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Session: P-72. Resistance Mechanisms

Background. The cefazolin (Cz) inoculum effect (CzIE), defined as an increase in the Cz MIC to ≥26 μg/mL at high inoculum (10^3 CFU/mL), has been associated with poor outcomes in MSSA bacteremia and osteomyelitis. The CzIE is associated with the BlaZ β-lactamase, encoded by blaZ and regulated by BlaR (antibiotic sensor) and BlaI (transcriptional repressor). Here, we aimed to obtain a machine-learning (ML) model to predict the presence of the CzIE based on the nucleotide sequence of the entire bla operon and its regulatory components.

Methods. Using whole genome sequencing, we analyzed the nucleotide sequences of the entire bla operon in 436 MSSA isolates recovered from blood, soft-tissue infections or pneumonia in adults (training-testing cohort, prevalence of the CzIE: 46%). Also, 32 MSSA recovered from pediatric patients with osteomyelitis with the CzIE were included as validation cohort. The CzIE was determined by broth microdilution at high inoculum. K-mer counts were obtained from the bla operon sequences of the isolates from the testing-training cohort, and then used in a ML pipeline which i) discards uninformative K-mers, ii) identifies optimal hyper-parameters and, iii) performs training of the model using 70% of the sequences as training set and 30% as testing set. The pipeline tested 11 different K-mer sizes and 2 models: Logistic Regression (LR) and Support Vector Machine (SVM). Finally, the model with best predictive ability was applied to the sequences of the MSSA osteomyelitis isolates (validation cohort).

Results. The ML approach had high specificity (>90%), accuracy (>80%) and ROC-AUC values (>0.7) for detecting the CzIE in the testing set of isolates (Figure 1), independently of the type of model or the K-mer size used. The best predictive ability was with LR using K-mers of 17 nucleotides, with an accuracy of 84%, specificity of 96%, and sensitivity of 70% in the testing set (Figure 2). In the validation cohort, the model was capable to correctly identify all the strains exhibiting the CzIE (100% sensitivity).

Conclusion. The ML approach is a promising genomic application to detect the CzIE in MSSA isolates from the testing-training cohort. Predictions are shown accordingly to the model and K-mer sizes tested.
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1250. Development of Linezolid and Daptomycin Resistance in Vancomycin Resistant Enterococcus faecium (VRE) during prolonged treatment for Intraabdominal Abscess

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Session: P-72. Resistance Mechanisms

Background. Vancomycin-resistant enterococci (VRE) are nosocomial pathogens with extensive intrinsic and acquired antimicrobial resistance (AMR) mechanisms. We report a case in which intraabdominal (IA) and blood cultures grew linezolid and daptomycin resistant VRE (DLVRE).

Methods. We report a case of DLVRE bacteremia after prolonged treatment with linezolid and daptomycin.

Results. The patient was a 65-year-old female with a history of multiple abdominal surgeries who presented for elective incisional hernia repair. Her post-operative course was complicated by the development of loculated IA abscesses. A drain was placed into the largest abscess, and aspiration cultures were polymicrobial containing vancomycin-resistant E. faecium (Isolate 1). The patient was treated meropenem, fluconazole and linezolid for 6 weeks. Clinical and radiographic improvement was achieved. However, 4 days after completing antibiotics she developed recurrent abdominal pain and a leukocytosis. Daptomycin was chosen out of concern for long-term linezolid toxicity and IA cultures demonstrated new linezolid resistance (Isolate 2, LVRE). After an additional three weeks of therapy, she developed a catheter-associated bloodstream infection (CLABSI). Blood cultures revealed daptomycin-resistant LVRE bacteremia (Isolate 3, DLVRE). She was started empirically on a combination of cefaroline and daptomycin, her PICC line removed, and her blood cultures cleared. Her antibiotic course is presented in Figure 1 and resistance patterns of the VRE in Table 1.

Conclusion. In this patient, an IA abscess known to harbor VRE developed resistance to both linezolid and daptomycin during prolonged treatment with both agents. Ultimately, the patient experienced an episode of CLABSI DLVRE. Limited data exists on appropriate antibiotic choice in such challenging situations. Based on prior clinical and experimental data, we elected to use daptomycin in conjunction with cefaroline for synergy, and the patient achieved the desired clinical response, clearance of her blood cultures and diminishing size of her IA abscess. Further work is needed to elucidate the best course of treatment for patients with VRE requiring long-term antibiotic therapy and for those who have developed extensively drug-resistant E. faecium.

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1251. Comparative Evaluation of Phenotypic Synergy Tests vs. Resist-4 O.K.N.Y. and NG Test Carba 5’ Lateral Flow Immunoassays for the Detection and Differentiation of Carbapenemases in Enterobacteriaceae and Pseudomonas aeruginosa

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Session: P-72. Resistance Mechanisms

Background. The spread of carbapenem resistant Pseudomonas aeruginosa and carbapenemase-producing Enterobacteriaceae (CPE) has had a great impact on morbidity and mortality. COVID-19 pandemic has favored the selection of these microorganisms because of the excessive and prolonged use of broad-spectrum antibiotics and the outbreaks related to patient transfer between hospitals and inadequate use of personal protective equipment. Therefore, detection is considered essential for their control. Our aim was to compare conventional phenotypic synergy tests and two lateral flow immunoassays for detecting carbapenemases in Enterobacteriaceae and P. aeruginosa.

Methods. We analysed 100 carbapenem-resistant Gram-negative bacilli isolates, 80 Enterobacteriaceae and 20 Pseudomonas aeruginosa, (86 isolates producing KPC, NDM, OXA-48, IMP and VIM carbapenemases and 14 non-carbapenemase-producing isolates). We performed a modified Hodge test, boronic acid and ethylenediamine-tetraacetic acid (EDTA) synergy tests, and two lateral flow immunoassays: RESIST-4 O.K.N.Y (Coris Biotechnics®) and NG Test Carba 5’ (NG Biotech®).

Results. In total, 76 KPC, 7 VIM, 1 NDM, 1 OXA-48 and 1 isolate coproducing KPC + NDM enzymes were included. The concordance of different methods estimated by Kappa index was 0.432 (Standard error: 0.117), thus showing a high variability with the synergy tests with boronic acid and EDTA and reporting 16 false negatives that were detected by the two immunochromatographic methods. Co-production was only detected using immunoassays.

Figure 1. Errors in synergy tests.

1) KPC-producing K. pneumoniae not detected with boronic acid and EDTA (1a). Positive result adjusting distance to 5 mm (1b) and positive result by NG Test Carba 5’ and RESIST-4 O.K.N.Y immunooassays (1c). 2) VIM-producing P. aeruginosa with inconclusive EDTA result (2a), Positive result adjusting distance to 5 mm (2b), confirmation of VIM by immunooassay (2c). 3) K. pneumoniae with KPC and NDM co-production without synergistic effect with boronic acid or EDTA (3a), positivity for both enzymes by immunooassay (3b). 4) Impact of distance between disks: False negative for serine-carbapenemases with 15 mm (4a) positive result at 10 mm (4b). Differences in boronic acid tests for serin-carbapenemases at 10 mm, 5 mm and 0 mm distance (4c, 4d). Differences in synergy between imipenem, meropenem and etarpenem discs at 0 mm distance (4e).

Table 1. Minimal Inhibitory Concentrations (MIC) for the patient’s samples of E. faecium as reported by Northwestern Memorial Hospital’s clinical microbiology laboratory.

Table 2. Results of synergy methods and immunoassay tests for Enterobacteriaceae and Pseudomonas aeruginosa