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

Salman Qureshi, MD
McGill University Faculty of Medicine
Department of Critical Care Medicine
McGill University Health Centre
Conflict of Interest Declaration

• I have no relevant disclosures or conflicts of interest to declare
KEEP CALM BECAUSE TWO IS BETTER THAN ONE
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
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
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

\(\beta\)-lactams are the most effective choice for MSSA bacteremia

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

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
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

**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

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

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)

**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

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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)
now I'm thinkin' two, is better than one

- Taylor Swift