82. The Association of Molecular Characteristics, Vancomycin MIC and Clinical Outcomes in Methicillin-susceptible Staphylococcus aureus Osteoarticular Infections in Children

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Background. Methicillin-resistant Staphylococcus aureus, particularly those belonging to the USA300 pulsotype and bearing Panton-Valentine leukocidin (pvl) have been well described to cause severe osteoarticular infection (OAI). Vancomycin minimum inhibitory concentration (MIC) ≥ 1.5 µg/ml has been demonstrated to contribute to disease severity in MRSA bacteremia. Little data exist to describe the spectrum of outcomes in MSSA OAI in terms of molecular characteristics and vancomycin MIC.

Methods. OAI isolates were identified from 2011 to 2016 and subjected to vancomycin E-tests. MSSA isolates underwent PFGE, PCR for pvl, and a stepwise assay to determine accessory gene regulator (agr) group. A review of the medical record was performed. Orthopedic complications included chronic osteomyelitis, pathologic fracture, and growth arrest.

Results. During the study period, 167 cases of S. aureus OAI were identified; 115 were MSSA (68.9%). 29.1 and 26.1% of MSSA isolates were USA300 and pvl positive, respectively. USA300 isolates were more likely to be pvl positive (66.7% v 13.6%, P < 0.001) and agr I (80% v 57.5%, P = 0.001). The presence of pvl was associated with agr I (P = 0.03), larger abscesses (6 v 2 cm, P = 0.04), ICU admission (16.7 v 3.5%, P = 0.03) and a longer length of stay (11 v 6 days, P = 0.05). agr III and IV were associated with a higher rate of orthopedic complications (36.4 v 13.9%, P = 0.03) and surgical procedures (90.1 v 64.5%, P = 0.02) than other agr groups. An increase in the proportion of MSSA isolates with a vancomycin MIC ≥ 1.5 µg/ml occurred in the study period (P = 0.007, Figure 1). In MSSA, vancomycin MIC ≥ 2 µg/ml was associated with agr III (p = 0.07) and higher rates of orthopedic complications (P = 0.08) and venous thrombosis (P = 0.06, Figure 2).

Conclusion. MSSA accounts for 70% of S. aureus isolates causing OAI at TCH. While pvl-positive strains are associated with worse short-term outcomes, agr III and IV are associated with long-term morbidity. Vancomycin E-test MICs appear to be increasing among MSSA; vancomycin MIC ≥ 2 µg/ml has been demonstrated to contribute to disease severity in MRSA bacteremia. Little data exist to describe the spectrum of outcomes in MSSA OAI in terms of molecular characteristics and vancomycin MIC.

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83. Impact of Vancomycin Serum Trough Concentrations and Vancomycin AUC/MIC on Vancomycin Response, In-Hospital Outcomes and Acute Kidney Injury in Pediatric Staphylococcus aureus Pneumonia

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Background. Vancomycin AUC/MIC > 400 was initially shown to be beneficial in adults with staphylococcal pneumonia. Current practice guidelines recommend targeting serum vancomycin trough concentrations (VTC) of 15–20 µg/ml in adults with severe MRSA infection to approximate these AUC/MIC goals. Small studies have shown no benefit to VTC > 15 µg/ml in children with osteomyelitis or bacteremia. We describe the impact of VTC and AUC/MIC on outcomes of pediatric S. aureus pneumonia.

Methods. Cases of S. aureus pneumonia from January 1, 2011 to December 31, 2016 were reviewed. Patients treated with vancomycin <48 hours were excluded. Serum vancomycin weighted response (SVR) was considered any combination of duration of fever, bacteremia, ICU stay, ventilator or hospital days or rates of SVR between patients with VTC > or <15 µg/ml. There were substantial increases in rates of AKI with higher VTC (66.7 vs. 24.2%, P < 0.001). Among 23 patients for whom AUC/MIC determinations were possible, none achieved an AUC/MIC >400; the median AUC/MIC = 42 (IQR: 32–51). Eighty-eight% of isolates had an MIC ≥1.5 µg/ml. There was no correlation between values of AUC/MIC and length of ICU or hospital stay or SVR (AUROC 0.45).

Conclusion. While the sample size is limiting, VTC >15 µg/ml did not provide clinical benefit in children with S. aureus pneumonia compared with lower VTC levels; while at the same time predisposing to nephrotoxicity. AUC/MIC >400 is rarely achieved in children with S. aureus pneumonia and may not be a realistic goal in this infection given the rarity with which this occurs, the frequency of high MICs and the very young age of the typical patient. Large multicenter studies are required to understand optimal vancomycin dosing and monitoring in children with invasive MRSA infections.

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Conclusion. While rates of treatment failure in children diagnosed with CAP in the outpatient setting were low, macrolides were associated with a lower failure rate than treatment with β-lactams. This may be due to residual confounding by indication or changing epidemiology of outpatient pneumonia.

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85. Comprehensive Detection of Pathogens in Immunocompromised Children with Bloodstream Infections by Next-generation Sequencing
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Background. Bloodstream infection (BSI) is a severe complication in immunocompromised patients. Prompt identification of causative microorganisms would improve the outcome of BSI due to optimization of antimicrobial treatment. Next-generation sequencing (NGS) allows us to analyze comprehensively and quantitatively all microorganisms present in a clinical sample in comparison with blood culture. However, there are currently no established methods to identify causative pathogens by NGS.

Methods. BSI was defined by the following criteria in a clinical setting: (i) pathogen isolated from blood culture and (ii) fever ≥38°C or C-reactive protein >1.0 mg/dl. Thirty-five pediatric patients (12 with BSI and 23 with suspected BSI/negative blood culture) were enrolled. Plasma/serum samples were used for sequencing and the results were compared with those from blood culture. The bacterial reads per million reads of the sequence depth (BR) and relative importance values of the dominant bacteria (P1) were applied to identify causative pathogens.

Results. Sequencing reads of bacteria isolated in blood culture were identified by NGS in all plasma/serum samples at the onset of BSI. Additionally, bacteria isolated in blood culture were identical to the dominant bacteria by NGS in 8 of 12 patients with BSI. Causative microorganisms were detected when the NGS results fulfilled the criteria of BR >200 and P1 >0.5. In two patients with catheter-related BSI, causative bacteria were detected in the plasma/serum at 7 days before disease onset. Causative pathogens (Tatlockia micdadei, Escherichia coli, and human adenovirus 2) were identified in three of 23 patients in the suspected BSI group. A total of 62 resistance genes were detected in nine patients with sequences covering 5–100% of references.

Conclusion. An NGS-based approach has great potential for analysis of causative microorganisms in BSI and may help to diagnose a disease before disease onset. Antimicrobial resistance genes can also be found through sequence data processing.

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