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CONTAGIOUS

A Dose of Stewardship: *Staphylococcus aureus* Edition

Treatment Highlights:

Synergistic Options for *Staphylococcus aureus* Bacteremia

By James McCracken-Goncalves, PharmD, BCIDP, AAHIVP

Bacteremia due to *Staphylococcus aureus*

Staphylococcus aureus bacteremia (SAB) is seen in up to 65 cases per 100,000 person-years,[1] with rates of SAB in pediatrics ranging from 8 to 26 out of every 100,000 children each year.[2] **Risk factors for SAB** such as presence of central venous catheters or cardiac devices, history of hospitalization, and complex comorbidities are concerns in both adult and pediatric patients. Pediatric patients with SAB, in fortunate contrast to adults, have a comparatively **lower incidence of 30-day mortality compared to adults (5% vs 21%)**.[2] Clinical data, especially controlled trial data, surrounding the treatment of SAB in pediatrics is particularly lacking. As a result, a majority of information we use to inform clinical decisions in SAB is inferred from data based in adult patients.

Persistent Bacteremia and Clinical Application

Persistent SAB, typically defined as bacteremia lasting 2 days or more despite appropriate antibiotic therapy,[3] is a predictor of increased mortality as well as higher risk for metastatic complications which is another reason an ID consult should be considered. Given the difficulty of clearance of *S. aureus* from blood cultures and the risks of complications due to persistent bacteremia, clinicians may decide to use combination therapies in hopes that synergistic activity will improve outcome.

Cefazolin (CFZ) + Ertapenem (ETP) for methicillin-susceptible *S. aureus* (MSSA)

Mechanism: takes advantage of key activity differences against MSSA resulting in complementary activity**:**

- Cefazolin primarily targets penicillin-binding protein 2 (PBP2), while
- Carbapenems (ex. ertapenem) demonstrate excellent affinity to PBP1.[4]
- Additionally, ETP is demonstrated to lower the required concentrations necessary for CFZ to penetrate and eradicate biofilms due to MSSA.[5]

Outcomes:

- **Reduced time to clearance of blood cultures.**[5,6]
- Hopefully resulting in decreased risks of complications.
- A RCT is underway to compare this regimen formally.[7]

Other:

- CFZ + ETP are most studied; however, studies support interchange of **cefazolin** with **nafcillin or oxacillin** and replacing **ertapenem** with **meropenem**.[8]
- **Synergistic agents should be utilized at typical dosing and stopped once blood cultures have cleared and patient is improving clinically.**

Ceftaroline (CPT) + Daptomycin (DAP) for methicillin-resistant *S. aureus* (MRSA)

Mechanism:

- Known synergy between daptomycin + β-lactams against *S. aureus*[10]
- Improvements in *S. aureus* MICs exposed to both agents at once[11,12] and
- Increased membrane binding of DAP when *S. aureus* is exposed to CPT.[12]

Outcomes:

- Improved clearance of blood cultures in refractory cases of persistent methicillin-resistant *S. aureus*
- (MRSA) bacteremia.[9]
- Improved patient outcomes and potential survival benefit in patients with high-risk complicated infections due to endovascular sources.[13,14]

*Of note, there is a much lower incidence of MRSA in our population at CHCO.

Frequently Asked Questions:

Can ampicillin or amoxicillin alone treat *Staphylococcus aureus*?

By Jason Child, PharmD, BCID

Penicillin was **discovered** in **1928** but was **not used clinically until 1941**.[1]

→

It took a couple years to increase production enough to treat soldiers who were dying from *Staphylococcus aureus* infections. It did not take long for the first strains of *S. aureus* to develop resistance.

→

By 1948, **60%** of hospital strains were **penicillin resistant**.

The **mechanism for resistance is** the production of a **penicillinase that destroys the beta-lactam ring** of penicillin (PEN) and **aminopenicillins like ampicillin and amoxicillin**.[2] *S. aureus* can asymptomatically colonize healthy people which is important in the spread of isolates and nasal carriage is found in 30-50% of individuals.[3] Most *S. aureus* isolates carry the penicillinase gene on their plasmid.[4]

2016 IDSA guidelines estimate **2% of *S. aureus* strains may be classified as PEN susceptible** but carry the penicillinase gene. MSSA susceptibility to penicillin is still rare, and most **screening procedures are unreliable.** That is why our CHCO micro lab (and other laboratories) do not release susceptibilities for penicillin or ampicillin to *S. aureus* and why **all MSSA should be considered penicillin (and thus amoxicillin/ampicillin) resistant.**

When *S. aureus* is oxacillin susceptible, your first line choices are **cefazolin** or **nafcillin**. Alternate options could be **ampicillin-sulbactam** or **amoxicillin-clavulanate** depending on the scenario and site of penetration as penicillinase is inhibited by sulbactam and clavulanic acid (and tazobactam). Ampicillin/amoxicillin alone is **NEVER** appropriate.

Staphylococcal Scalded Skin Syndrome: Is toxin coverage needed?

By Stacey Thomas, PharmD

BACKGROUND:

Staphylococcal Scalded Skin Syndrome (SSSS) is a rare but serious toxin-mediated dermatologic infection, most common in children <5 years old, that results in widespread blistering and sloughing of the skin.[1] The disease is caused by specific strains of *S. aureus* that produce exfoliative toxins A and B, which cleave desmoglein-1, a protein critical for skin integrity. Notably, not all *S. aureus* strains produce these exotoxins, and among those that do, the **majority are methicillin-susceptible (MSSA)** rather than methicillin-resistant (MRSA).[2]

Unlike many systemic infections, the bacterial load in SSSS is small and often localized, with the skin not directly infected.[1] Rather, the infection usually originates at a distant site, where exotoxins are produced during active bacterial replication before entering systemic circulation to cause the characteristic rash. Consequently, most of the toxin-mediated damage has already occurred by the time the patient presents to the hospital.[3]

ASSESSMENT:

β-lactam antibiotics (ex. cefazolin or cephalexin) exert their bactericidal effect by inhibiting cell wall synthesis, thereby halting bacterial replication. Protein synthesis inhibitors (ex. clindamycin and linezolid) suppress toxin production directly.[4] In SSSS, once bacterial replication ceases following treatment with a β-lactam antibiotic, toxin synthesis is inhibited, and the child can naturally clear the circulating toxins.[3] Therefore, antibiotics specifically targeting toxin production are generally unnecessary.

RECOMMENDATION:

Monotherapy with cefazolin or cephalexin is generally sufficient for patients admitted with SSSS, and additional **anti-toxin coverage is NOT required.** Treatment is typically **5-7 days** total and **enteral** therapy is reasonable if patient is able to take enteral medications.

MythBusters:

Myth or Fact: Cefazolin should not be used for CNS infections

Answer: ***it depends***

By Jennifer Ngo, PharmD Candidate

BACKGROUND:

For decades, cefazolin has not been used for central nervous system (CNS) infections, because of concerns that it does not adequately penetrate the CNS. As a consequence, frontline therapy for bacterial meningitis due to MSSA has relied on anti-staphylococcal penicillins with reliable CNS coverage (e.g. nafcillin). However, a growing body of pharmacokinetic (PK), pharmacodynamic (PD), and clinical data have challenged this — suggesting that **cefazolin can reach therapeutic concentrations in cerebrospinal fluid (CSF), especially at higher doses.**

MYTH: "Cefazolin should be avoided for meningitis — it cannot get into the CSF enough to work."

The resistance to using cefazolin for meningitis originates from early data, that had used cephalothin – a first-generation cephalosporin that was known for its poor CSF penetration. In the mid-1970s, a single 1-gram dose of cefazolin in adults without CNS infections was evaluated, producing understandably low CSF concentrations. These studies predated our understanding of time-dependent β-lactam activity and were conducted before clinicians began using higher, optimized dosing strategies (e.g., 50 mg/kg (max:2 g) q6h or continuous infusion). Unfortunately, these limited early findings became widespread belief and were continually repeated in textbooks and clinical references, creating the myth that cefazolin is inherently inadequate for CNS infections.

FACT: We can utilize cefazolin, especially at high doses, for pediatric CNS infections (and have!)

While the evidence presented below is derived from adult populations, we have utilized cefazolin in pediatric cases, generally with q6h dosing for MSSA CNS infections or septic cerebral emboli secondary to endocarditis.

A 2020 comparative study evaluated patients treated for post-operative or hematogenous staphylococcal meningitis. Patients received either continuous-infusion cefazolin (median daily dose 8 g, range 6–12 g) or cloxacillin. **Cefazolin achieved median CSF concentrations of 2.8 mg/L, well above the susceptible breakpoint for MSSA**. No failures occurred in the cefazolin group. The authors concluded that optimized, high-dose continuous-infusion cefazolin can reliably produce CSF exposures adequate for MSSA meningitis — one of the pieces of clinical evidence contradicting the long-standing prohibition of cefazolin in CNS infections.

In 2022, a prospective PK study evaluated CSF cefazolin concentrations. The investigators reported median CSF peak levels of ~3 mg/L, with trough concentrations near 1.6 mg/L. These concentrations consistently exceeded the MICs for MSSA, even several hours after dosing. The authors concluded that **cefazolin**, at commonly used clinical doses, ***does* penetrate CSF at potentially therapeutic levels** — contradicting historical belief and providing the first robust prospective human PK dataset supporting cefazolin's CNS viability.

CONCLUSION:

The long-standing view that cefazolin is unsuitable for CNS infections deserves revision.
The original data were based on limited, single-dose studies that do not reflect the dosing strategies, PK/PD understanding, or clinical contexts of today. **Emerging PK data demonstrates that cefazolin can penetrate the CSF at measurable and therapeutic concentrations — particularly when used at higher doses, with frequent dosing or continuous infusion.** Cefazolin should no longer be automatically excluded as a treatment option for CNS infections. In patients with MSSA CNS infections, **nafcillin is likely still the best first line option,** but in the setting of drug interactions or side effects, alternatives including cefazolin should be considered.

For CNS infections treated with cefazolin, we recommend 50 mg/kg/dose (max: 2g/dose) Q6H or continuous infusions – additional information here

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Thank you for your interest in our publication.

CONTAGIOUS COMMENTS
A Dose of Stewardship

Thank you for reading this edition of the quarterly newsletter! We would love your comments/questions/suggestions for future editions. If you have any thoughts, please email kira.frappa@childrenscolorado.org.

Special thanks to all who contributed to and/or reviewed this newsletter including:

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Matthew Miller, PharmD, BCIDP
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Lauren Reynolds, PharmD
Stacey Thomas, PharmD
CHCO Antimicrobial Stewardship Team

Resource Corner:

Firstline: Access CHCO-specific clinical pathways, antimicrobial dosing guidelines, pathogen information, infection prevention resources, and more. Available for iOS, Android, and web browsers.

- Link to access

2024 CHCO Bugs & Drugs Handbook: This handbook includes CHCO's antibiogram, microbiological testing details, therapeutic drug monitoring recommendations, and additional resources.

- Link to access **...**physical pocket-sized editions available on request

Red Book: Published by the American Academy of Pediatrics, this comprehensive resource provides the latest clinical guidance on the manifestations, etiology, epidemiology, diagnosis, and treatment of over 200 childhood infectious diseases.

- Link to access

SENTRY Antimicrobial Surveillance Program: Create a free account to access global susceptibility information for various common and rare bacteria, analyzed against a wide range of antibiotics.

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Clinical and Laboratory Standards Institute (CLSI): Access essential microbiology standards and susceptibility information for your clinical practice.

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Treatment Highlight: Synergistic Options for *Staphylococcus aureus* Bacteremia

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Frequently Asked Questions: Can ampicillin alone treat *Staphylococcus aureus*?

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Mythbusters: Myth or Fact: Cefazolin should not be used for CNS infections

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