

Epidemiology of Patients with ESKAPE Pathogen Bloodstream Infection in the US Military Health System



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Abstract

Background: Bloodstream infections (BSI) are associated with both inpatient mortality and substantial morbidity in the United States. We sought to characterize the epidemiology of BSIs with ESKAPE pathogens on patients served by the United States Military Healthcare System (MHS), which prospectively captures clinical and microbiological data from US service members and their beneficiaries.

Methods: We performed a retrospective cohort analysis of MHS patients with blood cultures positive for ESKAPE pathogens (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter spp.*), as well as *Neisseria gonorrhoeae* and *Raoultella spp.* between January 2010 and December 2015. Microbiological data from the Navy and Marine Core Public Health Center was retrospectively collated with clinical and demographic data from the MHS Data Repository.

Results: We identified 7,404 patients who experienced 8,791 episodes of ESKAPE (including *N. gonorrhoeae* and *Raoultella spp.*) BSI. The patients were predominately active duty (N=688) or retired (N=2,517) Armed Forces service members and their dependents (N=2,361). Further, 59.4% were male and 47.5% were ≥65 years old. A total of 5,594 (75.5%) of BSI episodes were associated with hospital admission, with an average length of stay of 14.9 days (SD of 27.5 days) and 47.4% (N=2,650) of those admissions were associated with an ICU stay averaging 8.6 days (SD of 18.0 days). The most common pathogens detected were *E. coli* (34.6%, N= 3,042) followed by *S. aureus* (28.0%, N=2,464), with 7.6% and 40.7% of isolates resistant to ceftriaxone and methicillin, respectively. We found a larger proportion of *E. coli* BSI in females (47.4% versus 26.2%) and *S. aureus* BSI in males (32% versus 21.9%). The frequency of *A. baumannii* BSI in younger patients, ages 18-30, was an average 4.5 fold higher than in older age groups (30-50, 50-65 and >65).

Conclusion: We noted epidemiological differences in the burden of ESKAPE pathogen BSIs, in various populations including sex and age specific risk factors in a population served by the MHS. Further work is underway to evaluate risk factors for infection and impact on outcomes with pathogens with in vitro resistance controlling for factors such as age, gender, co-morbid diseases and severity of illness.

Background

- Bloodstream infections (BSI) result in elevated inpatient mortality and healthcare-associated costs in the United States.
- BSI is the 12th leading cause of death and the most expensive in-hospital condition in the United States, causing 40,922 deaths and 23.7 billion dollars in aggregate costs per year respectively.
- Inpatient mortality rates for patients diagnosed with BSI, either hospital-acquired (HA) or community acquired (CA), are between 27% and 18% in recent studies.
- Antibiotic resistant (AR) organisms are an additional challenge to providers treating blood stream infections.
- Inappropriate antibiotic therapy, in the context of an antibiotic resistant blood isolate, have been strongly associated with increased 14-day mortality in CA-BSI.

- We examined BSI's among patients who received care within the MHS caused by ESKAPE pathogens (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp.*) due to their representation in pathogenesis, transmission and antimicrobial resistance paradigms common to almost all microorganisms of clinical relevance.

Methods

- Patient identifiers and clinical microbiological data, collected by The Navy and Marine Core Public Health Center from all MHS patients, were retrospectively collated with demographic and clinical data from the MHS Data Repository (MDR)
- Clinical and Laboratory Standards Institute Minimum Inhibitory Concentration break points and interpretive criteria were utilized to determine susceptibility or resistance after data collation.
- Inclusion criteria: >18 years of age and received treatment within the MHS Jan 2010 – Dec 2015
- Exclusion criteria: Patients with missing/conflicting patient identifiers recorded in the MDR (e.g., social security, patient birth date and gender)
- BSI cases defined by a single positive blood culture
- After patient's initial blood culture, repeat blood cultures were recorded after a 14-day censor window, to document multiple separate, non-associated BSI cases from each patient
- Clinical / co-morbidity data collected ≥7 days prior to patient's first recorded positive blood culture (demographic data collected +/- 7 days)
- Hospital stay data collected if blood culture collection date was found within the admission and discharge date
- Associated ICD9/10 codes collected from the MDR

Results

Table 1: Overall BSI Count by Bacterial Species, No. (%)

Bacterial species	All Bacteremia Events	Multiple Bacteremia Events
<i>Acinetobacter baumannii</i>	112 (1.3)	5
<i>Acinetobacter</i> species	72 (0.8)	0
<i>Enterobacter aerogenes</i>	131 (1.5)	3
<i>Enterobacter cloacae</i>	193 (2.2)	7
<i>Enterobacter</i> species	89 (1.0)	2
<i>Enterococcus faecalis</i>	648 (7.4)	35
<i>Enterococcus faecium</i>	235 (2.7)	12
<i>Enterococcus</i> species	204 (2.3)	11
<i>Escherichia coli</i>	3,042 (34.6)	93
<i>Klebsiella pneumoniae</i>	948 (10.8)	50
<i>Klebsiella</i> species	158 (1.8)	2
<i>Neisseria gonorrhoeae</i>	2 (0.02)	0
<i>Pseudomonas aeruginosa</i>	485 (5.5)	17
<i>Raoultella species</i>	8 (0.1)	0
<i>Staphylococcus aureus</i>	2,464 (28.0)	132
TOTAL	8,791	369

- *E. coli* was the most common pathogen implicated in BSI followed by *S. aureus*.
- *S. aureus* was more commonly found in subsequent blood cultures, even after a 14-day censorship period.

Results (cont.)

Table 2 : Rate of *in Vitro* Antimicrobial Resistance (%)

Antimicrobial drug	A. baumannii	Acinetobacter spp	E. aerogenes	E. cloacae	Enterobacter spp	Enterococcus spp	E. coli	K. pneumoniae	Klebsiella spp	P. aeruginosa	S. aureus
Amikacin	51.6	0.0	5.3	0.0	3.0	100.0	0.1	1.0	2.8	3.6	0.0
Amox-Clav	27.3	16.7	92.3	92.0	76.9		7.7	6.6	7.8	73.7	17.9
Ampicillin	87.0	33.3	87.3	96.5	75.0	43.5	49.6	92.6	91.6	17.1	78.4
Ampicillin Sulbactam	23.1	3.7	88.9	87.4	66.7		28.2	14.4	11.7	13.9	19.4
Aztreonam	9.1	0.0	18.2	16.2	0.0		8.2	8.4	1.9	25.3	
Cefazolin	6.3	16.7	93.5	97.3	97.6		16.3	12.7	44.4	18.2	34.0
Cefepime	57.0	3.7	4.1	5.1	6.8	0.0	5.7	5.1	0.6	7.5	0.0
Ceftazidime	58.0	8.7	10.4	12.2	25.0	100.0	7.1	7.5	3.3	9.5	
Ceftriaxone	70.5	17.0	14.6	22.6	18.0	0.0	7.6	7.0	5.2	47.9	18.4
Ciprofloxacin	62.1	1.8	6.7	14.3	6.7	68.0	24.2	8.1	7.7	17.7	42.7
Gentamicin	52.4	6.7	4.6	11.4	12.1	100.0	9.4	5.3	2.3	7.5	2.6
Levofloxacin	62.9	1.8	5.9	5.0	0.0	0.0	24.4	6.3	5.9	19.3	33.0
Meropenem	73.1	0.0	0.0	0.0	8.3	0.0	0.0	0.6	0.0	13.0	0.0
Oxacillin											40.7
Pip/Tazo	43.2	0.0	8.8	12.6	9.1		2.6	4.5	9.0	10.3	0.0
TMP/SMX	52.1	10.8	4.4	18.9	21.0		28.1	10.7	8.8	29.3	2.5
Vancomycin						49.3					0.1

Other resistance data:

- *Enterococcus faecalis*: ampicillin – 1.1% resistant; ciprofloxacin – 25% resistant; levofloxacin – 15.9% resistant; vancomycin -1.7% resistant
- *Enterococcus faecium*: ampicillin – 79% resistant; ciprofloxacin – 63.6% resistant; gentamicin – 50% resistant; levofloxacin – 94.4% resistant; vancomycin – 56.3% resistant

Table 3: Distribution of Bacterial Species by Sex and Age, No. (%)

Bacterial species	Sex		Age			
	Female	Male	18-29	30-49	50-64	≥65
<i>A. baumannii</i>	15 (0.4)	97 (1.8)	40 (4.2)	21 (1.75)	19 (0.8)	29 (0.7)
<i>Acinetobacter</i> spp	28 (0.8)	44 (0.8)	10 (1.0)	17 (1.4)	15 (0.65)	26 (0.6)
<i>E. aerogenes</i>	29 (0.8)	102 (1.9)	17 (1.8)	31 (2.6)	41 (1.8)	42 (1.0)
<i>E. cloacae</i>	72 (2.1)	121 (2.3)	28 (2.9)	39 (3.2)	51 (2.2)	70 (1.7)
<i>Enterobacter</i> spp	30 (0.9)	59 (1.1)	7 (0.7)	26 (2.2)	25 (1.1)	29 (0.7)
<i>E. faecalis</i>	206 (5.95)	442 (8.3)	52 (5.4)	57 (4.7)	172 (7.5)	354 (8.5)
<i>E. faecium</i>	74 (2.1)	161 (3.0)	31 (3.2)	33 (2.75)	58 (2.5)	108 (2.6)
<i>Enterococcus</i> spp	67 (1.9)	137 (2.6)	15 (1.6)	30 (2.5)	42 (1.8)	111 (2.7)
<i>E. coli</i>	1642 (47.4)	1396 (26.2)	339 (35.2)	414 (34.4)	746 (32.3)	1501 (36.0)
<i>K. pneumoniae</i>	326 (9.4)	622 (11.7)	63 (6.55)	115 (9.6)	250 (10.8)	506 (12.1)
<i>Klebsiella</i> spp	59 (1.7)	99 (1.9)	12 (1.25)	18 (1.5)	54 (2.3)	71 (1.7)
<i>N. gonorrhoeae</i>	0	2 (0.04)	1 (0.1)	1 (0.1)	0	0
<i>P. aeruginosa</i>	150 (4.3)	334 (6.3)	56 (5.8)	58 (4.8)	128 (5.6)	229 (5.5)
<i>Raoultella</i> spp	5 (0.1)	3 (0.06)	0	1 (0.1)	1 (0.04)	6 (0.1)
<i>S. aureus</i>	759 (21.9)	1705 (32.0)	291 (30.25)	341 (28.4)	705 (30.6)	1091 (26.1)
Total	3462	5324	962	1202	2307	4173

- *E. coli* BSI was more common in female patients compared to male patients.
- *S. aureus* and *Enterococcus spp.* BSI were observed more frequently in male patients.
- *A. baumannii* appear to demonstrate an association with younger age groups, while *E. coli* frequency remains consistent with age.

Results (cont.)

Table 4: Clinical Classifications Associated with Hospital Stay, No. (%)

Clinical Classification	In patient Admission (N=5594)
Septicemia (except in labor)	3669 (65.6)
Unspecified bacterial infection	2341 (41.8)
Essential hypertension	2278 (40.7)
Urinary tract infection	2200 (39.3)
Fluid and electrolyte disorders	1877 (33.6)
Disorders of lipid metabolism	1862 (33.3)
Unclassified residual codes	1776 (31.7)
Acute and unspecified renal failure	1729 (30.9)
Deficiency and other anemia	1690 (30.2)
Diabetes mellitus without complication	1431 (25.6)

- Inpatient admission associated with ESKAPE BSI in 5594 patients (75.5% of 7404)
- 47.4% (2650 of 5594) of patients hospitalized with BSI were admitted to ICU
- 26% of patients admitted to hospital had diagnosis of Diabetes Mellitus

Conclusions

- We observed epidemiological differences in the burden of ESKAPE pathogen BSI in different MHS patient populations
- Age and Sex appear to be specific risk factors in developing ESKAPE pathogen BSI
- *E. coli* and *S. aureus* are common pathogens implicated in MHS patients with BSI
- Further work to assess risk factors for both infection and survival in patients with ESKAPE BSI is needed

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