Empiric therapy for severe suspected *Staphylococcus aureus* infection

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• None

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Clinical vignette

- 53 year old male brought to ER by ambulance with altered level of consciousness; febrile; not in septic shock
- Generally healthy; no hospital contact; cocaine user
- CT head: large ischemic infarct right cerebral hemisphere
- Blood cultures: Gram-positive cocci in clusters
- Echo: Large vegetation on mitral valve with regurgitation
- Treated initially for pneumonia with IV ceftriaxone, azithromycin
  - switched to high dose cloxacillin after blood cultures show MSSA
  - Day 5: remains bacteremic; progression of valvular disease; daptomycin added
  - Day 7: sterilization of blood
  - Day 9: massive hemorrhagic transformation of infarct; cerebral herniation; death
S. aureus epidemiology

- Overall incidence rate of 15-40 cases per 100,000 population/year
  - 5000-14000 cases in Canada each year
- The second leading pathogen causing sepsis in industrialized countries
  - E. coli, S. aureus, S. pneumoniae
- Case fatality rates of approximately 15-30%
  - No change in overall mortality rates during the past 25 years
- Typical complications include:
  - relapse of bacteremia
  - metastatic infection
    - infective endocarditis
    - central nervous system embolism
    - septic arthritis

Clin Microbiol Infect 2013; 19: 492–500
Clin Infect Dis. 2009;49(12):e130–8
Infect Control Hosp Epidemiol. 2015;36(12):1417–22
S. aureus: a leading cause of infection

- **Community**
  - native valve endocarditis (31.6% of cases)
  - prosthetic valve endocarditis (23% of cases)
  - osteomyelitis (in 50% to 70% of cases)
  - community-onset bacteremia (15% to 23.5%)

- **Nosocomial**
  - surgical site infections (19.5% to 30%)
  - ventilator-associated pneumonia (20.5% to 28%)
  - catheter-related bacteremia

*JAMA*. 2005;293:3012-3021
*Nat Rev Cardiol*. 2011;8:322-336
Onset location for *S. aureus* bacteremia

- **Community-associated** *S. aureus* bloodstream infection classically occurs in patients without underlying conditions
  - mostly from antibiotic-susceptible organisms
  - often associated with a detectable infected focus, including SSTI, deep-seated abscesses, or osteoarticular infections, or with infective endocarditis
- **Community-onset** healthcare-associated SAB is comparable to nosocomial onset
  - multi-resistant organisms
  - presence of intravenous devices, a history of surgical treatment, and hemodialysis

- Thus, the distinction between community-acquired MSSA and healthcare-associated MRSA is becoming increasingly blurry
Prognostic factors/Predictors of outcome

• Pooled analysis of 5 observational studies from 2006-2011
  • n=3395 patients from Germany, Spain, United Kingdom, and United States
  • Median age 64 years; 63% male; 20% MRSA; 28% IV catheter-related

• **Age, endocarditis, pneumonia, or an unidentified focus** were independently associated with death from day 7-90

• MRSA infection had a significantly higher mortality, even after adjustment for confounders; however, it is unclear if this is due to:
  • delayed receipt of appropriate antimicrobials/less effective antimicrobials
  • confounding risk factors linked with the acquisition of MRSA/study design
  • poorer quality of medical care for patients in contact-isolation

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Age and 30-day mortality from *S. aureus* bacteremia

![Bar chart showing age and 30-day mortality from *S. aureus* bacteremia](chart.png)

J. Hosp. Infect. 77:16 –20
Source of SA infection and outcome

• The overall mortality rate from SAB varies depending on the primary focus of infection

• Stratification of mortality by site of infection
  • “low” risk: intravenous catheter; urinary tract; ear, nose, and throat; and gynecological foci
  • “intermediate” risk: bone and joint, soft tissue, and unknown foci
  • “high” risk: endovascular, lower respiratory tract, intra-abdominal, and central nervous system foci

• At presentation, the extent of S. aureus infection may not be obvious
  • approximately one-third of patients develop a metastatic or complicated SAB infection with increased mortality

Outcome of *S. aureus* bacteremia based on site of infection
Prosthetic device-associated Staphylococcal bacteremia

- *S. aureus* is the leading cause of nosocomial and HCA-BSI, together with coagulase-negative *Staphylococcus spp.*
- Patients on hemodialysis, particularly those with intravascular catheters, are at very high risk for staphylococcal endocarditis and represent a “new” at-risk group for this disease
- The risk for patients with catheter-induced *S. aureus* bacteremia to develop **infective endocarditis** is about **10%**
  - Approximately one-third of these patients develop metastatic complications
- The strongest indicator of clinical complication is a positive result of follow-up blood culture after 72 hours of treatment
Long term outcomes: MRSA vs. MSSA bacteremia

• Observational cohort study (Australia; 1997-2007; n=582)
  • Do patients with MRSA bacteremia have a higher risk of death and recurrent infections than those who had MSSA bacteremia?
• Crude survival time after MRSA was shorter than MSSA (14 vs 54 months)
• Adverse association between MRSA and all-cause mortality or infection-related mortality were not statistically significant after adjustment for important prognostic factors
  • age, comorbidities, severity of acute illness, metastatic infections, and long-term care facility resident status
• Conclusion: **Host factors** contribute substantially to mortality and probably account for the association between MRSA bacteremia and **increased risk of death**
Mortality of MRSA vs. MSSA bacteremia

• There are several plausible explanations for an increased mortality rate associated with MRSA in comparison to MSSA bacteremia
  • Uncharacterized pathogen-specific virulence factors
  • Differences in empirical prescribing
    • inadequate initial coverage for MRSA
  • Poor vancomycin efficacy
    • compared to semisynthetic penicillins, vancomycin has slower bactericidal activity *in vitro*, especially with high-inoculum infections and variable tissue penetration
  • MRSA infection may just be a surrogate for host factors such as comorbidities rather than methicillin resistance *per se*

Risk factors for persistent SA bacteremia

• Definitions vary (i.e. 3-7 days after appropriate therapy)
• Seen in 6-38% of SA infection episodes
• MRSA has been associated with a greater likelihood of persistence than MSSA (median time to clearance of 8-9 days vs 3 days)
• Risk factors include
  • source of infection (i.e., infective endocarditis or vertebral osteomyelitis)
  • pathogen phenotypes (vancomycin hetero resistance)
  • antibiotic treatment
  • presence or retention of prosthetic material and the ability to remove foci of infection by surgical drainage

Consequences of persistent SA bacteremia

• Bacteremic persistence is a surrogate for complicated SAB

• The likelihood of a metastatic infection increases with an increasing duration of bacteremia, to approximately 45% following 10 days of SAB and is associated with worse outcomes

• Even in the absence of metastatic complications, persistence *per se* portends a worse outcome

• MRSA infection-related mortality rates with persistence (3 days) and non-persistent episodes are 45.2% and 9.4%, respectively; p=0.002

Mechanism of drug resistance: *S. aureus*

- Resistance to most β-lactam antibiotics, including the semisynthetic penicillins such as cloxacillin, is due to the expression of the low-affinity penicillin binding protein PBP2a
- PBP2a is encoded by the *mecA* gene and is found on an integrated mobile genetic element called the staphylococcal cassette chromosome mec (SCC*mec*) element
- PBP2A confers high intrinsic resistance to virtually all β-lactams and is a target for further drug development (i.e. ceftobiprole, ceftaroline)
- In USA, hospital prevalence of MRSA is up to 60%
Molecular diagnosis of *S. aureus*

- Distinction of Methicillin Sensitive (MSSA) from Methicillin Resistant (MRSA) is possible in a few hours after growth of Gram-positive cocci
  - Time to conventional identification/antibiotic susceptibility profile is 48-72 hours
- **MALDI-TOF** (matrix-assisted laser desorption ionization/time-of-flight)
- **Multiplex real-time PCR** amplification
  - MRSA resistance gene is *mecA*, which encodes low-affinity penicillin-binding protein 2A (PBP2A); also found in coagulase-negative Staphylococci
  - Simultaneous amplification of additional regions that were specific for *S. aureus* vs. coagulase-negative *Staph spp.* (i.e. *femA*) or proprietary DNA sequences
- **Other**
  - high-throughput genome sequencing, RNomics, and proteomic

*Clin Infect Dis.* 2007;44:418-423
*Clin Chem.* 2015 Jan;61(1):100-11
Rapid molecular diagnostics for blood cultures

• Comparison of rapid multiplex PCR detection (rmPCR) directly from positive blood cultures and conventional phenotypic identification

• rmPCR reduced the time from positive Gram stain to microorganism identification from 22.3 hours to 1.3 hours (p<0.01)

• This dramatically reduces the duration of empiric therapy

• For bloodstream infections caused by organisms not requiring vancomycin therapy (eg, methicillin-susceptible S. aureus, S. pyogenes, S. agalactiae, or gram-negative or fungal organisms), the median duration of vancomycin use was reduced from 8.2 hours to 0 hours (p<0.03)
Still many unanswered questions about therapy

- Despite the frequency of *S. aureus* bacteremia (SAB), enrollment in clinical trials has been extremely limited
- As of 2011, 1500 patients had been enrolled in 16 controlled trials of therapy
- Thus, clinical practice is driven by the results of observational studies and anecdote
- There is a lack of evidence for:
  - the best antimicrobial drugs
  - the optimal dose
  - the mode of delivery
  - the duration of therapy

Lancet Infect Dis 2011; 11: 208–22
Drug therapy: Empiric considerations

• The harmful effects of delayed appropriate empirical therapy for the treatment of MSSA or MRSA bacteremia have been shown in multiple studies
  • A recent meta-analysis showed an overall 2-fold increased survival benefit with the administration of appropriate empirical therapy for MRSA bacteremia

• Unlike studies of sepsis, no “time response curve” (increasing mortality for every hour of delay in antibiotic administration) has been detected for SAB treatment
  • time cutoffs for appropriate antibiotic administration have been detected (24-72 hours) after which mortality is increased

• Theoretically, the greatest benefit is likely to occur when antibiotics are still able to affect the progression of infection and thus impact infection-related mortality
  • This suggests, therefore, that ill but less severely ill patients are most likely to benefit

Drug therapy: Empiric considerations

• The choice of empiric Staphylococcal therapy is based on the pre-test probability of MSSA vs. MRSA
  • Factors to consider include age, severity of illness, presumed source of infection presence of prosthetic material, history of previous MRSA infection, local bacterial epidemiology, etc.

• Treatment options for presumed MRSA could include vancomycin alone or vancomycin plus β-lactam until drug susceptibility testing results available

• Some recommend a combination of anti-MSSA agent and vancomycin should be administered pending susceptibility results
  • The reason for this is the superior activity of β-lactams compared with vancomycin for MSSA combined with the fact that vancomycin covers MRSA
  • No antagonism between these 2 agents is known for any pathogen

• But, empiric therapy with vancomycin alone is not inferior to combined therapy

JAMA. 2014;312(13):1330-1341
Drug therapy of MSSA bacteremia

• Cefazolin has been used for the treatment of MSSA since the 1970s
  • Case reports of treatment failures have suggested reduced efficacy compared to anti-staphylococcal penicillins
  • Potential explanations for this included an increased susceptibility of cefazolin to the inoculum effect and to staphylococcal β-lactamases

• Yet, a recent retrospective study of 3167 VA patients with MSSA bacteremia showed lower risk of mortality with cefazolin vs. nafcillin or oxacillin

• And, a prospective observational cohort study showed higher failure rate of nafcillin vs. cefazolin due to more adverse effects/more discontinuation

• But, no randomized control trial comparing these agents has been performed to definitively answer questions regarding relative efficacies

Clin Infect Dis 2017 Jul 1;65(1):100
J Antimicrob Chemother. 2015;70(5):1539
Drug therapy of MSSA bacteremia

• In another study, the 30-day mortality rate was higher for patients receiving empiric treatment with a third-generation cephalosporin or β-lactam β–lactamase inhibitor combinations than for patients receiving cloxacillin or cefazolin (i.e. within the first 48 h)

• Despite this, data shows that suboptimal therapy is better than ineffective or no therapy

• **Overall conclusion:**
  • Important questions remain about the comparative efficacy of cephalosporins and anti-staphylococcal penicillins – though both are effective
  • At this time the evidence for a preferred β-lactam for MSSA bacteremia is limited and contradictory

Vancomycin

• Large molecule; slowly bactericidal compared to β-lactams

• MIC vancomycin breakpoints for *S. aureus*:
  • ≤2 μg/mL, susceptible ("vancomycin creep" associated with heteroresistance)
  • 4 to 8 μg/mL, intermediate resistance (GISA; altered peptidoglycan structure)
  • ≥16 mg/L, high-level resistance (VRSA; modified peptidoglycan target)

• Pharmacokinetic optimization:
  • Drug dosages should be adapted to body weight and renal function
  • Trough levels of vancomycin should be between 15 and 20 μg/mL
  • A loading dose of 25 to 30 mg/kg must be considered
  • Peak levels do not correlate with toxicity


Vancomycin for MSSA bacteremia

• Vancomycin has consistently been associated with increased rates of treatment failure and high mortality rates compared to β-lactams when used for the management of MSSA bacteremia

• Thus, use of β-lactams is strongly preferred once the diagnosis of MSSA bacteremia has been confirmed

• It is recognized that this may not always be possible
  • Consider desensitization if severe allergy/hypersensitivity
Vancomycin for MRSA bacteremia

• Still a gold standard against severe MRSA infections
  • No other drug has been shown to be significantly more effective

• Bactericidal activity is concentration-independent once 4-5X the MIC for the organism is reached

• Trough levels of 15-20 ug/mL to achieve a 24-hour AUC/MIC ratio >400 is the best predictor of clinical efficacy
  • low trough levels <10 ug/mL → heteroresistance

• Continuous infusion at a dose of 30 mg/kg/day after a loading dose of 15 mg/kg has also been used: no greater efficacy

• Careful measurements of vancomycin levels are generally needed during CRRT

Clin Infect Dis. 2011;52:975-981
Daptomycin for MRSA bacteremia

• There is only 1 high quality trial of antibiotic therapy for MRSA bacteremia
  • 246 patients with *S. aureus* bacteremia
• Daptomycin was not inferior to vancomycin or an antistaphylococcal penicillin, each in combination with low-dose, short-course gentamicin (clinical success rate, 44.2% vs. 41.7%)
• High-dose daptomycin (9mg/kg) was not more effective than standard dose daptomycin or vancomycin
• Side-effects include myositis, peripheral neuropathy, or interstitial pneumonitis were not common
• This study led to approval by the US FDA of daptomycin for *S. aureus* bacteremia and right-sided infective endocarditis

Linezolid for MRSA bacteremia

• An oxazolidinone antibiotic with *in vitro* activity against gram-positive pathogens including MRSA
  • protein synthesis inhibitor; bacteriostatic

• No difference vs. vancomycin in bacteremia or for central line infections and similar to vancomycin or teicoplanin for prolonged bacteremia

• A direct comparison of treatment outcomes with linezolid compared to vancomycin in SAB is lacking

• In a systematic review and meta-analysis linezolid was equivalent in efficacy to vancomycin for the treatment of SAB
Other antimicrobials for MRSA bacteremia

• In open-label randomized trials, vancomycin also was compared with teicoplanin, trimethoprim-sulfamethoxazole, and dalbavancin

• None of these antibiotics performed significantly better than vancomycin

• Newer agents targeting PBP2A are a subject of intensive investigation

JAMA. 2014;312(13):1330-1341
Short-course therapy for *S. aureus* bacteremia

• In case of a removable infection source (e.g., a catheter), a 10- to 14-day antibiotic treatment course may be appropriate if all the following conditions are met:
  • after the removal of all prosthetic material and endovascular catheter
  • after the exclusion of endocarditis
  • as long as the follow-up blood cultures drawn 2 to 4 days after initial positive cultures are negative for *S. aureus*
  • if the fever has vanished within 72 hours after the initiation of antistaphylococcal therapy
  • when the absence of metastatic foci has been confirmed

• Some studies suggest that a 2-week intravenous course might be adequate in the treatment of right-sided endocarditis
Contraindications to short-course therapy for right-sided endocarditis in IV drug users

- slow clinical or microbiologic response (>96 hours) to the initial antibiotic treatment
- complicated right-sided endocarditis with heart failure, valve vegetations > 2 cm, acute respiratory failure, empyema, or septic metastatic foci outside the lung
- therapy with glycopeptides or first-generation cephalosporins
- right-sided endocarditis caused by MRSA or polymicrobial infection
- severe immunosuppression (<200 CD4 cells/L) or AIDS
Prolonged therapy for *S. aureus* bacteremia

- Long-term intravenous treatment (>4 weeks) remains standard practice for patients who have
  - left-sided SAE
  - an irremovable primary focus
  - metastatic infection
  - persistence of bacteremia after catheter removal
- Such patients are at high risk of treatment failure, disease recurrence, and death but there is little evidence that long-term therapy (>4 weeks) is superior to shorter courses
Combination therapy for *S. aureus* bacteremia

- Evidence for clinical effectiveness in human beings is limited to one report of 78 patients with *S. aureus* endocarditis in whom the addition of gentamicin to the first 2 weeks of nafcillin treatment reduced the time to defervescence and duration of bacteremia by 1 day
  - Gentamicin was an independent predictor of clinically significant renal toxicity without any observed benefit (mortality, treatment success)
  - Gentamicin is thus no longer routinely recommended for the treatment of *S aureus* native-valve endocarditis.

- Fluoroquinolones, rifampicin, and fusidic acid are also commonly used in the combination therapy of SAB, although there is little evidence to support their routine use and none of these are currently recommended

- Trials of combination therapy are ongoing
Value of ID consultation

• If ID consult is done and the recommendation are followed, a positive impact has been shown for SAB patients:
  • More often correctly diagnosed
    • more frequent follow-up blood cultures and echocardiography
  • Receive more appropriate therapies
    • type and duration of antibiotics
  • Fewer complications/shorter length of stay
    • less relapse of bacteremia
  • May need fewer antibiotics overall
    • highly targeted therapy
  • Higher hospital survival rates
    • 90-day mortality rate increased by 30%

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Take home messages I: *S. aureus* bacteremia

• *S. aureus* bacteremia is extremely common with a high mortality rate
  - True community-associ**ated** *S. aureus* bacteremia is more likely MSSA
  - Community-onset bacteremia may be MSSA or MRSA

• Be aware of hemodialysis catheter-associated *S. aureus* bacteremia
  - Device removal is essential to prevent relapse
  - Clearance of blood cultures by 72 hours is best predictor of uncomplicated course with good outcomes

• MRSA bacteremia appears to have a worse prognosis than MSSA
  - Yet, the reasons for this observation remain unclear

• ID consultation/implementation of suggestions improves outcomes
Take home messages II: therapy

• Choice of empiric therapy for *S. aureus* bacteremia depends on the pre-test probability of MRSA vs. MSSA

• Vancomycin or vancomycin plus anti-staphylococcal β-lactam are acceptable choices pending the results of antibiotic susceptibility testing

• Anti-staphylococcal β-lactams remain the drug of choice for MSSA bacteremia
  • Cephalosporins are the next best alternative

• Vancomycin remains the drug of choice for MRSA bacteremia
  • daptomycin is the next best alternative followed by linezolid

• Trials of combination therapy and new drugs targeting PBP2A are ongoing