Longitudinal Changes in Antimicrobial-resistant Bacterial Bloodstream Infections in the US Military Health System from 2010-2019

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Abstract

Background: The epidemiology of antibiotic-resistant pathogens guides empirical therapy for bacterial bloodstream infections (BSI) and stewardship efforts. We describe changes in antimicrobial-resistant BSI pathogens over time within the US Military Health System (MHS), which prospectively captures clinical and microbiological data from both retired and active-duty US Uniformed service members and their beneficiaries.

Methods: The study population included MHS beneficiaries with blood cultures positive for any bacterial pathogens (Jan 2010 – Dec 2019). Microbiological data were obtained from the Navy and Marine Corps Public Health Center and antibiotic resistance was interpreted using CLSI breakpoints corresponding to collection year. Blood contaminants were excluded. Difficult to treat resistance (DTR) was defined in Gram-negative bacteria (GNB) as isolates with *in vitro* resistance to three classes of antibiotics: carbapenems, extended-spectrum cephalosporins, and fluroquinolones.

Results: The 15 most frequent bacterial pathogens, representing 15,358 BSI episodes from 12,749 individuals, were subcategorized in four groups based on shared BSI microbiology. Lactose-fermenting GNB (LFGNB) were most common, accounting for 42% of BSI pathogens, following by *Streptococcus/Enterococcus* spp. (33%), *Staphylococcus aureus* (20%), and non-lactose fermenting GNB (NLGNB, 5.5%). The rate of LFGNB BSI increased from 7.57 per 100,000 beneficiaries in 2010 to 8.42 in 2019 (peak of 8.83 in 2016), resulting in an increase of 11.3% during the study period (Figure). Rates of BSI attributed to *Streptococcus/Enterococcus* spp., *S. aureus*, and NLGNB decreased 26%, 29%, and 45%, respectively, over the study period. The average annual rates of methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus* spp., and difficult to treat (DTR) GNB BSI were 1.30, 0.25, and 0.05 per 100,000 beneficiaries, respectively. Over the study period, these rates decreased 58.3%, 72.4% and 24.2%, respectively.

Conclusion: LFGNB BSI numerically increased over time while NLGNB BSI (e.g., *Pseudomonas aeruginosa* and *Acinetobacter* spp.) decreased. The burden of DTR GNB BSI also decreased, indicating that first-line antibiotics remain clinically available for most patients with BSI. Most infections were caused by susceptible organisms.

Background

- Bloodstream infections (BSI) including those with antibiotic-resistant bacterial isolates have been associated with increased morbidity, mortality, and healthcare-related costs
- While multiple definitions exist for "antimicrobial resistance", Kadri et. al., [*2018. Clin Infect Dis. 67(12): 1803-14*] posed a more clinically-relevant definition of antimicrobial resistance in Gram-negative bacilli (GNB) termed "Difficult to Treat" resistance (DTR) focusing on remaining active drugs, defined as resistance to 3 classes of antibiotics: carbapenems, extended-spectrum β-lactams, or fluoroquinolones
- We describe the epidemiologic trends of antimicrobial resistance, including DTR GNB, in bacterial blood isolates collected from Military Health System (MHS) beneficiaries diagnosed with a bacterial BSI

Methods

- Study population: ≥18 years, MHS beneficiary with BSI diagnosis treated at a MHS facility (Jan 2010 – Dec 2019) and attributed to a bacterial pathogen
- Demographics were collected prior to index BSI
- Microbiologic data were obtained from Navy and Marine Corps Public Health Center
- Clinically-relevant bacterial pathogens were subcategorized based on similarities using 4 organism categories (**Table 1**):
- Antibiotic susceptibility for each pathogen was interpreted using CLSI breakpoints corresponding to the year of collection
- DTR defined by resistance to 3 classes of antibiotics: carbapenems, extended-spectrum β-lactams, or fluoroquinolones
- Annual incidence calculated based on total individuals eligible for care within the MHS

Table 1: Subcategorization of bacterial BSI pathogens

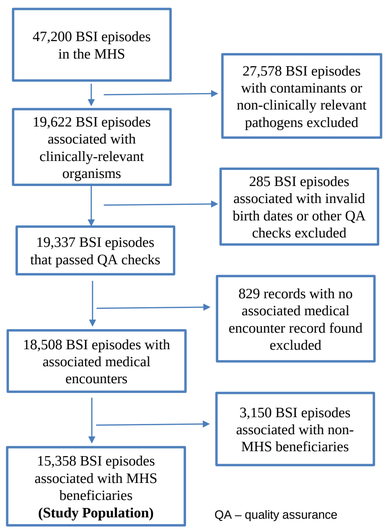
Lactose-Fermenting GNB	*Streptococcus / Enterococcus* spp.	*Staphylococcus aureus*	Non-Lactose-Fermenting GNB
Escherichia coli	*Streptococcus* β-Hemolytic group	*Staphylococcus aureus*	*Pseudomonas aeruginosa*
Klebsiella pneumoniae	*Streptococcus* spp.		*Acinetobacter* spp.
Serratia spp.	*Streptococcus* viridans group		*Stenotrophomonas* spp.
Citrobacter spp. *Enterobacter* spp. *Proteus* spp.	*Streptococcus pneumoniae* *Enterococcus* species		

GNB- Gram-negative bacilli

Results

12,749 MHS beneficiaries with bacterial BSI for a total of 15,358 BSI episodes

Figure 1: Flow diagram for BSI episodes diagnosed in MHS



QA – quality assurance

Results (cont.)

Figure 2: Rates of subcategories of BSI between 2010-2019

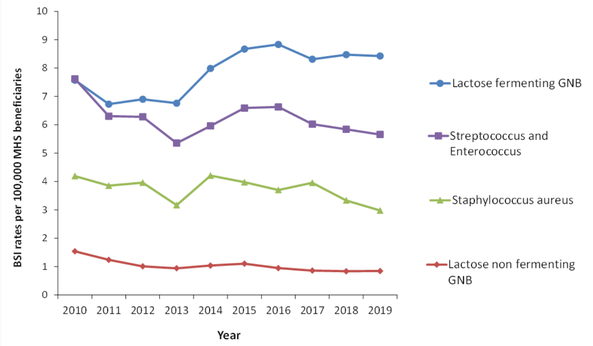
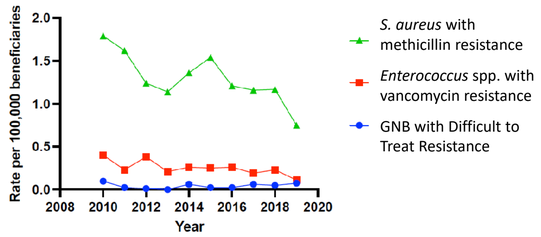


Table 2: Change in bacterial BSI rates among MHS beneficiaries (2010-2019)

	Change in BSI Rate per 100,000 MHS Beneficiaries		
	Direction of Absolute Rate Change	Absolute Rate Change	Rate Change %
Lactose-Fermenting GNB	Increase	0.85	11.3
Streptococcus / Enterococcus spp.	Decrease	1.96	25.8
Staphylococcus aureus	Decrease	1.22	29.0
Non-Lactose-Fermenting GNB	Decrease	0.69	45.1

GNB- Gram-negative bacilli

Figure 3: Rates of selected antibiotic-resistant pathogens of clinical importance



GNB- Gram-negative bacilli

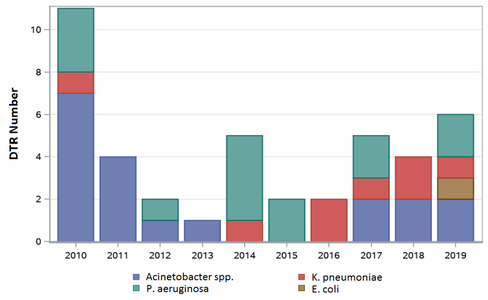
Table 3: Change in bacterial BSI rates for selected antibiotic-resistant pathogen among MHS beneficiaries (2010-2019)

	Change in BSI Rate per 100,000 MHS Beneficiaries		
	Direction of Absolute Rate Change	Absolute Rate Change	Rate Change %
GNB with Difficult to Treat Resistance	Decrease	-0.02	-24.2
S. aureus with methicillin resistance	Decrease	-1.05	-58.3
Enterococcus spp. with vancomycin resistance	Decrease	-0.29	-72.4

GNB- Gram-negative bacilli

Results (cont.)

Figure 4: Absolute number of organisms with Difficult to Treat Resistance (DTR) per year



Conclusions

- Rates of BSIs due to lactose-fermenting GNB increased during the study period, while all other bacterial subcategories (lactose-non-fermenting GNB, *S. aureus,* and *Streptococcus* and *Enterococcus* spp.) decreased
- The burden of BSIs attributed to DTR GNB remained low throughout the study period, indicating that use of first-line antibiotics to treat BSIs remain viable

Acknowledgments

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