Title: Outcomes associated with primary antibiotic therapy in spinal epidural abscess due to *Staphylococcus aureus*: does degree of CNS penetration matter?

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Background: Spinal epidural abscess (SEA) is an uncommon but potentially life-threatening infection that requires urgent intervention. In SEA, the extent of central nervous system (CNS) involvement is unknown. Two recent, small, retrospective studies failed to demonstrate a significant difference in clinical outcomes between cefazolin and anti-Staphylococcal penicillins in the treatment of methicillin susceptible *S. aureus* (MSSA) SEA. Comparative data in the treatment of methicillin-resistant *S. aureus* (MRSA) SEA are also limited.

Objective: To evaluate outcomes of treatment in *S. aureus* SEA based on the degree of CNS penetration achieved by the overall principal antimicrobial therapy received

Methods: This was a multisite, retrospective cohort study of adult patients (≥ 18 years old) admitted to an Atrium Health acute care or acute rehabilitation hospital between January 1, 2017 and September 10, 2021 with confirmed *S. aureus* SEA by radiology and microbiology (blood and/or relevant surgical cultures). Key exclusion criteria include recurrent SEA, polymicrobial infection, and non-contiguous concomitant infection excluding asymptomatic bacteriuria. Patients were categorized to a low or high CNS penetration group based on the administered overall principal therapy (definitive therapy received for > 50% of the overall treatment course) and stratified according to methicillin susceptibility of the Staphylococcal isolate. Overall principal therapy with cefazolin or daptomycin was categorized as low CNS penetration while overall principal therapy with nafcillin, vancomycin, linezolid, or ceftaroline was categorized as high CNS penetration. The primary outcome based on overall principal therapy was a composite of 90-day clinical failure, defined as one of the following: extension of original antibiotic course, need for unplanned surgical intervention related to SEA, recurrence of *S. aureus* bacteremia, and all-cause mortality. Secondary outcomes included individual components of the primary outcome and the composite 90-day clinical failure by methicillin susceptibility of the Staphylococcal isolate and by early principal therapy (definitive therapy received for > 50% of the first 2 weeks of treatment). Categorical baseline characteristics and outcomes were compared using the Chi-squared or Fisher's exact test. Continuous baseline characteristics were compared using a t-test or Wilcoxon rank-sum test, as appropriate.

Preliminary Results: 345 patients were identified, of these 130 met inclusion criteria with 81 in the low CNS penetration group and 49 in the high CNS penetration group. There was no statistically significant difference in 90-day clinical failure of overall principal therapy between low and high CNS penetration antibiotic groups, respectively (29.6% vs. 20.4%, p = 0.25). Among individual components of the composite primary outcome, only extension of the original antibiotic course was significantly different between low and high CNS penetration groups (18.5% vs. 4.1%, p = 0.03). The composite 90-day clinical failure of overall principal therapy also did not differ between low and high CNS penetration groups based on methicillin susceptibility of the Staphylococcal isolate (MSSA 31.3% vs. 16.0%, p = 0.19; MRSA 21.4% vs. 25.0%, p = 1.00). Similarly, there was no statistically significant difference in 90-day clinical failure based on early principal therapy received (32.7% vs. 21.3%, p = 0.14), regardless of methicillin

susceptibility, (MSSA 32.7% vs. 20.0%, p = 0.24; MRSA 33.3% vs. 22.9%, p = 1.00) between the low and high CNS penetration groups, respectively.

Conclusion: Although there was no statistically significant difference in the rate of 90-day composite clinical failure between low and high CNS penetration antibiotics, there was an absolute difference of 9.2% in 90-day composite clinical failure between low and high CNS penetration groups. This difference seems to be primarily driven by higher rates of 90-day composite clinical failure in the low CNS penetration antibiotic group in those with MSSA infection and was consistent whether looking at overall principal therapy or early principal therapy. Given the limited sample size and small expected difference between groups, further study with a larger patient population or as part of a prospective, randomized trial is warranted to better characterize the impact of CNS penetration on outcomes in Staphylococcal SEA.