1813

A Population-Based Multi-Year Assessment of the Incidence of High Inoculum Cefazolin (CZ) Resistance Amongst Methicillin-Susceptible *Staphylococcus aureus* (MSSA) Causing Bloodstream Infections (BSIs) over time in Calgary, Canada

Kristine Du[1], Barbara J. Waddell[1], Chloe Ligier[1], Julianna Svishchuk[1], Alexander Kipp[1], John Lam[2], Stephen Robinson[3], Ranjani Somayaji[1,4], John Conly[1,4], Daniel B. Gregson[1,4], and Michael D. Parkins[1,4]

University of Calgary[1], UCLA Division of Infectious Diseases, Department of Medicine[2], Dalhousie University[3], Alberta Health Services[4]

Introduction

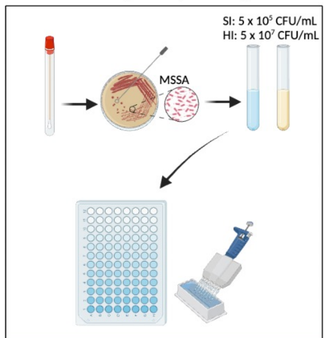
- *Staphylococcus aureus* is one of the most common pathogens in hospital and community-acquired infections making up 20-30% of all bloodstream infections (BSIs).[1]
- Cefazolin (CZ) is a first-generation cephalosporin used as the 1st line of therapy for MSSA BSIs due to its tolerability, minimal toxicity, and convenient dosing.[2]
- Some strains of MSSA have reduced susceptibility at high inoculum (HI: 5 x 10^7 CFU/mL) and/or resistance to CZ, the inoculum effect (IE) and pronounced inoculum effect (pIE), respectively.
- This study investigates the incidence of MSSA strains exhibiting IEs over time across a general population (1.4 million individuals).

Objectives

- Determine the prevalence of MSSA IEs causing BSIs in individuals residing in Calgary, Canada and its association with strain types and to provide a better understanding of HI CZ resistance in BSIs and ultimately, to understand how this influences clinical outcomes.
- Assess the stability of the IE phenotype in patients with recurrent MSSA BSI and its correlation with strain types.

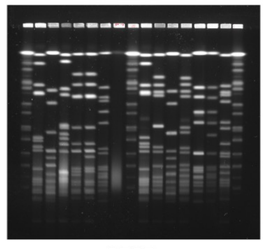
Methods

Susceptibility Testing



- All initial isolates of first episodes of confirmed MSSA BSIs from patients between 2012-2014 and 2019 were included and assessed.
- All isolates were tested for susceptibility with CZ at SI and HI.

Strain Typing



PFGE

- Pulsed-field gel electrophoresis (PFGE) was used to determine strain type of MSSA isolates from patients with recurrent episodes.
- Pulsotypes were broken down to identify common strain types.

Data Analysis

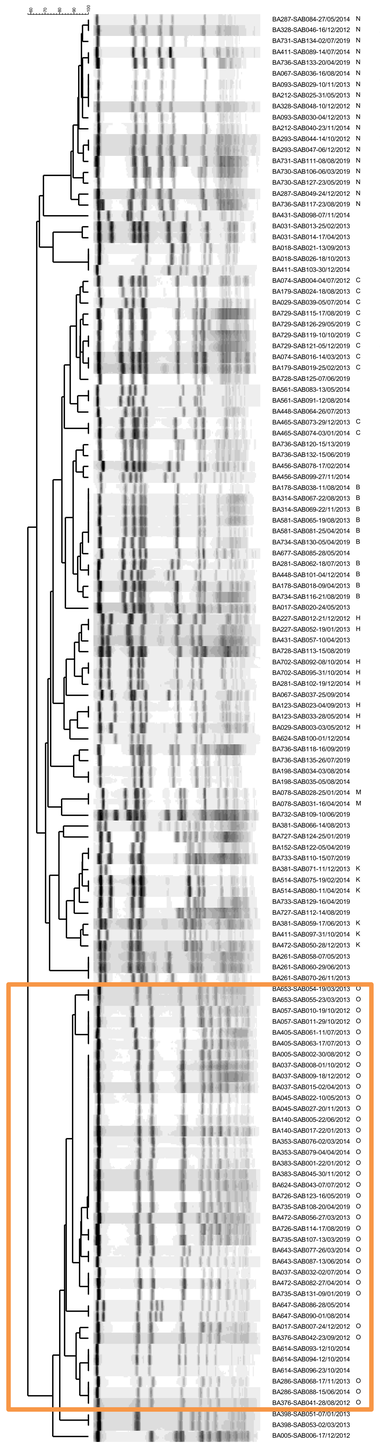
Clinical Data

- Annual incidence rates (IR) were calculated from population data, IE and pIE and IR ratios (IRR) by comparing rates throughout the years.
- A Fischer's exact test (two-tailed) was used to look at statistical associations between wet lab and clinical data.

Acknowledgements

The authors thank the patients who participated in this study. This study was supported by Alberta Precision Labs.

Results



A total of 1040 individuals were included in this study. Each experienced at least one episode of MSSA BSI. Year 2012 had the highest prevalence of IE and year 2014 had highest prevalence of pIE. The mean incidence rates of overall IE and pIE were 6.50 and 0.98 per 100,000 per person-years, respectively. (Figure 1)

- Comparing 2019-2012, rates of IE decreased significantly with an IRR of 0.67 (95% CI 0.47-0.95) but rates of pIE were not significantly changed (IEE 1.24; 95% CI 0.43-3.48).

A total of 128 isolates were typed using PFGE. (Figure 2). Out of 57 individuals with recurrent infections, 44 presented the same strain type (ST) with the remaining having multiple strain types.

- The most common STs identified were ST-30 (28.9%), ST-45 (11.7%), ST-25 (10.2%), and ST-5 (8.6%) which are associated with pulsotype O, N, B, and H, respectively.

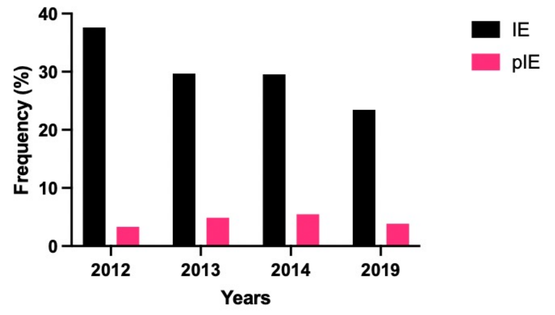


Figure 1 (on top): Frequency distribution of IE and pIE in MSSA isolates tested against cefazolin from 2012-2014 and 2019 in Calgary, Canada.

Figure 2 (on left): PFGE dendrogram of MSSA recurrent isolates from 2012-2014 and 2019. Highlighted is the most common strain type identified.

Table 1: Summary of the total MSSA BSIs tested for CZ susceptibility between 2012-2014 and 2019 compared to population. Number of IE and pIE included alongside MIC50 and MIC90.

Year	Population	Methicillin Sensitive *Staphylococcus aureus*								
		Total BSI	IE	IE per 100,000	pIE	pIE per 100,000	MIC50 (µg/mL)		MIC90 (µg/mL)	
							SI	HI	SI	HI
2012	1,120,225	210	79	7.0	7	0.6	0.5	1	1	8
2013	1,156,686	272	79	7.0	13	1.1	0.5	1	1	8
2014	1,195,114	298	86	7.4	16	1.4	0.5	1	1	8
2019	1,285,711	260	61	4.8	10	0.8	0.5	1	1	4

Contact

Kristine Du
Kristine.du1@ucalgary.ca
University of Calgary, AB, Canada

Conclusion

- The incidence of MSSA BSIs with pIE have not changed but those with the IE have decreased over time.
- CZ IE is associated with ST-30 suggesting a strain-specific phenomenon in MSSA BSIs with no association (P>0.99) between early and late infections.
- Population-based multi-year studies reveal IE and pIE phenotypes that, when combined with clinical data, can aid with understanding future patient outcomes.

References

1. Diekema, J. D., *et. al*. Twenty-Year Trends in Antimicrobial Susceptibilities Among *Staphylococcus aureus* From the SENTRY Antimicrobial Surveillance Program. Open Forum Infectious Disease. 6(1): 37-53. (2019).
2. Wang, K. S., *et. al*. Prevalence of a Cefazolin Inoculum Effect Associated with *blaZ* Gene Types among Methicillin-Susceptible *Staphylococcus aureus* Isolates from Four Major Medical Centers in Chicago. Antimicrobial Agents and Chemotherapy. 62(8): e00328-18. (2018).