

The cefazolin and piperacillin-tazobactam inoculum effects are persistent amongst serial isolates of methicillin-sensitive *Staphylococcus aureus* (MSSA) derived from the sputum of persons with cystic fibrosis, despite variation in other phenotypes.

Svishchuk, J.¹, Waddell, B.J.M.¹, Lee, S.², Rabin, H.¹, Lisboa, L.¹, Gregson, D.¹, Surette, M.³, and Parkins, M.¹

¹University of Calgary, ²University of Alberta, and ³McMaster University



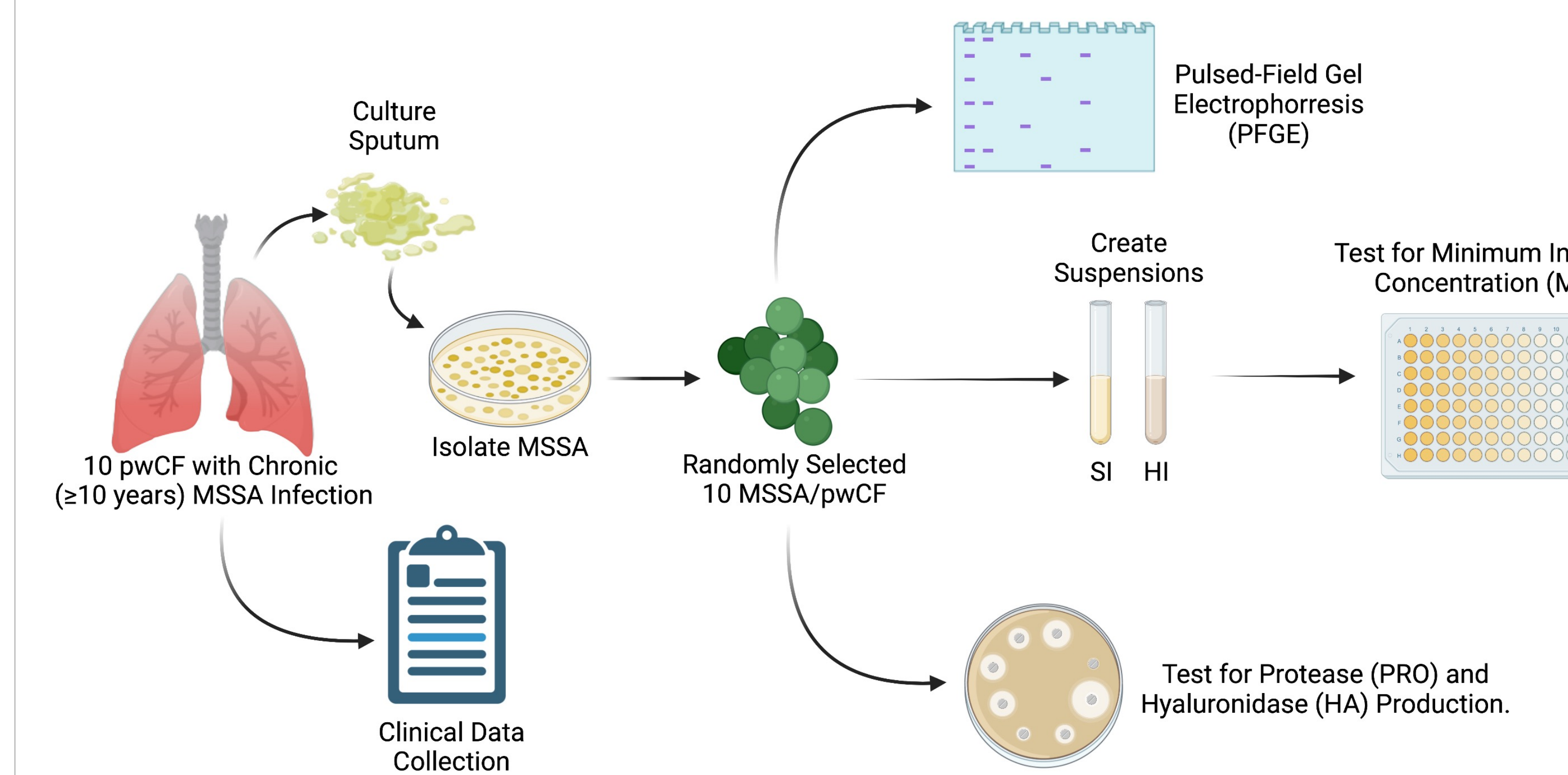
UNIVERSITY OF CALGARY

Poster Number: 511

BACKGROUND & OBJECTIVE

- Cystic fibrosis (CF) is an autosomal recessive disorder, characterized by recurrent and ultimately chronic airways infections¹.
- Staphylococcus aureus* is the most common pathogen isolated from the airways of persons with CF (pwCF)².
- Phenotypic diversity among chronically infecting pathogens in pwCF is increasingly recognized, limiting susceptibility testing-directed decision-making³.
- The inoculum effect (IE) is defined as an increased susceptibility to certain antimicrobials when pathogens are present at high inoculum → predominantly studied in acute infection models⁴.
- We sought to explore variation in IEs amongst serial isolates of methicillin-sensitive *S. aureus* (MSSA) derived from single sputum cultures of pwCF.**

METHODS



- Adults frequenting the Calgary Adult CF Clinic in Alberta, Canada were screened for MSSA production in their sputum.
- 10 individuals with chronic MSSA infection were randomly selected for sputum culture (2015-2016).
- 10 MSSA isolates from each sputum culture were selected, also at random.
 - Total: 100 MSSA isolates**
- All isolates were strain-typed by PFGE (and matched to multilocus sequence types/STs) and assessed for MIC with cefazolin (CZ) and piperacillin-tazobactam (TZP) at standard (SI: 10⁵ CFU/mL) and high inoculum (HI: 10⁷ CFU/mL), as well as PRO and HA production.

RESULTS

- PwCF had a median age of 30.5 years, forced vital capacity of 93%, forced expiratory volume in one second of 66% predicted, and a BMI of 21.5 kg/m².
- Amongst the 10 patients, median sputum MSSA burden was 10⁶ CFU/mL.
- The IE was more common with TZP than CZ: 47% vs 33%, respectively.
- Median MIC₅₀ and MIC₉₀ for CZ increased between SI and HI; MIC₅₀: 0.5 to 1µg/mL, MIC₉₀: 2 to 32µg/mL and TZP; MIC₅₀: 2 to 4µg/mL, MIC₉₀: 8 to 128µg/mL (p<0.0001 for all).
- The most prevalent pulsotypes identified corresponded to multilocus sequence types (ST)-5 (20%), ST-30 (15%), and ST-1 (5%), where ST-30 isolates were more likely to exhibit the CZ and TZP IE (p<0.0001 for both).
- 8/10 patients had all isolates belonging to the same pulsogroup. Of patients infected with a single strain, discordance between IE phenotype was not noted, though PRO and HA production varied. Among these patients, the standard deviation of zone clearance diameter ranged from 0-0.9cm (mean range: 0-1.4cm) and 0-1.8cm (mean range: 0-7.2cm), respectively, between individual isolates.

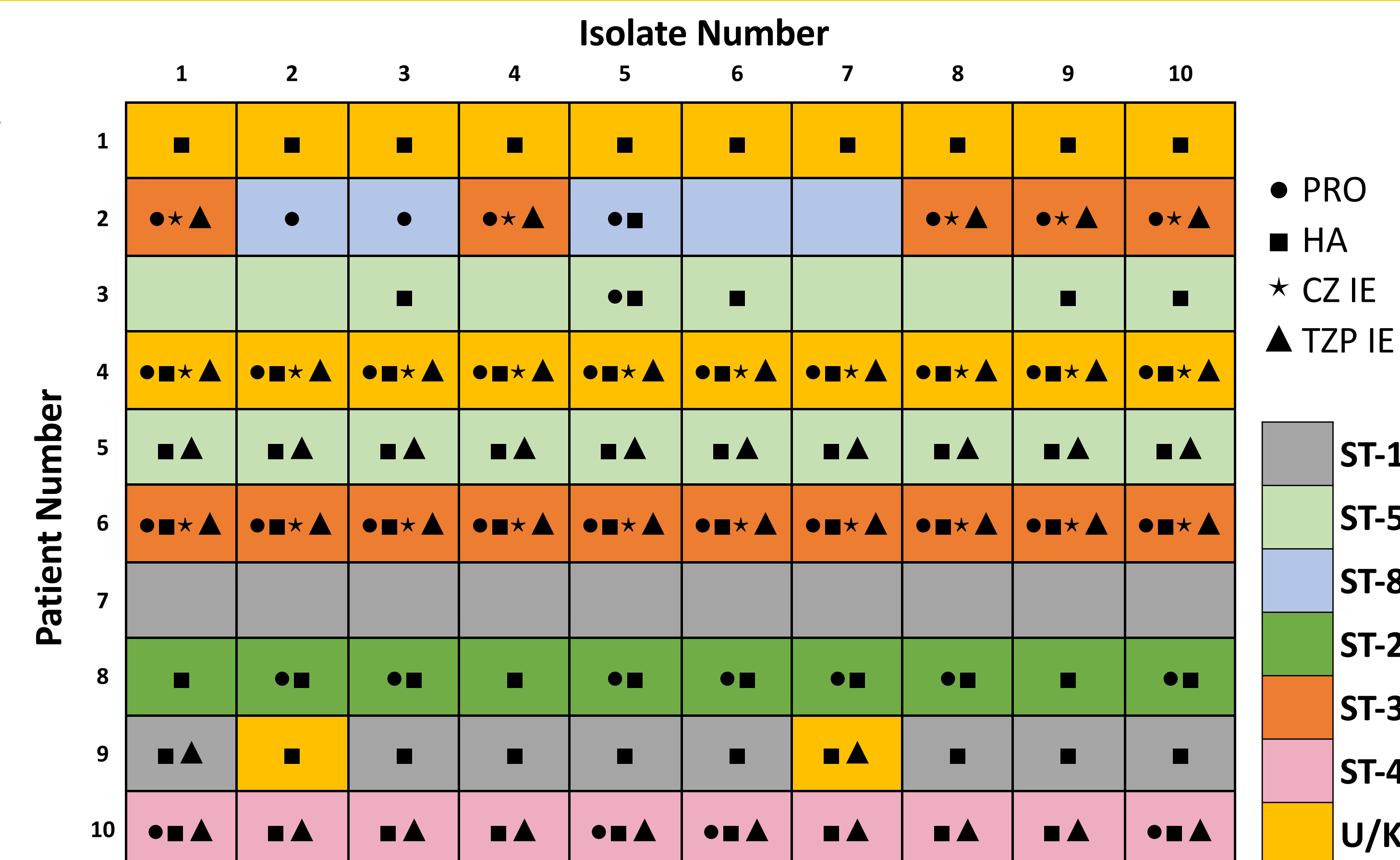


Figure 1: Phenotypic profiles of 100 MSSA isolates, derived from 10 pwCF, including protease production (PRO), hyaluronidase production (HA), the cefazolin inoculum effect (CZ IE) and the piperacillin-tazobactam inoculum effect (TZP IE), across identified or unknown (U/K) multilocus sequence types (STs). Each set of 10 isolates was derived from one sputum culture, obtained from individuals with chronically infecting MSSA.

CONCLUSIONS & FUTURE DIRECTIONS

- Previous studies have noted associations between inoculum effects and strain type⁵ → this study supports the IE as a strain-, rather than person-specific phenomenon.
- Phenotypic profile varies depending on the strain of MSSA selected, indicating a necessity for considering strain variation amongst single sputum cultures in pwCF.
- Given previous findings where IEs were found to associate with worse patient outcomes⁴, improved means of detecting MSSA phenotypic behavior in the clinic is warranted.

REFERENCES

- Lyczak JB, Cannon CL, Pier GB. Lung Infections Associated with Cystic Fibrosis. *Clin Microbiol Rev.* 2002;15(2):194-222. doi:10.1128/CMR.15.2.194-222.2002.
- Hurley MN. *Staphylococcus aureus* in cystic fibrosis: problem bug or an innocent bystander? *Breathe.* 2018;14(2):87-90. doi:10.1183/20734735.014718.2019;18(2):236-243. doi:10.1016/j.jcf.2019.01.008.
- Somayaji R, Parkins MD, Shah A, et al. Antimicrobial susceptibility testing (AST) and associated clinical outcomes in individuals with cystic fibrosis: A systematic review. *J Cyst Fibros.* 2019;18(2):236-243. doi:10.1016/j.jcf.2019.01.008.
- Miller WR, Seas C, Carvajal LP, et al. The Cefazolin Inoculum Effect Is Associated With Increased Mortality in Methicillin-Susceptible *Staphylococcus aureus* Bacteremia. *Open Forum Infect Dis.* 2018;5(6):ofy123. doi:10.1093/ofid/ofy123.
- Rincón S, Reyes J, Carvajal LP, et al. Cefazolin high-inoculum effect in methicillin-susceptible *Staphylococcus aureus* from South American hospitals. *J Antimicrob Chemother.* 2013;68(12):2773-2778. doi:10.1093/jac/dkt254.

Contact Information:
Julianna Svishchuk
 Graduate Student
 University of Calgary
 jsvishchuk@ucalgary.ca

