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140. Evolution of Antibiotic Tolerance During Oxacillin, Daptomycin and Dalbavancin Therapy Results in Breakthrough Staphylococcus aureus Bacteremias

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Background. Clinicians can employ suppressive antimicrobial therapy in patients with persistent or relapsing bacteremia. However, bacteria with favorable susceptibility profiles may exhibit antimicrobial tolerance wherein bacteria cannot proliferate yet can survive in high concentrations of antibiotics. The antimicrobial tolerance phenotype can thwart efforts to prevent bacteremia recurrence with prolonged exposure to antimicrobials and may contribute to breakthrough bacteremias while the patient is receiving active therapy. Here we present a patient case consisting of multiple episodes of breakthrough Staphylococcus aureus bacteremia over several years in the setting of appropriately dosed antimicrobial suppressive therapy and describe organism mutations that developed during therapy.

Methods. Six clinical bloodstream isolates were recovered from the patient during distinct episodes of MSSA bacteremia over a 5-year period. The identified source for each bacteremia was a central line infection (CLABSI). Isolates recovered were susceptible to the individual therapies received, which included oxacillin, daptomycin, and dalbavancin. Bacterial whole genome sequence data were collected using Illumina technology.

Results. The first two isolates (USA600) and the last four isolates (USA800) represent distinct populations and suggest that a distinct MSSA strain displaced the previous population between bacteremia episodes 2 and 3. Of note, all of these strains were able to survive and establish breakthrough bacteremias despite favorable susceptibility profiles to the agents used as suppressive therapy. Although the MICs remain low and in the susceptible range to oxacillin, daptomycin, and dalbavancin, these isolates progressively developed significant antimicrobial tolerance phenotypes, which coincided with mutations in walK (yycG), htrA2, fnw, ebb and sarB that may be advantageous to survival under antibiotic pressure.

Conclusion. These genetic, phenotypic and patient case data identify important changes that can occur in bacterial populations over time that are distinct from antibiotic susceptibility. These findings point to factors that may result in breakthrough bacteremia, limiting the clinical utility of antimicrobial suppressive therapy.

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141. Carbapenem-resistant Enterobacteriaceae (CRE) or Delayed Appropriate Therapy (DAT)—Does One Affect Outcomes More Than the Other Among Patients With Serious Infections Due to Enterobacteriaceae

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Background. While CRE and DAT are both associated with worse outcomes, their relative impact to the clinical and economic burden among patients with infections due to Enterobacteriaceae is not well understood. This study assessed the independent and combined effect of these two items on selected outcomes among patients with these infections.

Methods. Hospitalized adults between July 2011 and September 2014 were identified from Premier Hospital Database. Patients were diagnosed with complicated urinary tract infection, complicated intra-abdominal infection, hospital-associated pneumonia, or bloodstream infection, and had a positive culture for Enterobacteriaceae from a site consistent with infection type (date of culture draw was index date). Patients were required to receive antibiotics on this date or ≤2 days after. Delayed therapy was defined as receipt of an antibiotic with microbiologic activity against the pathogen after 24 hours from the index culture draw. CRE was defined as resistant to ≥1 carbapenems. Inverse probability weighting and multivariate regression analyses were used to estimate the associations between CRE status, DAT and outcomes. Logistic models were used for composite mortality (in-hospital death and discharge to hospice), in-hospital mortality, and discharge to home (reference group was timely therapy plus non-CRE); generalized linear models, for post-index duration of antibiotic therapy, hospital length of stay (LOS), and costs.

Results. A total of 50,669 patients were included in the analyses; 514 had CRE and 16,114 received DAT. A gradient effect was observed across strata as the burden of serious infections was least among the reference group, and greatest among patients with CRE infection who received DAT (Figure). For example, as compared with the reference group, the risk of composite mortality increased nearly fourfold in patients with CRE infection who received DAT, total in-hospital costs more than doubled.

Conclusion. DAT has a stronger association than CRE on outcomes, and their effects are synergistic. Given these findings, better methods of early pathogen identification (especially organisms such as CRE) should reduce time to appropriate therapy, thereby improving outcomes in this patient population.