307. Rapid Resistance Development to Three Antistaphylococcal Therapies in Daptomycin-tolerant *Staphylococcus aureus* Bacteremia

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Session: P-9. Bacteremia

Background: We report a patient case of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia which over 30 days developed resistance to all three primary antistaphylococcal antibiotics. Index blood cultures displayed susceptibility to vancomycin (VAN, MIC=1), ceftaroline (CPT, MIC=0.5) and daptomycin (DAP, MIC=0.5). The patient was maintained on VAN/CPT with negative blood cultures by hospital day 7. The regimen was later modified to DAP/piperacillin-tazobactam. One month after initial presentation, during the same encounter, blood cultures were again positive for MRSA, now displaying intermediate resistance to VAN (MIC=2) and CPT (MIC=2), and resistance to DAP (MIC=4).

Methods: Isolates were collected from the initial bacteremia episode (B325) and the recurrence (B326). *In-vitro* one-compartment pharmacokinetic/pharmacodynamic modeling was performed on each isolate to determine which antibiotics or combinations would effectively eradicate cultures. Regimens examined included DAP (10mg/kg), DAP/cefazolin (CFZ), VAN/CFZ and penicillin/clavulanate. Draft whole-genome sequences are pending for each clinical isolate using hybrid assembly (Unicycler v0.4.2) of MinION and Illumina (150bp PE) reads.

Results: DAP/CFZ combination reduced viability of both B325 and B326 below limit of detection by 12 hours and maintained efficacy for 72 h. DAP, initially effective in reducing B326 cell concentrations below limit of detection, allowed regrowth by 36 h. All other modeled therapies were less effective. Interestingly, DAP took significantly longer to kill B325 relative to *S. aureus* collected contemporaneously from other patients. For DAP-containing regimens, the time to 3-log viability reduction ($MDK_{99.9}$) was five-fold longer in B325 compared to similar clinical isolates with the same DAP MIC. Comparative genomics of sequential isolates is pending, although single nucleotide polymorphisms in *vraT* and *mprF* were identified in B326 compared to B325.

Conclusion: Delayed kill kinetics of B325 when exposed to DAP may indicate antibiotic tolerance, which could partially account for B325's rapid transition to a multi-drug resistant organism. DAP/CFZ therapy appears to be the most active combination against both antibiotic-tolerant and multidrug resistant *S. aureus* strains.

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308. Re-purposing Beta-lactam Antibiotics as Fluoroquinolone Sparing Stepdown Therapy for the Treatment of Enterobacteriales Bloodstream Infections

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Session: P-9. Bacteremia

Background: Oral antimicrobial therapy for Enterobacteriales bloodstream infection (EB-BSI) is advantageous to reduce the risk of central line complications, cost of care, and length of stay. Fluoroquinolones (FQ) given their high bioavailability have been utilized as the standard for stepdown therapy (SDT) for EB-BSI. Given the recent increased warnings around FQ use including *Clostridioides difficile* infection (CDI) and the increasing FQ resistance alternative oral options for treatment are warranted. Recent literature has suggested beta-lactams (BLM) may be an option for EB-BSI. To enhance the antimicrobial stewardship goal of reducing FQ use, our team began recommending de-escalation to a BLM for EB-BSI and the objective of this study is to evaluate the outcomes of this approach.

Methods: This study was a retrospective chart review of patients with EB-BSI due to ceftriaxone sensitive monomicrobial *E. coli, Klebsiella spp.,* or *P. mirabilis* who received a BLM or a FQ as SDT. Patients were excluded if < 18 years of age; pregnant; ANC < 1000 cells/μL; had endocarditis, a bone/joint, or a CNS infection; discharged to hospice or expired prior to discharge; anaphylactic BLM allergy; or prior kidney transplant. SDT was defined as a switch to a definitive oral antibiotic after empiric IV therapy. The primary outcome was clinical cure defined as completion of therapy without signs of infection (increase in WBC > 2000 cells/mL if WBC was ≥ 12,000 cells/mL, fever (>38°C), or change in antibiotic due to failure). Secondary outcomes included 30 day re-admission rates, reinfection rate defined as positive culture within 30 days of completion of therapy, antibiotic associated adverse events defined as side effects leading to discontinuation and/or CDI within 90 days from start of treatment.

Results: A total of 159 patients were included in the study (Figure 1). The BLM patients had a higher median age (78 vs 72, p=0.008), higher median PITT bacteremia score (2 vs 1, p=0.037), were less likely to be immunosuppressed (9% vs 25%, p=0.045), and had shorter median duration of therapy (13 vs 14, p=0.034). There was no difference in the primary or secondary outcomes (Table 2).

Figure 1. Inclusion and Exclusion

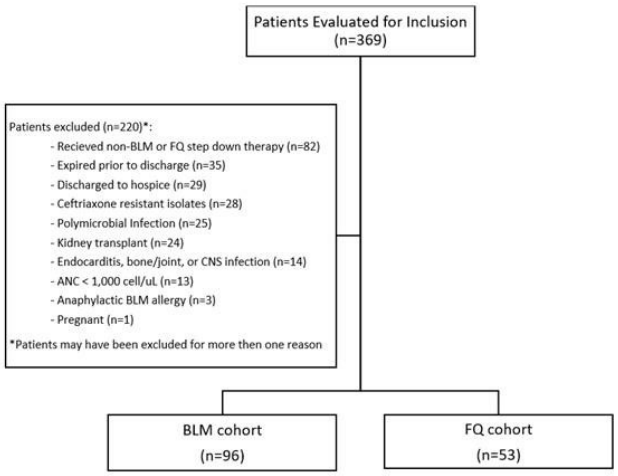

Table 1. Baseline and Clinical Characteristics

Baseline Demographics	BLM (n=96)	FQ (n=53)	P-value
Age, median (IQR)	78 (70-84)	72 (65-80)	0.008
Female Sex, n (%)	47 (49)	19 (36)	0.121
Body Mass Index 30-40 Kg/m², n (%)	30 (31)	13 (25)	0.5
Body Mass Index ≥40 Kg/m², n (%)	10 (10)	6 (11)	0.715
Chronic kidney disease (Stage III or greater), n (%)	15 (16)	12 (23)	0.359
Dialysis, n (%)	1(1)	2 (4)	0.339
Heart failure, n (%)	17 (18)	7 (13)	0.463
Cirrhosis, n (%)	3 (3)	2 (4)	0.839
Diabetes, n (%)	42 (44)	18 (34)	0.762
Neurogenic bladder, n (%)	7 (7)	4 (8)	0.955
History of Malignancy, n (%)	30 (31)	21 (40)	0.207
Immunosuppression*, n (%)	9 (9)	13 (25)	0.045
Chronic indwelling Foley catheter, n (%)	14 (15)	4 (8)	0.099
Charlson comorbidity index, median (IQR)	3 (2-4)	3 (2-4)	0.11
PITT score, median (IQR)	2 (1-3)	1 (1-2)	0.037
Clinical Characteristics			
Source of infection			
• Urinary Tract	69 (72)	37 (70)	0.793
• Biliary	17 (18)	9 (17)	0.911
• Gastrointestinal	5 (5)	1 (2)	0.263
• Pneumonia	2 (2)	2 (4)	0.577
• Other	2 (2)	1 (2)	0.935
• Central line associated bloodstream infection (CLABSI)	1 (1)	3 (6)	0.175
Empiric Antimicrobial Therapy^, n (%)			
• Piperacillin/tazobactam or ceftazidime	73 (76)	46 (87)	0.1
• Ceftriaxone	23 (24)	13 (25)	0.95
• Fluoroquinolone	8 (8)	1 (2)	0.1
Step Down Therapy, n (%)			
• Cefuroxime	60 (63)	0	N/A
• Amoxicillin/clavulanic acid	18 (19)	0	
• Cephalexin/cefadroxil	11 (11)	0	
• Amoxicillin	6 (6)	0	
• Cefpodoxime	1 (1)	0	
• Ciprofloxacin	0	52 (98)	
• Levofloxacin	0	1 (2)	
Days from empiric to oral therapy, median (IQR)	3 (2-5.25)	3 (2-5)	0.469
Total days of antibiotic therapy, median (IQR)	13 (9-15)	14 (12-15)	0.034

*Cancer treatment within 1 year, the use of an immunosuppressive drug (TNF-alpha agents, prednisone ≥ 20 mg or equivalent, mycophenolate, sirolimus, rituximab, vedolizumab, abatacept, eculizumab), bone marrow transplant recipient, human immunodeficiency virus, acquired immunodeficiency syndrome, leukemia, lymphoma, solid organ transplant recipient, lupus erythematosus & vasculitis
^Empiric therapy could have included multiple agents

Table 2. Results

Result	BLM (n=96)	FQ (n=53)	P-value
Clinical cure, n (%)	95 (99)	52 (98)	0.7
30 Day Re-admission, n (%)	17 (18)	12 (23)	0.483
30 Day Re-admission due to any infection, n (%)	5 (5)	5 (9)	0.366
Antibiotic associated adverse events, n (%)	0 (0)	2 (4)	0.16
• Diarrhea	0 (0)	1	
• Nausea/vomiting	0 (0)	1	
• Cardiotoxicity	0 (0)	0	
• Nephrotoxicity	0 (0)	0	
• Hepatotoxicity	0 (0)	0	
CDI within 90 days from start of treatment	1 (1)	2 (4)	0.34

Conclusion: BLM may enhance stewardship efforts as a FQ sparing option for treatment of EB-BSI; however, prospective studies in this area are warranted.

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