Vancomycin Heteroresistance in Coagulase Negative Staphylococci (CoNS) Causing Central Line Associated Bloodstream Infection (CLABSI) in Pediatric Patients With Leukemia

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ABSTRACT

Vancomycin is the last resort treatment option against infections caused by multi-antibiotic resistant bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA). However, therapeutic failures with vancomycin have been reported in heterogeneous vancomycin-intermediate S. aureus (hVISA) cases where clinical testing showed susceptibility to vancomycin. In a heterogeneous population, the majority of the population is susceptible to vancomycin, while a small proportion of bacterial cells demonstrate intermediate resistance to vancomycin. Vancomycin resistance is a significant threat to the healthcare community when it occurs in multi-resistant or opportunistic pathogens, for example S. epidermidis and S. haemolyticus. To further confound the situation, many patients undergoing immunosuppressive therapy, such as chemotherapy, are treated with vancomycin for months as a prophylaxis against bacterial infection. In this retrospective study, we aimed to evaluate frequency, risk factors, and clinical impact of heteroresistance in CoNS CLABSI in immunocompromised patients at St. Jude Children’s Research Hospital. Population analysis profiles (PAP) were performed in a double-blinded fashion to detect hVIsps (heterogeneous vancomycin-intermediate staphylococci species) from 74 clinical isolates obtained from 69 patients undergoing treatment for leukemia with CoNS isolated from the blood between 2010 and 2016. These clinical isolates were then compared to the hVISA strain Mu3. Clinical data regarding vancomycin exposures, identity of the Staphylococcal species responsible for the bloodstream infection, and vancomycin therapeutic outcomes were collected and tested for associations with vancomycin heteroresistance results from PAP analysis. From all first CoNS infection episodes, 25/69 (36%) showed heteroresistance to vancomycin. We concluded that the longer the duration of vancomycin treatment, the higher the risk of having an infection with a heteroresistant CoNS. Our results suggest that vancomycin exposure may induce the emergence of hVIsps in an immunocompromised patient. Understanding the effect of long-term vancomycin prophylaxis and the mechanism of hVIsps would lead to the implementation of more selective antimicrobial use and the development of strategies for diagnosis and alternative antibiotics that are more affordable.

METHODS

Population Analysis Profile (PAP)

Isolates With Heteroresistance Phenotype

RESULTS

Risk for vancomycin heteroresistance is associated with cumulative vancomycin exposure

Heteroresistance predicts poor response to vancomycin and treatment failure

CONCLUSIONS

- Long-term vancomycin exposure promotes the development of vancomycin heteroresistance in CoNS responsible for CLABSI in pediatric patients with leukemia.
- Vancomycin heteroresistance is associated with poor response and treatment failure.

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Figure 1: PAP curves of controls and select clinical isolates classified as vancomycin-susceptible and heterogeneous vancomycin-intermediate staphylococci (hVISA). hVISA, a positive control for heterogeneous vancomycin-intermediate 3. aureus strain (hVISA) is shown in red with its AUC being shaded. VRE, a vancomycin-resistant enterococcal strain, serves as a positive control for resistance, is shown in black, whereas MRSA, a vancomycin-susceptible S. aureus strain, serves as a negative control (shown in green). Strains 2.0 (g/mL) and 4.20 (hVISA, light green) are two examples of the clinical isolates. Bacterial growth was expressed in log10 CFU/mL.

Figure 2: PAP analysis results. Area under the Curve (AUC) of each clinical isolate was compared to that of Mu3, the standard hVISA strain. Isolates that have AUC > 2.0 are classified as heteroresistant.