	…	92 (66)	…
Intra-abdominal																					
Enterobacterales																					
Enterobacter cloacae complex	88 (1.8)	100 (55)	…	4 (57)	…	71 (62)	0 (71)	95 (86)	57 (42)	66 (82)	95 (75)	82 (44)	99 (86)	…	…	99 (83)	72 (87)	…	…	97 (59)	83 (84)
Escherichia coli	623 (12.8)	99 (294)	50 (580)	52 (505)	85 (47)	79 (313)	42 (564)	86 (474)	89 (240)	82 (531)	63 (488)	90 (310)	87 (618)	99 (158)	68 (169)	99 (489)	84 (552)	63 (65)	100 (82)	81 (372)	65 (599)
Klebsiella pneumoniae	293 (6.0)	99 (167)	7 (219)	77 (262)	…	89 (148)	62 (253)	91 (243)	87 (134)	89 (256)	88 (252)	90 (136)	94 (290)	97 (72)	97 (69)	98 (243)	91 (251)	82 (34)	100 (43)	89 (192)	79 (286)
Klebsiella oxytoca	44 (0.9)	…	2 (42)	61 (36)	…	…	31 (36)	91 (35)	…	93 (42)	92 (37)	97 (32)	100 (42)	…	…	97 (39)	98 (41)	…	…	100 (31)	83 (41)
Nonfermenters																					
Pseudomonas aeruginosa	73 (1.5)	100 (49)	…	…	…	73 (40)	…	95 (73)	…	…	82 (61)	…	94 (72)	…	…	91 (64)	85 (71)	…	…	98 (60)	…

[a]AMK, amikacin; AMP, ampicillin; SAM, ampicillin-sulbactam; AMC, amoxicillin-clavulanate; ATM, aztreonam; CFZ, cefazolin; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; CIP, ciprofloxacin; ETP, ertapenem; GEN, gentamicin; IPM/CS, imipenem-cilastatin; LVX, levofloxacin; MEM, meropenem; ; TZP, piperacillin-tazobactam; TET, tetracycline; TGC, tigecycline; TOB, tobramycin; SXT, trimethoprim-sulfamethoxazole.

87% for *K pneumoniae* (n = 703). Susceptibility to cefepime was higher at 96% (n = 222) in comparison with ceftriaxone for the *E cloacae* complex. Of the 422 *P aeruginosa* isolates tested, 88% were susceptible to cefepime.

Piperacillin-tazobactam susceptibility was 90% for *E coli* (n = 2051), 86% for *K pneumoniae* (n = 717), but only 74% for the *E cloacae* complex (n = 225). Of 420 *P aeruginosa* isolates, 82% were susceptible to piperacillin-tazobactam.

Among isolates tested, imipenem-cilastatin and meropenem susceptibilities were almost 100% for *E coli* (n = 623/625 and 1918/1926, respectively) and 99% and 98% for *K pneumoniae* (n = 204/207 and 683/699). For the *E cloacae* complex, imipenem-cilastatin susceptibility was 86% (n = 51) and meropenem susceptibility was 93% (n = 213). Of 102 *P aeruginosa* isolates tested, 76% were susceptible to imipenem-cilastatin, and of the 378 *P aeruginosa* isolates, 89% were susceptible to meropenem.

Fluoroquinolone Susceptibility

After the 2021 fluoroquinolone susceptibility criteria were applied to all isolates, ciprofloxacin and levofloxacin susceptibilities were within 10% of each other, with levofloxacin slightly higher for Enterobacterales, a difference not deemed significant [6]. Of all *E coli* isolates tested, 64% (n = 1959) were susceptible to ciprofloxacin, and 72% (n = 606) were susceptible to levofloxacin. Susceptibility of *E coli* from a urinary source was lower than that from respiratory and intra-abdominal sources (54%, 74%, and 63%, respectively). For *K pneumoniae*, 84% (n = 706) were susceptible to ciprofloxacin, and 94% (n = 232) were susceptible to levofloxacin. For the *E cloacae* complex isolates, 93% (n = 190) were susceptible to ciprofloxacin, and 99% (n = 77) were susceptible to levofloxacin. An overall 80% of *P aeruginosa* isolates (n = 343) were susceptible to ciprofloxacin, and 82% (n = 132) were susceptible to levofloxacin.

Aztreonam Susceptibility

Of the 1393 *E coli* isolates tested and of the 536 *Klebsiella* species (*K pneumoniae*, *K oxytoca*) tested, 80% and 84% were susceptible to aztreonam, respectively. Susceptibility to aztreonam was 73% for the *E cloacae* complex (n = 153) and 73% for *P aeruginosa* (n = 248).

Trimethoprim-Sulfamethoxazole Susceptibility

Among Enterobacterales, 60% of the 2421 *E coli* isolates and 75% of *Klebsiella* species isolates (*K pneumoniae*, *K oxytoca*) were susceptible to trimethoprim-sulfamethoxazole. Of 46 *K aerogenes* isolates, 45 (98%) were susceptible to trimethoprim-sulfamethoxazole, as were 165 (77%) of the 215 *E cloacae* complex isolates. Among nonfermenters, 92% of the 37 *Stenotrophomonas maltophilia* isolates and 73% of all *Acinetobacter* species isolates (*A baumannii* and other, n = 49 tested) were susceptible to trimethoprim-sulfamethoxazole.

DISCUSSION

ASIC sites represent a diverse group of hospitals across the United States with overlapping patient populations, antibiotic formularies, microbiologic methods for pathogen identification, stewardship policies, and provider practices. The aim of the present study was to describe the characteristics of practice settings, patient populations, and bacteria isolated, with a focus on antibiotic susceptibility data for common antibiotics initiated empirically. Several important susceptibility trends were observed: 16% of Enterobacterales at high risk for ESBL production (eg, *E coli, K pneumoniae, K oxytoca,* and *P mirabilis*) were likely ESBL producers based on predefined criteria [9]. Less than 2% of all Enterobacterales were carbapenem resistant; carbapenem resistance was mostly observed among nonfermenters—specifically, *P aeruginosa* and *A baumannii* at 24% and 17%, respectively. Interestingly, while percentages of carbapenem-resistant organisms were not different, non-White patients had a statistically higher percentage of GN-BSI produced by ESBL-producing organisms. Racial disparities in antimicrobial resistance and resulting clinical outcomes are a critical research priority for future studies.

We believe that these results have important public health implications, shedding light on antibiotic susceptibility patterns by US geographic region. To some degree, results may help influence empiric antibiotic selection per region; however, patient-level decisions, such as appropriateness of empiric carbapenem therapy and intravenous-to-oral switch, should be informed by institutional antibiograms and guidelines, if available. Moreover, generally favorable susceptibilities to the non–β-lactam regimens observed in our cohort have additional stewardship implications for patients requiring these agents due to severe drug allergies. Yet, given the globally increasing rates of multidrug resistance since 2019, the need for new antibiotics with novel mechanisms of action is exceedingly important. A recent critical report from the Centers for Disease Control and Prevention indicates an alarming increase in multidrug resistance occurring in acute care hospitals because of the COVID-19 pandemic, undermining significant gains in antimicrobial resistance and stewardship over the past decade [10]. While the present study was conducted prepandemic, it nevertheless highlights the crucial need for well-coordinated, large, multicenter stewardship studies in the current era. Therefore, establishment and maintenance of collaboratives such as ASIC are vital for developing our understanding of the antimicrobial resistance patterns and optimal stewardship strategies to address setbacks caused by the pandemic. Creation of a national postpandemic antibiogram for Gram-negative, Gram-positive, and fungal isolates with the established ASIC infrastructure would be of great importance to drive stewardship policy, federal funding, and public and private partnerships to reduce antimicrobial resistance. The Centers for Medicare and

Medicaid Services recently added, as a condition of hospitals participating in the Promoting Interoperability Program, the reporting of antibiotic use and resistance data to the Centers for Disease Control and Prevention's National Healthcare Safety Network, effectively providing similar susceptibility data as ASIC [11]. Moreover, advocacy for stewardship and microbiology staffing support commensurate to facility size are pivotal to conduct antimicrobial resistance surveillance and action results of positive blood culture results.

There are several study limitations. No hospitals in the southern United States were included, and all ASIC sites were characterized as urban or suburban academic centers, which may limit applicability to rural centers—although several sites included rural patient catchment areas. Furthermore, given that 14 of 24 sites are in the Northeast, this region may appear overrepresented in terms of contribution of the number of ESBL-producing isolates, although Western sites had the highest percentage of ESBL producers of total isolates contributed at 16%. As only first isolates of a species within 90 days per patient were included and the median time from admission to collection of the blood culture that subsequently turned positive was 0 days, the susceptibility data reported are likely underestimates of the resistance that develops during a patient's hospital stay. Additionally, small differences in ciprofloxacin and levofloxacin susceptibilities were observed among Enterobacterales and nonfermenting Gram-negative species. This phenomenon has been reported for Enterobacterales, with higher rates of resistance to ciprofloxacin due to specific patterns of GyrA, a subunit of DNA gyrase mutations [12]. Unfortunately, no ASIC site tested the same isolate against ciprofloxacin and levofloxacin to understand if true differences in susceptibilities existed. Additionally, although the 2021 CLSI interpretive criteria were applied, not all institutions had validated automated susceptibility testing instruments to apply the most up-to-date CLSI criteria, and this may have affected results. For example, if a susceptibility testing panel did not have updated breakpoints that include low-enough dilutions of ciprofloxacin, the laboratory may have categorized a ciprofloxacin MIC ≤0.5 mcg/mL against *E coli* as susceptible. By applying the 2021 CLSI criteria (as done by the ASIC), this isolate would be considered nonsusceptible to ciprofloxacin, as it would not be known whether the MIC was 0.5 mcg/mL (intermediate) or ≤0.25 mcg/mL (susceptible). If there were differences in the uptake of revised ciprofloxacin and levofloxacin breakpoints, this may have influenced the susceptibility percentages among the organisms.

A strength of the present study is inclusion of blood culture isolates with various initial sources of infection, thereby enhancing applicability of findings (eg, urine, respiratory, intra-abdominal). These limitations notwithstanding, we believe that this work demonstrates the feasibility of collecting data across a large multicenter stewardship collaborative that can establish the basis for future comparative effectiveness studies to fill critical gaps in clinical knowledge. Future ASIC studies will address GN-BSI outcomes in immunocompromised hosts, the role of repeat blood cultures, the duration of therapy, transitioning from intravenous to oral therapy, and other clinically imperative questions.

Notes

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Conflicts of interest. S.E.C. has received consulting fees from the Duke Clinical Research Institute outside of the submitted work and has participated on an advisory board for Debiopharm. All other authors report no potential conflicts.

Patient consent. Informed consent was not obtained for the study. The institutional review board of each participating site approved the study, with waivers of informed consent. The design conforms to standards currently applied in the United States.

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