Background. Ceftolozane-tazobactam (TOL-TAZ) is a novel cephalosporin antibiotic combined with a known β-lactamase inhibitor. It has activity against some extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and multidrug-resistant Pseudomonas aeruginosa (MDRPA). To date, little experience has been published on outcomes with TOL-TAZ for MDRPA infections in immunocompromised patients.

Methods. This was a retrospective study of adult patients (≥18 years) with an immunocompromising condition (solid-organ transplant; hematologic malignancy; solid tumors; metabolic cancer) at 20 academic medical centers who had microbiologically confirmed MDRPA isolated in culture and received TOL-TAZ for at least 24 hours. 30-day survival, in-hospital mortality, and the rates of microbiologic and clinical cure were assessed.

Results.

| Characteristic                  | Result (n = 65)                                                                 |
|--------------------------------|------------------------------------------------------------------------------|
| Immunocompromising condition   | n (%)                                                                       |
| Solid-organ transplant         | 35 (53.8)                                                                   |
| Solid tumor                    | 20 (30.7)                                                                   |
| Leukemia                       | 4 (6.1)                                                                     |
| Lymphoma/multiple myeloma      | 3 (4.6)                                                                     |
| Metastatic cancer              | 3 (4.6)                                                                     |
| Male, n(%)                     | 38 (58.4)                                                                   |
| Age (median, IQR)              | 64 (20–87)                                                                  |
| Charlson Comorbidity Index (median, IQR) | 6 (1–12)                     |
| APACHE II score (median, IQR)  | 20 (4–41)                                                                   |
| ICU, n(%)                      | 37 (56.9)                                                                   |
| Hospital day index infection diagnosed (median, IQR) | 17 (9–265)                  |
| Hospital day TOL-TAZ started (median, IQR) | 19 (6–284)                  |
| 3grs qHrs, n(%)                 | 23 (35.3)                                                                   |
| 1.5grs qHrs, n(%)               | 23 (35.3)                                                                   |
| Concomitant IV antibiotics, n(%)| 15 (23.2)                                                                   |
| Aminoglycoside, n(%)           | 7 (15.6)                                                                    |
| Fluoroquinolone, n(%)          | 4/15 (26.7)                                                                 |
| Polymyxin, n(%)                | 3/15 (20)                                                                   |
| B-lactam, n(%)                 | 1/5 (15.6)                                                                  |
| TOL-TAZ susceptible isolates, n/N (%) | 35/37 (94.6)                  |

Conclusion. In this study of 65 critically-ill immunocompromised patients, the 30-day survival was 8.16%; clinical cure was 78.4% and microbiologic cure 75.3%. TOL-TAZ is a viable option for immunocompromised patients with MDRPA infections in immuno compromised patients. The in vitro activity of C/T was superior to CZA vs. antimicrobial NA PC clinical isolates (including MDR and XDR isolates) recovered from patients across Canada.

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2384. In vitro Activity of Ceftolozane–Tazobactam in Comparison With Ceftazidime–Avibactam vs. Antibacterial Non-Susceptible Pseudomonas aeruginosa Clinical Isolates, Including Multidrug-Resistant and Extensively Drug-Resistant Subsets: CANWARD, 2007–2017

Background. Pseudomonas aeruginosa (PA) is an important nosocomial pathogen. Treatment options for infections caused by multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates remain limited. Ceftolozane-tazobactam (C/T) and ceftazidime–avibactam (CZA) are two newer antimicrobials with antipseudomonal activity. The purpose of this study was to directly compare the in vitro activity of C/T and CZA vs. antimicrobial non-susceptible (NS) PA clinical isolates obtained as part of the CANWARD study.

Methods. Annually from 2007 to 2017, sentinel hospitals across Canada submitted blood, respiratory, urinary, and wound isolates (consecutive, one per patient/infected site) from patients attending ERs, medical and surgical wards, hospital clinics, and ICUs (CANWARD). Susceptibility testing was performed using broth microdilution (and breakpoints) as described by CLSI. MDR PA were defined as isolates that tested NS to at least one antimicrobial from 2 classes. XDR PA were defined as isolates that tested NS to at least one antimicrobial from 4 classes.

Results. 4224 PA isolates were obtained as a part of CANWARD. 628 (14.9%) were MDR, and 129 (3.1%) were XDR. The in vitro activity of C/T and CZA (plus relevant comparators) is presented below.

Conclusion. The in vitro activity of C/T was superior to CZA vs. antimicrobial NA PA clinical isolates (including MDR and XDR isolates) recovered from patients across Canada.
GNB, however its ability to improve patient outcomes may be attenuated if initiation is delayed or it is reserved for salvage therapy. We sought to determine the impact of delayed C/T initiation on 30-day mortality in patients with MDR GNB infections.

Methods. This was a multicenter, retrospective cohort study including adult patients treated with C/T (≥72 hours) for suspected or confirmed MDR GNB (resistant to ≥3 drug classes). The primary outcome measure was 30-day mortality. Classification and regression tree (CART) analysis was used to determine the time point of C/T initiation from index culture or diagnosis most predictive of 30-day mortality. Clinical characteristics and outcomes were compared between patients receiving early (defined as C/T initiated ≤3 days) vs. delayed C/T initiation. Multivariable logistic regression was conducted to determine the independent association between early C/T initiation and 30-day mortality.

Results. A total of 144 patients were included. The median (IQR) age was 61 (49, 71) years with a male (65%) and African American (53%) predominance. The most common source of infection was respiratory (64%) and MDR Pseudomonas aeruginosa was isolated from 92% of cultures. A breakpoint in time was identified of 119 hours (95% CI 115, 123), indicating that delaying C/T initiation by approximately 5 days substantially increases the risk of mortality in patients with MDR GNB infections, underscoring the importance of early appropriate therapy and the need for incorporation of C/T into automated susceptibility testing panels to support earlier initiation.

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3285. Cefazidine–Avibactam in Combination With Fosfomycin: A Novel Therapeutic Strategy Against Multidrug-Resistant Pseudomonas aeruginosa

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Session: 250. Treatment of AMR Infections

Saturday, October 6, 2018: 12:30 PM

Background. By targeting penicillin binding protein-3, the AmpC β-lactamase, and MraU, another enzyme involved in cell wall synthesis, with the cefazidine–avibactam–fosfomycin combination, we previously overcame multidrug resistance (MDR) in vitro in an archived collection of Pseudomonas aeruginosa clinical isolates. Here, we further validate the cefazidine–avibactam–fosfomycin combination, we previously overcame multidrug resistance (MDR) in vitro in an archived collection of Pseudomonas aeruginosa clinical isolates. We found to reduce CFUs by 5–6 logs compared with vehicle-treated mice, while cefazidine–avibactam and fosfomycin alone decreased CFUs by >1 log and 2–3 logs, respectively.

Conclusion. The combination of cefazidine–avibactam–fosfomycin is highly likely to offer patients who suffer from infections with a high bacteria burdens (i.e., pneumonia, cystic fibrosis) a therapeutic hope against MDR P. aeruginosa.

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2386. Efficacy of Lefamulin (LEX) vs. Moxifloxacin (MOX) Against Common Respiratory Pathogens in Adults With Community-Acquired Bacterial Pneumonia (CABP): Results From the Phase 3 Lefamulin Evaluation Against Pneumonia (LEAP) Study

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Session: 250. Treatment of AMR Infections

Saturday, October 6, 2018: 12:30 PM

Background. New CABP treatments with targeted activity and improved tolerability are needed. LEX, a novel pleuromutilin antibiotic that binds to a conserved region of the bacterial ribosome, is in development for IV or oral CABP treatment. This Phase 3 clinical study evaluated the efficacy of LEX vs. MOX in adults with CABP.

Methods. This multicenter, randomized, double-blind study, 351 adult patients with a baseline CABP pathogen detected by respiratory tract or blood culture, were enrolled. LEX 150 mg IV Q12 hours (n = 276) or MOX 400 mg IV Q24 hours (n = 275). After 6 IV doses, qualifying patients could be switched to oral therapy. Adjunctive linezolid was given with MOX for suspected methicillin-resistant S. aureus. Primary outcomes were cured and improved (C/I) patients at 48 hours in patients with baseline CABP pathogens detected by respiratory tract or blood culture, including serology, and real-time PCR from sputum, oropharyngeal and nasopharyngeal swabs. The microTFT2 population included all patients with a baseline CABP pathogen detected by respiratory tract or blood culture, urinary antigen test, serology, and real-time PCR from sputum, oropharyngeal and nasopharyngeal swabs. The microTFT2 population included all patients with a CABP pathogen detected by methods excluding PCR. Confirmatory identification and susceptibility testing of isolated S. aureus, and PCR were performed by a central laboratory.

Results. LEX was noninferior to MOX for ECR and IACR (LEX 87.3% [ITT], 81.7% [MiITT], 86.9% [CE-TOC]; MOX 90.2% [ITT], 84.2% [MiITT], 89.4% [CE-TOC]). The most common pathogen identified was S. pneumoniae. In the microTFT population (n = 159 per arm), LEX and MOX demonstrated similar ECR and IACR rates (figure). LEX was efficacious against S. pneumoniae (including resistant phenotypes). H. influenzae, M. catarrhalis, S. aureus, and atypical pathogens. In the microTFT2 population, response rates remained similar across baseline pathogens but showed more variation likely due to smaller sample sizes.

Conclusion. In this first Phase 3 clinical trial, LEX showed similar efficacy to MOX against the most commonly identified CABP pathogens. LEX demonstrates promise as a targeted monotherapy for the treatment of CABP in adults.