Vancomycin + a β-lactam for empiric therapy of all suspected *S. aureus* bloodstream infection

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Conflict of Interest Declaration

- I have no relevant disclosures or conflicts of interest to declare


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S. aureus bacteremia is common and lethal

- 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*
- 30-day case fatality rates of approximately 15-30%
  - No change in overall mortality rates during the past 25 years
- Infection with MRSA has a higher mortality rate than MSSA (30% vs. 17.7%)
- Typical complications include:
  - failure to clear/persistent bacteremia, relapse (recurrence)
  - metastatic infection: infective endocarditis CNS 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; Clin Infect Dis 2003; 36:53–9

S. aureus bacteremia has a poor long-term outcome

- Observational cohort study (Australia; 1997-2007; n=582)
  - Comparison of MSSA and MRSA bacteremia outcomes
- Crude survival time after MRSA was shorter than MSSA (14 vs. 54 months)
- There are several plausible explanations for an increased mortality rate associated with MRSA in comparison to MSSA bacteremia
  - Uncharacterized pathogen-specific virulence factors/host factors
  - Differences in empirical prescribing
  - Inadequate initial coverage for MRSA
  - Poor vancomycin efficacy

Lancet Infect Dis 2014; 14: 967–75
Arch. Intern. Med. 2000 160:1001; Antimicrob. Agents Chemother. 2004 48:4665
J. Clin. Microbiol. 2004 42:2398; Arch. Intern. Med. 1998 158:182

Clinical distinction of MSSA vs. MRSA is not reliable

- 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

Initial drug therapy is necessarily empiric

- 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
  - Time cutoffs for appropriate antibiotic administration have been detected (24-72 hours) after which mortality is increased
  - A treatment delay of 44 hours is associated with a nearly 4-fold increase in the odds of infection-related mortality
- 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 provides a rationale for the most effective therapy at the earliest possible time point

J. Antimicrob. Chemother. 2010 65:2658 –2665
Clin. Microbiol. Infect. 2010 16:747–752
Clin Infect Dis 2003; 36:1418–23

β-lactams are the most effective choice for MSSA bacteremia

- Antibiotic selection plays an important role in outcomes of *S. aureus* bacteremia
- Higher rates of relapse and mortality are seen in patients treated with vancomycin compared to those treated with an anti-staphylococcal β-lactam
- The risk of treatment failure (recurrent infection or death) is 2- to 3-fold higher with vancomycin than nafcillin or cefazolin across reports

BMC Infect Dis 2011; 11:279–86.

Outcome of MSSA bacteremia

- Large retrospective cohort study (2003-2010) of medical or surgical admissions to the 122 acute care VA medical centers with MSSA bacteremia
- The primary outcome was 30-day all-cause mortality after the collection of the first blood culture positive for MSSA (16 793 patients; 16% mortality)
- Patients who were prescribed a β-lactam **for definitive therapy** of MSSA bloodstream infections had a 35% lower hazard of dying within 30 days compared with patients who received vancomycin
- Patients who received **guideline-concordant definitive therapy** with either cefazolin or an antistaphylococcal penicillin had a 43% reduced hazard of mortality compared with patients who received vancomycin

Clin Infect Dis. 2015 Aug 1;61(3):361-7

Recurrence of *S. aureus* bacteremia

- In a multicenter, prospective observational study in 6 university hospitals that enrolled 505 consecutive patients with *S. aureus* bacteremia:
  - Recurrences occurred in 9.4% of *S. aureus* bacteremias; most were relapses
  - Endocarditis and therapy with vancomycin (versus nafcillin) were significantly associated with relapse by multivariate analysis
  - Duration of antistaphylococcal therapy was not associated with relapse, but type of antibiotic therapy was
  - Nafcillin was superior to vancomycin in efficacy in patients with MSSA bacteremia

Medicine (Baltimore) 2003 82: 333-339

Empiric vancomycin monotherapy with de-escalation is suboptimal for MSSA bacteremia

- Evidence suggests that the practice of vancomycin monotherapy with de-escalation to a β-lactam still results in worse outcomes than initiating empirical β-lactam therapy for MSSA
- In a cohort of 72 MSSA infective endocarditis patients, those initially treated with vancomycin and de-escalated to a β-lactam had 4-fold increased mortality risk than those initially treated with a β-lactam (9/22 [40.9%] vs 5/44 [11.4%])
- The median time to de-escalation was 3.0 days
- Addition of β-lactam therapy to even the short window of empirical therapy (3 days) for MSSA is associated with improved clinical outcomes compared to initial vancomycin monotherapy

Antimicrob Agents Chemother 2007; 51:3731–3.

De-escalation from vancomycin to β-lactams

- Schweizer et al. demonstrated a 30-day lower mortality risk in patients who were de-escalated from vancomycin compared to continuing therapy (HR, 0.31; 95% CI, .1–.95)

- Among those who died, time to nafcillin or cefazolin de-escalation was 4.0 days versus 2.5 days among those who lived

- *Importantly*, initial therapy of *S. aureus* bacteremia with a β-lactam is superior to a de-escalation strategy

BMC Infect Dis 2011; 11:279–86.

Vancomycin is an important antimicrobial for MRSA bacteremia but has limitations

- Compared to anti-staphylococcal β-lactams, vancomycin demonstrates:
  - slower bactericidal activity
  - slower clearance of bacteremia
  - poorer tissue penetration
  - This results in higher rates of infection relapse and higher mortality
- *S. aureus* sub-populations with intermediate resistance to vancomycin (hVISA) pre-exist, are selected during therapy, and are difficult to detect
- Importantly, hVISA is associated with treatment failure

Antimicrob Agents Chemother. 1990;34:1227–31; Clin Infect Dis. 2006;42 Suppl 1:S35–9; Pharmacotherapy. 1997;17:990–7; Rev Infect Dis. 1981;3(Suppl):S250–8; Antimicrob Agents Chemother. 2007;51:3731–3; Clin Infect Dis. 2007;45:S191–S5. Infect Genet Evol. 2014;21:575–82; J Antimicrob Chemother. 2007;60:788–94; Semin Respir Crit Care Med. 2015;36:3–16; *Clin Infect Dis*. 2004;38:448-451; *Clin Infect Dis*. 2008;46:193-200

In vitro synergy of β-lactams and vancomycin

- At least 16 *in vitro* studies have explored synergy between vancomycin and β-lactams against MRSA isolates
- All but one of these studies found evidence of synergy in some or all of the tested strains with no evidence of antagonism
- There was a general tendency across these studies to an increasing degree of synergy with increasing vancomycin MICs
  - The “see-saw” effect
- Paradoxically, increasing vancomycin resistance in *S. aureus* is associated with decreasing MICs to oxacillin
  - Due, at least in part, to downregulation or deletion of the *mecA* gene in some strains of VISA and vancomycin-resistant *S. aureus* (VRSA)
  - Possibly due to other structural changes in penicillin-binding proteins and cell wall thickness

J Antimicrob Chemother. 2010;65:24–36
Clin Infect Dis. 2009;49:1072–9

Animal models of synergy

- The few studies that have assessed combinations of vancomycin with β-lactams in animal models have all found evidence of synergy
  - In a MRSA rabbit endocarditis and a renal abscess model, vancomycin plus nafcillin resulted in faster sterilization of infection
  - In a rat endocarditis model with a MRSA or a VISA strain, the combination of vancomycin plus ceftobiprole led to faster killing on time-kill curves, but similar rates of mortality and of sterilization of vegetations compared with ceftobiprole alone

Antimicrob Agents Chemother. 1999;43:1747–53
Antimicrob Agents Chemother. 2012;56:1476–84

Combination therapy of MRSA bacteremia improves microbiological outcomes

- A retrospective single center cohort study analyzed patients with MRSA bacteremia who received vancomycin plus β-lactam therapy (for at least 24 h at the clinician's discretion) or vancomycin alone

- Eradication was achieved in 48/50 (96%) patients with combination therapy and 24/30 (80%) of patients with vancomycin monotherapy (p=0.021)

- The effect persisted in a multivariate model attempting to control for potential confounders (adjusted odds ratio for achieving microbiological eradication in the combination group = 11.24, P = 0.01)

Antimicrob Agents Chemother. 2013; 58(2):1028-33

β-lactam plus vancomycin is more efficacious than vancomycin for MRSA bacteremia

- CAMERA-1:
- An open label multicenter feasibility trial that randomized 60 patients with MRSA bacteremia to vancomycin (n=29) or vancomycin plus flucloxacillin (n=31)
- Patients receiving combination therapy cleared bacteremia at a mean of 2 days compared to 3 days with standard therapy (P = 0.06)
- Fewer patients in the combination therapy group had persistent bacteremia at days 3 and 7 after randomization
- No difference in the secondary end points of 28- and 90-day mortality, metastatic infection, nephrotoxicity, or hepatotoxicity

Clin Infect Dis. 2015;62(2): 173-80

β-lactam + vancomycin is superior to the *status quo*

- *S. aureus* bacteremia is too common and far too lethal to manage with empiric monotherapy
- Optimal empiric therapy of SAB requires timely administration of the most efficacious antimicrobials – in combination
  - β-lactams are inexpensive, widely available, and are associated with a low risk of adverse reactions
  - Nothing is better than vancomycin for MRSA but it kills slowly, penetrates poorly, and is associated with adverse outcomes
- MSSA: Initial therapy with β-lactams is the best approach and superior to vancomycin (even with a de-escalation strategy)
- MRSA: Combined therapy shows *in vitro* evidence of synergy and reduced development of antimicrobial resistance
- Combined therapy *in vivo* leads to improved outcomes (microbiological eradication, shortened duration of bacteremia)

- Taylor Swift