Antimicrobial Stewardship Guidelines

Guideline for Initial Treatment of *S. aureus* Bacteremia

This guideline was developed by the following multidisciplinary group:
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These recommendations surround the initial antibiotic selection in cases of *S. aureus* bacteremia without concern for central nervous system (CNS) infection. Infectious Diseases Consult is strongly recommended for *S. aureus* bacteremia. This guideline is not intended to guide therapy for other non-specific clinical situations (e.g., "rule outs", pneumonia, bacteremia caused by Gram-positive cocci while awaiting speciation, etc.). Final antibiotic selection and duration of therapy should be determined based on the patient's clinical course and the results of susceptibility testing. In addition, source control is critical.

I. Background

Staphylococcus aureus bacteremia poses risk for significant morbidity and mortality. Each additional day of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia is associated with a 50% increased odds of bacteremia-related complications, including septic emboli and metastatic foci of infection.[1]

Vancomycin therapy is associated with increased risk of treatment failure in pediatric patients with MRSA and methicillin-susceptible *S. aureus* (MSSA) bacteremia.[1-3] Optimum therapeutic vancomycin levels in pediatric patients are unclear, attaining therapeutic levels can be challenging, and higher vancomycin troughs (i.e. ≥15 µg/mL) are associated with acute kidney injury.[2,4-8] Vancomycin alternatives should be considered in pediatric patients with MRSA bacteremia.[9]

Daptomycin is associated with lower mortality and clinical failure rates when compared to vancomycin for treatment of MRSA bacteremia in adult patients.[10] Early initiation of daptomycin therapy (within 72 hours) is associated with improved outcomes compared to late initiation in adult patients with MRSA bacteremia.[10,11]

Ceftaroline salvage therapy has been used successfully in patients (primarily adult) with MRSA bacteremia with or without endocarditis.[12]

Combination therapy with daptomycin plus ceftaroline is associated with decreased mortality and improved microbial clearance in adults with MRSA bacteremia.[13,14]

Empirically, the use of combination antimicrobials pending culture results often consists of vancomycin and a broad-spectrum beta-lactam (i.e. cefepime). In these cases, some data suggest synergy may exist between both agents against MRSA.

Combination therapy with cefazolin or oxacillin plus ertapenem has been associated with clearance of bacteremia in patients with persistent MSSA bacteremia with evidence of in vitro synergy.[15-20]

II. Recommended treatment for patients with <u>uncomplicated MRSA</u> bacteremia (or with *S. aureus* bacteremia while awaiting susceptibility results)

- **Daptomycin**
  - FDA approved in 2003, licensed for children aged 12 months and older with SSTI and *S. aureus* bacteremia
  - Should not be used in the setting of pneumonia (inactivated by pulmonary surfactant)
  - Caution with use if creatinine kinase (CK) >3 times the upper limit of normal
  - There is insufficient evidence regarding CNS penetration for daptomycin
  - Animal studies (7-week-old juvenile dogs) demonstrated neurologic and muscular toxicity after prolonged, high doses of daptomycin (50-150 mg/kg/day for 28 days)[21]
    - Daptomycin has been successfully used in infants in clinical settings, including premature infants[22-25]
  - Dosing (doses infused over 1 hour):[21,26,27]
    - Limited data exist to inform daptomycin dosing in children <18 years with severe infections. Suggested dosing is extrapolated from maximum safe dosages investigated in children and adults, but children clear daptomycin more rapidly than adults.
    - Dosing is based on adjusted body weight when actual body weight is >120% of ideal body weight.

Age	CrCl ≥ 50 mL/min	CrCl 30-49 mL/min	CrCl 10-29 mL/min	CrCl < 10 mL/min	Peritoneal Dialysis	Int. Hemodialysis*	CRRT
0-2 months	10 mg/kg q12h		10 mg/kg q24h		10 mg/kg q24h		10 mg/kg q12h
2-11 months^	12 mg/kg q24h		12 mg/kg q48h		12 mg/kg q48h		12 mg/kg q24h
1-11 years	12 mg/kg q24h		12 mg/kg q48h		12 mg/kg q48h	12 mg/kg q48h	12 mg/kg q24h
≥ 12 years	10 mg/kg q24h		10 mg/kg q48h		10 mg/kg q48h	10 mg/kg q48h	10 mg/kg q24h
*Doses scheduled on dialysis days should be given after dialysis. Instead of q48h dosing, daptomycin can be dosed after each IHD session if receiving stable three times weekly IHD, in which case a higher dose may be considered on the third day (Friday) of IHD given the longer interdialytic period. Additional post-dialysis doses may be considered if receiving more than three times weekly IHD.							

  - Most common toxicities of therapy:
    - CK elevation (seen in 2-4% of patients)[10,28]
      - Need to obtain CK level prior to initiation of daptomycin and weekly thereafter

OR

- **Ceftaroline**
  - FDA approved in 2010, licensed for children aged 2 months and older with *S. aureus* SSTI and community-acquired bacterial pneumonia (including cases with concurrent bacteremia)
  - Incompatible with amphotericin B and caspofungin
  - There is insufficient evidence regarding CNS penetration for ceftaroline, although pediatric case reports and animal studies are encouraging, particularly in the setting of inflamed meninges.[29-31]
  - Dosing (doses infused over 1 hour):[32-34]

Age	CrCl > 50 mL/min	CrCl 30-50 mL/min	CrCl 10-29 mL/min	CrCl < 10 mL/min	Peritoneal Dialysis	Int. Hemodialysis*	CRRT
< 2 months	6 mg/kg q8h	4 mg/kg q8h	3.5 mg/kg q8h	2.5 mg/kg q8h	No information	2.5 mg/kg q8h	4 mg/kg q8h
2-5 months	10 mg/kg q8h	8 mg/kg q8h	6 mg/kg q8h	4 mg/kg q8h	No information	4 mg/kg q8h	8 mg/kg q8h
≥ 6 months	15 mg/kg q8h (max 600 mg)	10 mg/kg q8h (max 400 mg)	8 mg/kg q8h (max 300 mg)	6 mg/kg q8h (max 200 mg)	No information	6 mg/kg q8h (max 200 mg)	10 mg/kg q8h (max 600 mg)
*Doses scheduled near dialysis should be administered after dialysis							

- In critically ill children with invasive MRSA infections, higher dosing of 15 mg/kg/dose IV Q 6 hours may be considered on a case-by-case basis.[32]
- If desire to use for a CNS infection, contact clinical pharmacist to discuss dosing and other considerations.

- Most common toxicities of therapy:
  - Neutropenia (most commonly after 2-3 weeks of therapy), hemolytic anemia[12]

III. Recommended treatment for patients with <u>persistent MRSA</u> bacteremia (3 or more days of positive blood cultures)

- Combination therapy with daptomycin + ceftaroline until bacteremia has cleared and the patient has demonstrated clinical improvement (dosing recommendations above).
- Evaluate for unaddressed foci of infection, including echocardiogram.
- Obtain daily blood cultures until there are at least 2 consecutive negative blood cultures.[35]
- Once blood cultures have cleared (i.e., 2 consecutive negative blood cultures), narrow to one agent.

IV. Recommended treatment for patients with <u>uncomplicated MSSA</u> bacteremia

- **Oxacillin** (Nafcillin if the patient has central venous access)
  - Recommended Dosing (dose infused over 1 hour):
    - Neonate:
      - For meningitis or severe infection: 50 mg/kg/dose IV (frequency based on premenstrual age and postnatal age as provided below)
        - Can consider 25 mg/kg/dose IV when meningitis has been ruled out or not suspected depending on the clinical scenario

Postmenstrual age (weeks)	Postnatal age (days)	Interval
≤ 29	0 – 28 > 28	q 12 hr q 8 hr
30 – 34	0-7 8-28 > 28	q 12 hr q 8 hr q 6 h
35 - 44	0-7 >7	q 8 hr q 6 hr
>/= 45	All	Please refer to Pediatric Dosing in EPIC

    - Pediatric: 50 mg/kg/dose IV Q 6 hours (maximum 2000 mg/dose)
      - To take advantage of pharmacodynamic properties (%T>MIC), consider 33 mg/kg/dose IV Q4 (maximum 2000 mg/dose)

*section IV continued on next page

OR

- **Cefazolin**
  - Should not be used if there is concern for CNS infection
  - Recommended Dosing (dose infused over 30 minutes):

Neonate:

≤ 32 weeks PMA					
0 - 7 days	8-28 days		> 28 days		
Any CrCl	**CrCl ≥ 10**	**CrCl < 10**	**CrCl ≥ 30**	**CrCl 10 - 29**	**CrCl < 10**
25 mg/kg IV q12h	25 mg/kg IV q8h	25 mg/kg IV q12h	25 mg/kg IV q8h	25 mg/kg IV q12h	25 mg/kg IV q24h
32-44 weeks PMA					
0 - 7 days	> 7 days				
Any CrCl	**CrCl ≥ 30**		**CrCl 10 - 29**	**CrCl < 10**	
50 mg/kg IV q12h	50 mg/kg IV q8h		50 mg/kg IV q12h	50 mg/kg IV q24h	
Renal Replacement Therapy					
CVVHDF	50 mg/kg IV q8h				
PD	50 mg/kg IV q24h				
Aquapheresis	Dosing should be based on patient's CrCl				

Pediatric:

Age	CrCl > 50 mL/min	CrCl 30-50 mL/min	CrCl 10-29 mL/min	CrCl < 10 mL/min	Peritoneal Dialysis	Int. Hemodialysis*	CRRT
Standard Dosing	33 mg/kg q8h (max 2000 mg)	33 mg/kg q8h (max 2000 mg)	33 mg/kg q12h (max 1000 mg)	33 mg/kg q24h (max 1000 mg)	33 mg/kg q24h (max 1000 mg)	33 mg/kg q24h (max 1000 mg)	33 mg/kg q8h (max 1000 mg)
*Doses scheduled near dialysis should be administered after dialysis							

  - Limited data exist to support higher dosing in the setting of MSSA bacteremia, but dosages up to 150 mg/kg/day divided every 6-8 hours (maximum 2000 mg/dose) have been tolerated in children with close monitoring (particularly for cytopenias).

V. Recommended treatment for patients with <u>persistent MSSA</u> bacteremia

- In patients with persistent MSSA bacteremia, there is increasing evidence of faster clearance of bacteremia with combination therapy (oxacillin or cefazolin PLUS a carbapenem). In addition to optimizing dosing of oxacillin or cefazolin, options include:
  - Oxacillin or cefazolin PLUS ertapenem until bacteremia has cleared and the patient has demonstrated clinical improvement.
    - Ertapenem dosing for patients ≥1 month old:
      - ≥1 month – 11 years: 15 mg/kg/dose IV (max 500 mg/dose) Q 12 hours
      - ≥12 years: 1000 mg/dose IV Q 24 hours
    - Meropenem dosing for infants <1 month old based on PMA and PNA:

Indication	Postmenstrual age	Postnatal age	CrCl ≥ 50 mL/min	CrCl 30-49 mL/min	CrCl 10-29 mL/min	CrCl < 10 mL/min	Peritoneal Dialysis	CRRT
Standard Dosing	< 32 weeks	0-7 days	20 mg/kg IV q12h				20 mg/kg IV q24h	20 mg/kg IV q8h
		8-14 days	20 mg/kg IV q12h	20 mg/kg IV q12h	20 mg/kg IV q12h	20 mg/kg IV q24h		
		> 14 days	20 mg/kg IV q8h	20 mg/kg IV q8h	20 mg/kg IV q12h	20 mg/kg IV q24h		
	≥ 32 weeks	0-7 days	20 mg/kg IV q8h					
		8-14 days	20 mg/kg IV q8h	20 mg/kg IV q12h	20 mg/kg IV q12h	20 mg/kg IV q24h		
		> 14 days	30 mg/kg IV q8h	30 mg/kg IV q12h	30 mg/kg IV q12h	30 mg/kg IV q24h		
CNS infection, Critical illness[#], and/or ECMO[#]	< 32 weeks	0-7 days	40 mg/kg IV q12h				40 mg/kg IV q24h	40 mg/kg IV q8h
		8-14 days	40 mg/kg IV q12h	40 mg/kg IV q12h	40 mg/kg IV q12h	40 mg/kg IV q24h		
		> 14 days	40 mg/kg IV q8h	40 mg/kg IV q8h	40 mg/kg IV q12h	40 mg/kg IV q24h		
	≥ 32 weeks	0-7 days	40 mg/kg IV q8h					
		8-14 days	40 mg/kg IV q8h	40 mg/kg IV q12h	40 mg/kg IV q12h	40 mg/kg IV q24h		
		> 14 days	40 mg/kg IV q8h	40 mg/kg IV q12h	40 mg/kg IV q12h	40 mg/kg IV q24h		

[#]For severe non-CNS gram-negative infections in critically ill patients, including those receiving ECMO, prolonged infusions over 3 hours may be considered on a case-by-case basis in the absence of meningitis.

  - If addition of a carbapenem is not used, other options include:
    - Monotherapy with oxacillin or cefazolin at optimized dosing.
    - Oxacillin or cefazolin PLUS daptomycin until bacteremia has cleared and the patient has demonstrated clinical improvement.
- Evaluate for unaddressed foci of infection, including echocardiogram.
- Obtain daily blood cultures until there are at least 2 consecutive negative blood cultures.

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