Literature Highlight:
Polymyxin B Versus Other Antimicrobials for the Treatment of Pseudomonas aeruginosa Bacteremia

*Pseudomonas aeruginosa* is a major source of hospital-acquired infections and is associated with high mortality rates. Additionally, many *P. aeruginosa* isolates are multi-drug resistant (MDR) and are often only susceptible to antibiotics of the polymyxin class (polymyxin B and colistin [polymyxin E]). Polymyxin antibiotics are old medications that have recently come back into use as a therapy of last resort for MDR Gram-negative infections. This retrospective, cohort study compared the efficacy of polymyxin B to other antibiotics in the treatment of pseudomonal bacteremia.

The six-year study enrolled all patients at one hospital who had *P. aeruginosa* isolated from blood cultures ≥48 hours after hospital admission; patients with cultured *Pseudomonas* <48 hours from admission were also enrolled if they had been hospitalized in the past 60 days. Patients were excluded if they were less than 18 years old, had received antibiotic treatment for less than 48 hours or had received inappropriate antibiotic therapy or if necessary data were not available in patient records. One hundred and thirty-three patients were included; 45 were treated with polymyxin B and 88 with comparator antibiotics. Frequency of administration and doses varied widely, with an average daily dose of 141 ± 54 mg of polymyxin B administered every 12 hours in 73.3% of patients. A total of 24.4% of polymyxin B-treated patients received adequate dosage regimens (defined as a total daily dose of ≥200 mg of polymyxin B). Comparator antibiotics used to treat *Pseudomonas* bacteremia were cefepime, imipenem, ciprofloxacin, meropenem, ceftazidime, aztreonam, and piperacillin/tazobactam. Patients given comparator antibiotics received adequate dosage regimens 78.4% of the time (defined as a total daily dose of ≥6 g of aztreonam, cefepime, and ceftazidime, ≥1200 mg of ciprofloxacin, ≥2 g of imipenem, ≥3 g of meropenem, and ≥13.5 g of piperacillin/tazobactam). The primary outcome was all-cause mortality while hospitalized. In-hospital mortality was significantly higher in polymyxin B-treated patients (66.7%) than in patients treated with comparator antibiotics (28.4%; RR 2.35, 95% CI 1.59-3.47; p≤0.001). Although there were several significant differences in baseline characteristics between the two populations, only polymyxin B treatment, higher Pitt bacteremia score, and mechanical ventilation at the onset of bacteremia were found to be significant factors in mortality. After adjusting for confounders, the summary relative risk of in-hospital mortality was 1.91 for polymyxin B-treated patients compared to those on other antibiotics (95% CI 1.05-3.45; p=0.033). Polymyxin B treatment was associated with renal toxicity in 24.4% of patients compared to 4.5% with other antibiotics (RR 5.38, 95% CI 1.81-15.94; p=0.002). The authors concluded that treatment of *P. aeruginosa* bacteremia with polymyxin B had lower efficacy than treatment with other antimicrobial agents. Limitations of the study included the low rate of treatment with appropriate polymyxin B dosage regimens. In addition, the disc diffusion method used to assess susceptibility of isolates to polymyxin B may not have been accurate enough to detect resistance.

**SUMMARY:** Treatment of *Pseudomonas* bacteremia with polymyxin B was associated with increased mortality compared to treatment with other antibiotics. Polymyxin B treatment was also associated with significantly higher renal toxicity.


*By William Zollinger, Pharm.D. Candidate*
Metastatic breast cancer (MBC) is the second leading cause of death due to cancer in the United States. Treatment for MBC can include chemotherapy, surgery, radiography, and hormone therapy. Despite multiple treatment options, there are still many patients that fail initial therapy, leading to a five-year survival rate of 26%. Many different antineoplastic agents have shown effectiveness, including taxanes, epothilones, and vinca alkaloids. However, adverse drug events (ADEs) associated with these treatments often lead to early therapy discontinuation.

On November 15, 2010, Halaven® (eribulin mesylate) was approved for the treatment of MBC that has recurred despite treatment with at least two antineoplastic drug regimens. Eribulin has a unique mechanism compared to the other taxanes, affecting both growth and shortening of microtubules. Eribulin is a treatment option for taxane-resistant tumors.

An open-label, single-arm, phase II study evaluated the efficacy and tolerability of eribulin in patients (n=103) previously treated for MBC. Patients were at least 18 years old and diagnosed with MBC that was not treatable with surgery or radiation and did not respond to previous anthracycline or taxane therapy. Other inclusion criteria included measurable tumors, disease progression within six months of the last antineoplastic therapy, a life expectancy of at least three months, and pre-existing sensory neuropathy, grade two or less (sensory alterations not interfering with activities of daily living). Patients were excluded if they had antineoplastic therapy, radiation, hormonal therapy, or trastuzumab within two weeks of the study, had symptomatic brain metastases, or were using warfarin. Initially, 59 patients (group 1) were given eribulin mesylate 1.4 mg/m² IV infusion over two to five minutes on days 1, 8, and 15 in a 28-day-cycle. The dosing protocol was changed due to neutropenia occurring on day 15, and 28 additional women (group 2) were given the same dose on days 1 and 8 in a 21-day-cycle. Patients were continued on the treatment until they had no additional clinical benefit or they had disease progression or unacceptable toxicity. The primary endpoint was the overall tumor response rate to eribulin based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and the secondary endpoints were the duration of response, progression-free survival (PFS), overall survival (OS), and safety of drug treatment. The patients in group 1 had a median of 2.5 treatment cycles, and group 2 had a median of four cycles. In the per protocol population, the objective response rate was independently reviewed. The tumor response rate was 10.2% (95% CI 3.8-20.8%) in group 1 and 14.3% (95% CI 4-32.7%) in group 2. The overall objective response rate was 11.5% (95% CI 5.7-20.1%). The median duration of response for all subjects was 171 days (range 44-363 days), the median PFS for all subjects was 79 days (range 1-453 days), and the median OS for all subjects was 275 days (range 15-826 days). The most common ADEs were neutropenia, fatigue, alopecia, nausea, and anemia. Neutropenia incidence occurred in 83% of all the subjects with no difference between groups. The most notable differences in ADEs between the two groups were anemia (group 1=45%, group 2=15%), thrombocytopenia (group 1=12%, group 2=3%), and anorexia (group 1=19%, group 2=6%). Overall, the authors concluded that the drug regimen in group 2 was better tolerated and the ADEs were more mild than in group 1. The authors also concluded that eribulin was effective in treating MBC with manageable ADEs when given as 1.4 mg/m² IV on days 1 and 8 of a 21-day cycle in women who were previously treated with a median of four antineoplastic drug regimens. This study was limited because of its single-arm design and small sample size.

Serious ADEs associated with eribulin include neutropenia (6%), peripheral neuropathy (5%), and QT prolongation (26 reported cases). The most common ADEs (incidence >25%) were mild neutropenia, anemia, fatigue, alopecia, nausea, and constipation.

The recommended dose of eribulin is 1.4 mg/m² given IV over two to five minutes on days 1 and 8 in a 21-day cycle. Dose reductions are recommended for hepatic impairment, renal impairment, and ADEs such as neutropenia and thrombocytopenia.

Halaven® (eribulin mesylate) is a new medication approved for the treatment of recurrent MBC in women previously treated with at least two antineoplastic drug regimens. The benefits of eribulin include activity against MBC after treatment failure with other antineoplastic drug regimens; however, additional studies are needed to compare eribulin to current treatment options for MBC to better define its role in recurrent MBC therapy.

By Nicholas Mozena, Pharm.D. Candidate

References:
Teflaro™ (ceftaroline) for Skin and Skin-Structure Infections

Skin and skin-structure infections are common in the United States, and beta-lactam antibiotics are the mainstays of treatment for susceptible isolates of the causative pathogens (e.g., *Staphylococcus aureus*). However, pathogens resistant to traditional treatments have been increasing in number, and it is estimated that almost 60% of isolates from cutaneous infections are due to methicillin-resistant *S. aureus* (MRSA). Infections caused by these resistant pathogens are normally treated with vancomycin and other potent antibiotics, but as a matter of antimicrobial stewardship, it is desirable that new agents be developed with efficacy against these resistant bacteria.1-3 Teflaro (ceftaroline), approved in October 2010, is a cephalosporin antibiotic with activity against resistant Gram-positive pathogens as well as many Gram-negative pathogens.1,4

Two large, randomized, double-blind, trials (CANVAS 1 and 2) investigated the efficacy and safety of ceftaroline in the treatment of complicated skin and skin-structure infections (cSSSIs). The CANVAS trials enrolled a total of 1396 patients ≥18 years old with a cSSSI (deep cellulitis, major abscess, infected wound or ulcer, or infected burn) and purulent drainage, erythema, localized warmth, fluctuance, tenderness to palpation, fever or hypothermia, a white blood cell count >10,000/mm³, or >10% immature (band) neutrophils. Patients were excluded if they had a creatinine clearance <30 mL/min, a vancomycin-resistant, pseudomonal, or anaerobic infection, osteomyelitis, necrotizing fasciitis, human or animal bites, diabetic or decubitus ulcers, gangrene, burns covering >5% of the body, or mediastinitis. Patients in the treatment arms (n=701) received 600 mg of ceftaroline IV every 12 hours, and patients in the comparator arms (n=695) received 1 g each of vancomycin and aztreonam IV every 12 hours. Treatment duration was 5 to 14 days. Dose adjustment for renal function was performed for all drugs. The primary objective was to determine the non-inferiority of ceftaroline to vancomycin plus aztreonam with respect to cure rate. Clinical response was divided into cure, failure, or indeterminate outcomes. The initial cultures taken from patients in CANVAS 1 were 75% *S. aureus*, and of these, 43% were MRSA. CANVAS 2 cultures were 84% (32% of which were MRSA) and 81% (27% of which were MRSA) *S. aureus* in the ceftaroline and vancomycin groups, respectively. The median number of treatment days in both groups was 7 days in CANVAS 1 and 6.5 in CANVAS 2. CANVAS 1 showed almost identical cure rates between study arms (86.6% for ceftaroline vs. 85.6% for vancomycin plus aztreonam; difference 1.0%, 95% CI 4.2 to 6.2%). High cure rates were found across all infection types: cellulitis (91.0% for ceftaroline vs. 91.6% for vancomycin plus aztreonam; difference -0.6%, 95% CI -8.5 to 7.4%), major abscess (88.6% for ceftaroline vs. 94.9% for vancomycin plus aztreonam; difference -6.2%, 95% CI 15.3 to 2.6%), infected wound (88.9% for ceftaroline vs. 89.5% for vancomycin plus aztreonam; difference -0.6%, 95% CI -14.9 to 14.7%), infected burn (100% for ceftaroline vs. 100% for vancomycin plus aztreonam; difference 0.0%, 95% CI -14.1 to 18.8%), and infected ulcer (90.9% for ceftaroline vs. 93.3% for vancomycin plus aztreonam; difference -2.4%, 95% CI -22.4 to 14.1%). The overall cure rates for CANVAS 2 were similar (85.1% for ceftaroline vs. 85.5% for vancomycin plus aztreonam; difference 0.0%, 95% CI -1.4 to 1.4%), with no significant differences in cure rates between groups for any infection type. The authors concluded that ceftaroline was an effective addition to treatment strategies for cSSSIs. The study was limited because of the exclusion of severe infections, such as necrotizing fasciitis, patients with severe renal impairment, and patients under 18 years of age.1,2

In these trials, the rate of significant adverse events in the ceftaroline groups was similar to that in the vancomycin plus aztreonam groups (4.3% and 4.1%, respectively). The most common adverse effects of ceftaroline were nausea (5.9%), headache (5.2%), diarrhea (4.9%), pruritis (3.5%), and rash (3.2%). These rates were generally higher than those for vancomycin plus aztreonam, except for pruritus. The percentage of patients experiencing at least one treatment-emergent renal adverse event was similar between the two groups (1.3% in the ceftaroline groups and 0.75% in the vancomycin plus aztreonam groups); treatment-emergent hepatic adverse events occurred more frequently (2.7% in the ceftaroline groups, and 4.2% in the vancomycin plus aztreonam groups). Ceftaroline is dosed at 600 mg IV every 12 hours.3

In conclusion, ceftaroline is a new cephalosporin approved for the treatment of cSSSIs and has been found to be non-inferior to vancomycin plus aztreonam. Ceftaroline has activity against resistant pathogens, including MRSA. Adverse events are uncommon and generally occur at rates similar to those for comparator antibiotics.

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References:


Acute otitis media (AOM) is a common infection in children caused by both viral and bacterial pathogens. However, treating AOM with antibiotics has only modest benefit compared to a watchful-waiting approach and greatly increases antibiotic consumption. This randomized, double-blind, placebo-controlled study evaluated the effects of amoxicillin/clavulanate versus placebo in resolving AOM and its symptoms.

A total of 319 children with AOM, 6 to 35 months of age, were randomly assigned to receive either amoxicillin/clavulanate at 40 mg/5.7 mg per kilogram per day (n=161) or placebo (n=158) for seven days. Parents were given a diary and asked to record the doses of medications given to their child and any symptoms, absences of the child from day care or the parent from work, and adverse events. Follow-up was scheduled on day three and eight. On the final visit, children were examined and the parents were asked if they thought there was improvement in the symptoms. At any visit the physician could switch to rescue treatment, which was open-labeled antibiotic therapy based on clinical judgment. The primary outcome was treatment failure determined by the occurrence of one of six independent factors: no improvement in condition by day three, worsening of condition at any time, no improvement in otoscopic signs by day eight, tympanic membrane perforation at any time, severe infection requiring systemic antibiotic treatment at any time, or any other reason for discontinuing the study medication at any time. The secondary outcome was the need for rescue treatment in patients with treatment failure. Treatment failed in 18.6% (n=30) of the antibiotic arm and 44.9% (n=71) of the placebo arm. The antibiotic treatment group had a 62% reduced risk of treatment failure (HR 0.38, 95% CI 0.25 to 0.59; p<0.001). Rescue treatment was used in 11 of the 30 patients in the antibiotic treatment failure group (36.7%) and 53 of the 71 patients in the placebo treatment failure group (74.6%). The need for rescue treatment was decreased by 81% when using antibiotics (HR 0.19, 95% CI 0.1 to 0.36; p<0.001). More patients experienced adverse events in the antibiotic arm (52.8%) than the placebo arm (36.6%), a treatment difference of 16.2% (95% CI 5.8 to 27.6; p=0.003). Diarrhea occurred in 47.8% of antibiotic patients and 26.6% of the placebo patients, which was a difference of 21.2% (95% CI 10.6 to 31.9). Eczema occurred in 8.7% of the patients in the antibiotic arm and 3.2% of the patients in the placebo arm (p=0.04). All other adverse events spontaneously resolved by the follow-up visit on day eight. The authors concluded that the use of antibiotics for the treatment of AOM in children does provide some benefit when compared to placebo, although there are more side effects with drug treatment. This trial was limited because it examined only one antibiotic medication.

**SUMMARY:** The use of an eight-day treatment regimen with amoxicillin/clavulanate in children with AOM resulted in fewer treatment failures and fewer requirements of rescue therapy but more AEs.


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