

Manuscript Title: Demographics, Epidemiology, Mortality, and Difficult-To-Treat Resistance Patterns of Bacterial Bloodstream Infections in the Global United States Military Health System from 2010-2019: A Retrospective Cohort Study

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Supplemental Table 1. Categorization of Bacterial Subspecies that are associated with Bloodstream Infection

Lactose-Fermenting Gram-negative Bacilli	<i>Streptococcus</i> and <i>Enterococcus</i> species	<i>Staphylococcus aureus</i>	Non-Lactose-Fermenting Gram-negative Bacilli
<i>Escherichia coli</i>	<i>Streptococcus</i> β-Hemolytic group	<i>Staphylococcus aureus</i>	<i>Pseudomonas aeruginosa</i>
<i>Klebsiella pneumoniae</i>	β -hemolytic <i>Streptococcus</i> spp.		<i>Acinetobacter</i> spp.
<i>Serratia</i> spp.	β -hemolytic <i>Streptococcus</i> spp, Group A		<i>Acinetobacter baumannii</i>
<i>Serratia ficaria</i>	β -hemolytic <i>Streptococcus</i> spp, Group B		<i>Acinetobacter baumannii calcoaceticus</i> complex
<i>Serratia liquefaciens</i>	β -hemolytic <i>Streptococcus</i> spp, Group C		<i>Acinetobacter haemolyticus</i>
<i>Serratia marcescens</i>	β -hemolytic <i>Streptococcus</i> spp, Group D		<i>Acinetobacter lwoffii</i>
<i>Serratia odorifera 1</i>	β -hemolytic <i>Streptococcus</i> spp, Group F		<i>Acinetobacter radioresistens</i>
<i>Serratia plymuthica</i>	β -hemolytic <i>Streptococcus</i> spp, Group G		<i>Acinetobacter</i> spp.
<i>Serratia rubidaea</i>	<i>Streptococcus agalactiae</i>		<i>Acinetobacter ursingii</i>
<i>Serratia</i> spp.	<i>Streptococcus canis</i>		<i>Stenotrophomonas</i> spp.
<i>Citrobacter</i> spp.	<i>Streptococcus dysgalactiae</i>		<i>Stenotrophomonas maltophilia</i>
<i>Citrobacter amalonaticus</i>	<i>Streptococcus dysgalactiae</i> SS. <i>dysgalactiae</i>		
<i>Citrobacter braakii</i>	<i>Streptococcus dysgalactiae</i> SS. <i>equisimilis</i>		
<i>Citrobacter farmeri</i>	<i>Streptococcus equi</i>		

Lactose-Fermenting Gram-negative Bacilli	<i>Streptococcus</i> and <i>Enterococcus</i> species	<i>Staphylococcus aureus</i>	Non-Lactose-Fermenting Gram-negative Bacilli
<i>Citrobacter freundii</i>	<i>Streptococcus equisimilis</i>		
<i>Citrobacter koseri (diversus)</i>	<i>Streptococcus porcinus</i>		
<i>Citrobacter</i> spp.	<i>Streptococcus pyogenes</i>		
<i>Citrobacter youngae</i>	<i>Streptococcus</i> spp.		
<i>Enterobacter</i> spp.	<i>Streptococcus</i> spp.		
<i>Enterobacter agglomerans</i>	<i>Streptococcus</i> nutritionally variant		
<i>Enterobacter amnigenus</i> 1	<i>Streptococcus viridans</i> group		
<i>Enterobacter amnigenus</i> 2	α hemolytic <i>Streptococcus</i> spp., viridans group		
<i>Enterobacter asburiae</i>	<i>Streptococcus acidominimus</i>		
<i>Enterobacter cancerogenus</i>	<i>Streptococcus alactolyticus</i>		
<i>Enterobacter gergoviae</i>	<i>Streptococcus anginosus</i>		
<i>Enterobacter sakazakii</i>	<i>Streptococcus constellatus</i>		
<i>Enterobacter</i> spp.	<i>Streptococcus cristatus</i>		
<i>Enterobacter taylorae</i>	<i>Streptococcus gordonii</i>		
<i>Proteus</i> spp.	<i>Streptococcus mitis</i>		
<i>Proteus penneri</i>	<i>Streptococcus mutans</i>		
<i>Proteus</i> spp.	<i>Streptococcus parasanguinis</i>		
<i>Proteus vulgaris</i>	<i>Streptococcus salivarius</i>		
	<i>Streptococcus sanguinis</i>		
	<i>Streptococcus sanguis</i>		
	<i>Streptococcus sanguis I</i>		
	<i>Streptococcus sanguis II</i>		
	<i>Streptococcus sobrinus</i>		
	<i>Streptococcus thermophilus</i>		
	<i>Streptococcus thoraltensis</i>		

Lactose-Fermenting Gram-negative Bacilli	<i>Streptococcus</i> and <i>Enterococcus</i> species	<i>Staphylococcus aureus</i>	Non-Lactose-Fermenting Gram-negative Bacilli
	<i>Streptococcus vestibularis</i>		
	<i>Streptococcus pneumoniae</i>		
	<i>Enterococcus</i> species		
	<i>Enterococcus avium</i>		
	<i>Enterococcus casseliflavus</i>		
	<i>Enterococcus durans</i>		
	<i>Enterococcus faecalis</i>		
	<i>Enterococcus faecium</i>		
	<i>Enterococcus gallinarum</i>		
	<i>Enterococcus hirae</i>		
	<i>Enterococcus raffinosus</i>		
	<i>Enterococcus</i> spp.		

Supplemental Table 2. Geographic Location of Facilities Where Bloodstream Infections (BSI) Were Diagnosed

Geographic Location	BSI Episodes No. (%) (N=15,357)
Continental United States	14,653 (95.4)
Texas	3128 (20.4)
California	2171 (14.1)
Maryland	1621 (10.6)
Virginia	1272 (8.3)
Georgia	971 (6.3)
North Carolina	840 (5.5)
Florida	532 (3.5)
Nevada	403 (2.6)
Ohio	327 (2.1)
Mississippi	274 (1.8)
Kentucky	218 (1.4)
District of Columbia	202 (1.3)
Missouri	202 (1.3)
Colorado	160 (1.0)
Illinois	71 (0.5)
Oklahoma	64 (0.4)
Kansas	53 (0.4)
Louisiana	36 (0.2)
South Carolina	34 (0.2)
New York	12 (0.1)
Idaho	7 (0.1)
Nebraska	4 (0.03)
Tennessee	2 (0.01)
New Mexico	1 (0.01)
South Dakota	1 (0.01)
Outside of Continental United States	
Hawaii	794 (5.2)
Alaska	196 (1.3)
Guam	287 (1.9)
Germany	194 (1.3)
Japan	124 (0.8)
South Korea	44 (0.3)
United Kingdom	24 (0.2)
Italy	15 (0.1)
Spain	11 (0.1)

Cuba	3 (0.02)
Bahrain	1 (0.01)
Turkey	1 (0.01)

Supplemental Table 3. Comorbidities Prior to Development of Bloodstream Infections (BSI)

Comorbidity	BSI Episodes No. (%) (N=15,357)
No comorbidity	2,501 (16.3)
Chronic pulmonary disease	7,617 (49.6)
Diabetes without chronic complication	6,939 (45.2)
Peripheral vascular disease	5,354 (34.9)
Renal disease	5,260 (34.3)
Malignancy, including lymphoma and leukemia ^a	5,238 (34.1)
Congestive heart failure	4,761 (31.0)
Cerebrovascular disease	4,531 (29.5)
Diabetes with chronic complications	4,104 (26.7)
Mild liver disease	3,391 (22.1)
Myocardial infarction	2,903 (18.9)
Metastatic solid tumor	1,765 (11.5)
Peptic ulcer disease	1,612 (10.5)
Rheumatic disease	1,372 (8.9)
Dementia	1,370 (8.9)
Hemiplegia or paraplegia	1,230 (8.0)
Moderate or severe liver disease	653 (4.3)
AIDS/HIV	89 (0.6)
Pre-Bloodstream Infection Updated CCI, Median score (+/- SD)	3.0 (3.37)

CCI – Charlson Comorbidity Index; SD – standard deviation

^a Excludes non-melanoma malignant neoplasms of the skin

Supplemental Table 4. Demographics and Comorbidities Stratified by Bloodstream Infection (BSI) Organisms

Characteristics	Total BSI Episodes, No. (%) (N=15,357)	BSI Episodes, No. (%)			
		Lactose- Fermenting GNB (N=6,401)	<i>Streptococcus</i> / <i>Enterococcus</i> spp. (N=5,072)	<i>Staphylococcus</i> <i>aureus</i> (N=3,040)	Non-Lactose- Fermenting GNB (N=844)
<i>Age Group, years</i>					
18-25	1,302 (8.5)	431 (6.7)	484 (9.5)	286 (9.4)	101 (12.0)
26-35	1,121 (7.3)	436 (6.8)	388 (7.7)	225 (7.4)	72 (8.5)
36-45	951 (6.2)	391 (6.1)	303 (6.0)	211 (6.9)	46 (5.5)
46-64	4,288 (27.9)	1,820 (28.4)	1,381 (27.2)	886 (29.1)	201 (23.8)
≥65	7,695 (50.1)	3,323 (51.9)	2,516 (49.6)	1,432 (47.1)	424 (50.2)
<i>Sex</i>					
Female	6,811 (44.4)	3,408 (53.2)	2,039 (40.2)	1,076 (35.4)	288 (34.1)
Male	8,546 (55.6)	2,993 (46.8)	3,033 (59.8)	1,964 (64.6)	556 (65.9)
<i>Race</i>					
African American	2,524 (16.4)	1,051 (16.4)	859 (16.9)	439 (14.4)	175 (20.7)
Asian or Pacific Islander	1,162 (7.6)	608 (9.5)	312 (6.2)	186 (6.1)	56 (6.6)
Caucasian	8,798 (57.3)	3,436 (53.7)	3,022 (59.6)	1,884 (62.0)	456 (54.0)
Other	2,873 (18.7)	1,306 (20.4)	879 (17.3)	531 (17.5)	157 (18.6)
<i>Comorbidities preceding BSI^a</i>					
Chronic pulmonary disease	7,617 (49.6)	2,960 (46.2)	2,657 (52.4)	1,568 (51.6)	432 (51.2)
Diabetes without chronic complication	6,939 (45.2)	2,902 (45.3)	2,222 (43.8)	1,464 (48.2)	351 (41.6)
Peripheral vascular disease	5,354 (34.9)	2,023 (31.6)	1,833 (36.1)	1,184 (38.9)	314 (37.2)
Renal disease	5,260 (34.3)	2,003 (31.3)	1,762 (34.7)	1,169 (38.5)	326 (38.6)

Malignancy, including lymphoma and leukemia ^b	5,238 (34.1)	2,152 (33.6)	1,762 (34.7)	948 (31.2)	376 (44.5)
Congestive heart failure	4,761 (31.0)	1,659 (25.9)	1,712 (33.8)	1,096 (36.1)	294 (34.8)
Pre-Bloodstream Infection Updated CCI, Median score (+/- SD)	3.0 (3.4)	3.0 (3.3)	3.0 (3.4)	4.0 (3.4)	4 (3.6)

CCI – Charlson Comorbidity Index; GNB – Gram-negative bacilli; SD – standard deviation

^a Most frequent comorbidities are listed. Categories are not mutually exclusive. These comorbidities are an amalgamation of the Clinical Classification Software diagnosis mapping categories.

^b Excludes malignant neoplasms of the skin

Supplemental Table 5. Rates of *In Vitro* Antimicrobial Resistance of Pathogens associated with BSI Episodes

Antimicrobial Resistance	BSI episodes with Gram-Negative (GN) Bacteria, No. (%)					
	All GN Bacteria BSI Episodes (N=3,707)	<i>Acinetobacter</i> spp. (N=81)	<i>Citrobacter</i> spp. (N=71)	<i>Escherichia coli</i> (N=2,382)	<i>Klebsiella pneumoniae</i> (N=769)	<i>Pseudomonas aeruginosa</i> (N=404)
Carbapenem-class antibiotic resistance	113 (3.0)	24 (29.6)	3 (4.2)	6 (0.3)	10 (1.3)	70 (17.3)
Extended-spectrum Cephalosporin-class antibiotic resistance	400 (10.8)	30 (37.0)	2 (2.8)	266 (11.2)	63 (8.2)	39 (9.7)
Fluoroquinolone-class antibiotics resistance	865 (23.3)	27 (33.3)	5 (7.0)	677 (28.4)	79 (10.3)	77 (19.1)
Piperacillin-tazobactam resistance ^a	218 (7.9% of 2,758)	15 (33.3% of 45)	1 (1.8% of 56)	85 (5.0% of 1,694)	56 (9.6% of 583)	61 (16.1% of 380)
Difficult to Treat resistance	42 (1.1)	19 (23.5)	0	1 (0.04%)	8 (1.0%)	14 (3.5)
	BSI Episodes with Gram-Positive Bacteria, No. (%)					
	<i>Staphylococcus aureus</i> (N=2,936)	<i>Streptococcus</i> β -hemolytic group (N=553)	<i>Streptococcus</i> spp. (N=223)	<i>Streptococcus pneumoniae</i> (N=375)	<i>Streptococcus viridans</i> group (N=568)	<i>Enterococcus</i> spp. (N=1,187)
Methicillin resistance	1,057 (36.0)	0	0	0	0	0
Penicillin resistance	0	2 (0.4)	55 (24.7)	0	199 (35.0)	0
Vancomycin resistance	4 (0.1% of 2,811) ^b	0	0	0	0	205 (17.3)
Daptomycin resistance	2 (0.5% of 401) ^b	0	0	0	0	0
Extended-spectrum cephalosporin class resistance	0	2 (0.7 % of 283) ^c	6 (3.4% of 177) ^c	8 (2.1)	20 (5.7% of 348) ^c	0

^a 949 Gram-negative isolates were not tested for piperacillin-tazobactam resistance. The proportion for each organism is calculated from the total tested.

^b 125 *S. aureus* isolates were not tested for vancomycin resistance and 2,535 isolates were not tested for daptomycin resistance. The proportions are calculated from the total tested.

^c 536 *Streptococcus* isolates were not tested for extended-spectrum cephalosporin class resistance. The proportions are calculated from the total tested.

Supplemental Table 6. Demographics and Comorbidities Among Patients Who Died Within One Year of Bloodstream Infection (BSI) Diagnosis, Stratified by BSI Organisms

Characteristics	Total Patients Who Died, No. (%) (N=2,977)	BSI Organism Group, No. (%)				
		Lactose-Fermenting GNB (N=922)	<i>Streptococcus / Enterococcus</i> spp. (N=933)	<i>Staphylococcus aureus</i> (N=707)	Non-Lactose-Fermenting GNB (N=180)	Multiple Organism Groups (N=235)
<i>Age Group, years</i>						
18-25	38 (1.3)	8 (0.9)	15 (1.6)	6 (0.8)	3 (1.7)	6 (2.5)
26-35	52 (1.7)	18 (1.9)	15 (1.6)	10 (1.4)	4 (2.2)	5 (2.1)
36-45	78 (2.6)	29 (3.1)	18 (1.9)	18 (2.5)	7 (3.9)	6 (2.5)
46-64	607 (20.4)	190 (20.6)	201 (21.5)	124 (17.5)	37 (20.6)	55 (23.4)
≥65	2,202 (74.0)	677 (73.4)	684 (73.3)	549 (77.6)	129 (71.7)	163 (69.4)
<i>Sex</i>						
Female	1,112 (37.3)	383 (41.5)	344 (36.9)	241 (34.1)	70 (38.9)	74 (31.5)
Male	1,865 (62.7)	539 (58.5)	589 (63.1)	466 (65.9)	110 (61.1)	161 (68.5)
<i>Race</i>						
African American	499 (16.8)	162 (17.6)	155 (16.6)	100 (14.1)	37 (20.6)	45 (19.1)
Asian or Pacific Islander	213 (7.1)	73 (7.9)	61 (6.5)	39 (5.5)	21 (11.7)	19 (8.1)
Caucasian	1,869 (62.6)	554 (60.1)	594 (63.7)	472 (66.8)	106 (58.9)	143 (60.9)
Other	396 (13.3)	133 (14.4)	123 (13.2)	96 (13.6)	16 (8.9)	28 (11.9)
Had ≥1 comorbidity preceding BSI	2,889 (97.0)	898 (97.4)	900 (96.5)	691 (97.7)	175 (97.2)	225 (95.7)
<i>Comorbidities preceding BSI^a</i>						
Chronic pulmonary disease	1,801 (60.5)	506 (54.9)	590 (63.2)	460 (65.1)	103 (57.2)	142 (60.4)
Malignancy, including lymphoma and leukemia ^b	1,659 (55.7)	554 (60.1)	503 (53.9)	337 (47.7)	124 (68.9)	141 (60.0)
Diabetes without chronic complication	1,597 (53.6)	480 (52.1)	486 (52.1)	426 (60.3)	90 (50.0)	115 (48.9)

Renal disease	1,505 (50.6)	429 (46.5)	489 (52.4)	397 (56.2)	82 (45.6)	108 (46.0)
Peripheral vascular disease	1,499 (50.4)	423 (45.9)	479 (51.3)	406 (57.4)	87 (48.3)	104 (44.3)
Congestive heart failure	1,484 (49.8)	413 (44.8)	470 (50.4)	401 (56.7)	88 (48.9)	112 (47.7)

GNB – Gram-negative bacilli

^a Most frequent comorbidities are listed. Categories are not mutually exclusive. These comorbidities are an amalgamation of the Clinical Classification Software diagnosis mapping categories.

^b Excludes malignant neoplasms of the skin