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The Empirical Combination of Vancomycin and a β-Lactam for Staphylococcal Bacteremia

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The high prevalence of methicillin resistance among *Staphylococcus aureus* bacteremias leads to common use of vancomycin as empirical therapy. However, investigators have reported poor outcomes with vancomycin treatment for methicillin-susceptible *Staphylococcus aureus* bacteremia. We review the evidence supporting empirical combination of both vancomycin and a β-lactam agent for *Staphylococcus aureus* bacteremia. Vancomycin therapy for methicillin-susceptible *Staphylococcus aureus* bacteremia is associated with 2–3 times the risk of morbidity and mortality compared to an antistaphylococcal penicillin (oxacillin and nafcillin) or first-generation cephalosporin (cefazolin). De-escalation of empirical vancomycin to definitive β-lactam therapy still appears inferior to initial β-lactam therapy. Although there is no clinical trial supporting combination therapy, a scientific rationale for benefit exists and should be weighed against the risks (adverse events, antibiotic resistance, and cost) of additional pharmacotherapy. The empirical combination of vancomycin and a β-lactam (either nafcillin, oxacillin, or cefazolin) for staphylococcal bacteremia may improve infection-related clinical outcomes.

Keywords. MRSA; MSSA; empirical therapy; vancomycin; nafcillin.

The pharmacotherapy for serious infections is guided by key principles that include (1) empirical therapy with broad-spectrum antimicrobials, dose-adjusted to achieve pharmacodynamic targets and effectively treat potential drug-resistant organisms; (2) broad-spectrum therapy, subsequently de-escalated to treat the causative pathogen; (3) a hospital-wide system of infection control measures and antimicrobial stewardship to decrease the spread of antimicrobial resistance and improve clinical outcomes; (4) source control, a critical component of treatment that includes removal of infected catheters, abscess drainage, and surgical intervention; and (5) timely initiation of appropriate therapy, which can be life-saving [1, 2].

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Staphylococcus aureus bacteremia remains a significant healthcare burden, with an estimated 10.3 episodes per 1000 hospital discharges, and a life-threatening infection with an estimated 30-day mortality of 21% in the United States [3, 4]. In the patient with positive blood cultures, Gram stain, or a high clinical suspicion of serious staphylococcal bacteremia, initial therapy includes either an antistaphylococcal penicillin (nafcillin or oxacillin), first-generation cephalosporin (cefazolin), or vancomycin depending on clinical suspicion for methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA, respectively). Delays in initiation of appropriate empirical antibiotics for staphylococcal bacteremia are a critical determinant of outcome. A treatment delay of 44 hours is associated with a nearly 4-fold increase in the odds of infection-related mortality (odds ratio [OR], 3.8; 95% confidence interval [CI], 1.3–11.0) [5]. Investigators have suggested that the empirical combination of both a β-lactam and anti-MRSA agent to cover both potential staphylococcal pathogens (MSSA and MRSA) may improve clinical outcomes [6, 7].

The purpose of this manuscript is to review the clinical evidence supporting combination therapy with

vancomycin and an antistaphylococcal penicillin or first-generation cephalosporin for empirical treatment of *Staphylococcus aureus* bacteremia, and provide recommendations as to where combination therapy would be of greatest benefit. Studies were obtained by a search of Medline (January 1962–May 2013); Medical Subject Heading terms included *Staphylococcus aureus*, *bacteremia*, *vancomycin*, *nafcillin*, *cefazolin*, and *empirical therapy*, limited to English-language literature and screened for topical relevance.

USE OF EMPIRICAL VANCOMYCIN MONOTHERAPY FOR STAPHYLOCOCCAL BACTEREMIA

MRSA in the United States is endemic in the community and hospital setting. In one study, approximately 50% of emergency department visits for skin and soft tissue infections were positive for MRSA [8]. Risk factors for community-acquired MRSA (USA300 strain) bloodstream infections include age 59 or younger, intravenous drug use, homelessness or marginal housing, hepatitis C infection, human immunodeficiency virus (HIV) infection, and prior skin and soft tissue infection [9]. Hospital-acquired staphylococcal isolates were reported to be 54% methicillin resistant during 2009–2010 [10]. Risk factors for nosocomial MRSA bacteremia include admission for surgery, prolonged length of stay, age 65 or older, mechanical ventilation, and central venous catheter [11]. Other important risk factors to be considered include colonization with MRSA, severity of illness, immunosuppression, and prior healthcare exposure [12]. Vancomycin is the standard treatment for MRSA [13]. Delays in starting appropriate antimicrobial therapy for MRSA bacteremia are associated with increased morbidity and mortality [14–18]. A meta-analysis of 9 studies demonstrated that the odds of mortality are nearly doubled with inappropriate empirical therapy for MRSA bacteremia compared to appropriate initial therapy (pooled OR, 1.99; 95% CI, 1.6–2.4) [18].

Because of the prevalence of MRSA, any patients with suspected staphylococcal bacteremia should be empirically treated with an anti-MRSA agent (most commonly vancomycin) until MRSA infection is excluded, because delays in antibiotic therapy can increase mortality.

VANCOMYCIN MONOTHERAPY COMPARED TO β-LACTAMS FOR MSSA BACTEREMIA

MSSA bacteremia should be treated with an antistaphylococcal penicillin (nafcillin or oxacillin) or first-generation cephalosporin (cefazolin) as several cohort studies have reported poor clinical outcomes with vancomycin-treated MSSA bacteremias. These results are summarized in Table 1 [19–24]. Stryjewski

Table 1. Summary of Published Studies Evaluating Empirical Therapy for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

Study	Year	Design	Study Size, No.	Outcome	Vancomycin vs β-Lactam	Result[a]
Vancomycin therapy vs β-lactam therapy[b]						
Chang et al [19]	2003	Prospective cohort	505	Bacteriologic failure[c]	19% vs 0%	OR, 6.5 (1.0–53)
Khatib et al [20]	2006	Prospective cohort	120	Overall mortality	27% vs 12%	HR, 2.3 (1.1–4.9)
Stryjewski et al [21][d]	2007	Prospective cohort	123	Treatment failure	31% vs 13%	OR, 3.5 (1.2–13)
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	39% vs 11%	OR, 6.5 (1.4–29)
Kim et al [22]	2008	Retrospective case-control	27	Infection-related mortality	37% vs 11%	OR, 3.3 (1.2–9.5)
Schweizer et al [23]	2011	Retrospective	267	30-day in-hospital mortality	20% vs 3%	HR, 4.8 (2.1–11)[f]
Chan et al [24]	2012	Retrospective cohort	293 094	Hospitalization rate	12.5 vs 7.2[g]	HR, 1.6 (1.2–2.2)[f]
Vancomycin therapy vs vancomycin therapy de-escalated to β-lactam						
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	33% vs 41%	NS
Schweizer et al [23]	2011	Retrospective cohort	267	30-day in-hospital mortality	20% vs 7%	HR, 3.2 (1–10)
Vancomycin therapy de-escalated to β-lactam therapy vs β-lactam therapy						
Khatib et al [25]	2006	Prospective cohort	168	Persistent bacteremia	56% vs 37%	$P = .03$
Lodise et al [6][e]	2007	Retrospective cohort	84	Infection-related mortality	41% vs 11%	Not reported

Abbreviations: HR, hazard ratio; NS, not statistically significant; OR, odds ratio.

[a] Odds or hazard ratio for vancomycin therapy (95% confidence interval).

[b] Studies defined primary therapy for patients as receipt of the antibiotic for at least the majority of the treatment course (ie, 75% of time or 10/14 days).

[c] Defined as either relapsed infection or persistent bacteremia for >7 days.

[d] Study included patients on hemodialysis, and treatment failure was defined as death or recurrent infection.

[e] Study focused on infective endocarditis.

[f] Study reported hazard ratio with vancomycin as referent group; it is inverted here (1/HR) for conformity with other study results.

[g] Hospitalization event rate per 100 patient-months.

et al reported a prospective analysis of treatment failure among patients with MSSA bacteremia (N = 240) treated with vancomycin or cefazolin [21]. Failures were reported with 31.2% of vancomycin-treated and 13% of cefazolin-treated patients ($P = .02$). This occurred despite the cefazolin group having a higher proportion of patients with metastatic cancer (36.7% vs 11.7%) and infective endocarditis (17.4% vs 5.2%). Kim et al performed a propensity score–matched case-control analysis (n = 27) of vancomycin-treated cases compared to β-lactam–treated cases and demonstrated an increased odds of infection-related mortality with vancomycin (37% vs 11%; adjusted OR, 3.3; 95% CI, 1.2–9.5) [22]. Schweizer et al reported a retrospective cohort (N = 267) of MSSA bacteremia and demonstrated that patients treated with cefazolin or nafcillin had a lower 30-day mortality risk than vancomycin-treated patients (3% vs 20%, respectively; hazard ratio [HR], 0.21; 95% CI, .09–.47) [23]. A prospective, observational study of MSSA bacteremia by Chang et al demonstrated that odds of persistent bacteremia (blood cultures positive >7 days) or relapse were 6.5 times higher with vancomycin compared to nafcillin (OR, 6.5; 95% CI, 1.0–53) [19]. Khatib et al reported on 120 cases of hospitalized patients with MSSA bacteremia and demonstrated a higher mortality risk in vancomycin-treated versus β-lactam–treated patients (27.5% vs 12.1%; HR, 2.3; 95% CI, 1.1–4.9; $P = .03$) [20]. A large (N = 293 094) retrospective cohort of hemodialysis outpatients also demonstrated that treatment of MSSA bacteremia with cefazolin versus vancomycin was associated with a significantly lower combined risk of hospitalization or death (HR, 0.6; 95% CI, .5–.8) [24].

Whether outcomes differ between β-lactams (nafcillin vs cefazolin) has not been widely evaluated. One propensity score–matched case-control study evaluated nafcillin versus cefazolin for MSSA bacteremia and demonstrated equivalent rates of treatment failure (15% vs 15%) [26]. A retrospective cohort study of MSSA bacteremia also found similar 90-day mortality rates for oxacillin versus cefazolin (32% vs 40%, respectively; adjusted OR, 0.9; 95% CI, .5–1.8) [27].

Although these studies differ in underlying severity of illness, source of bacteremia, definitions of outcome, and method of analysis, there is a consistent conclusion that nafcillin or cefazolin improved treatment-related outcomes compared to vancomycin for MSSA bacteremia. The risk of treatment failure (recurrent infection or death) is 2- to 3-fold higher with vancomycin than nafcillin or cefazolin across these reports. As current evidence suggests that nafcillin and cefazolin are more clinically effective, de-escalation from empirical vancomycin is common practice. The study by 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) [23]. The median time to de-escalation in the Schweizer report was 3.0 days (interquartile range, 2.4–3.9) and among those who died, time to nafcillin or cefazolin de-escalation was 4.0 days versus 2.5 days among those who lived.

DE-ESCALATION FROM VANCOMYCIN IS INFERIOR TO INITIAL THERAPY WITH NAFCILLIN OR CEFAZOLIN

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. Lodise et al studied a cohort of 72 MSSA infective endocarditis patients and demonstrated an increased risk of infection-related mortality in vancomycin compared to β-lactam–treated controls (39.3% vs 11.4%; $P = .005$) [6]. Additionally, 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. Khatib et al also reported that persistent rates of MSSA bacteremia (blood cultures positive for >3 days) were similar between patients continued on vancomycin or de-escalated to β-lactams (47% vs 56%, respectively), whereas those initially treated with either a β-lactam or both vancomycin and β-lactam were lower (37% and 0%, respectively) [25]. The reported mean time to vancomycin de-escalation was 75 hours.

Addition of β-lactam therapy to even the short window of empirical therapy (eg, 3 days) for MSSA is associated with improved clinical outcomes compared to initial vancomycin monotherapy. To achieve adequate coverage of both MSSA and MRSA, empirical coverage should include both a β-lactam and vancomycin.

IMPACT OF RAPID DIAGNOSTIC TESTING ON EMPIRICAL THERAPY

Modern polymerase chain reaction testing methods are improving time to identification of infectious pathogens including *Staphylococcus aureus*. There are several MRSA tests currently available in the United States [28]. Of these, the Xpert MRSA/SA BC test has demonstrated improvements in time to initiation of antistaphylococcal therapy for MSSA (mean, 5.5 hours vs 49 hours) and reduced empirical initiation of vancomycin therapy [29]. An alternative approach is matrix-assisted laser desorption/ionization-time of flight mass spectrometry, which has the ability to rapidly identify *Staphylococcus aureus* and methicillin-resistant organisms [30]. Limitations compared to rapid MRSA testing include its use is pending Food and Drug Administration approval, the methodology typically requires bacterial culture of the organism, and acquisition of the testing equipment is expensive. Although these tests reduce time to identification of *Staphylococcus aureus*, they have not been

widely implemented in US hospitals. Also, to effectively reduce the empirical therapy window, the results must be promptly communicated to and acted upon by the clinician. However, the impact of rapidly available microbiology results on prescriber practice has not been widely evaluated. Rapid testing is a promising solution but until widespread implementation, determining the most appropriate empirical therapy regimen is critical.

RISKS ASSOCIATED WITH COMBINATION THERAPY

Empirical addition of nafcillin or cefazolin to vancomycin monotherapy for *Staphylococcus aureus* is a novel regimen, albeit with well-characterized agents; therefore, the risks should be carefully considered. Bactericidal activity has been evaluated in vitro for the combination of oxacillin and vancomycin for 10 clinical MSSA isolates, and antagonism was not observed [31]. Addition of a β-lactam to vancomycin monotherapy carries a risk of allergic reaction, but serious reactions including anaphylaxis are relatively uncommon with penicillin (0.04%) and cephalosporins (0.02%) and can be screened for with a careful history [32, 33]. Nafcillin may cause interstitial nephritis and induces liver cytochrome enzymes that could interfere with concomitant drug therapies (eg, warfarin), and both medications may rarely cause leukopenia or thrombocytopenia. However, the relatively short duration of empirical therapy (3 days) until susceptibilities are determined would limit these risks. Increasing β-lactam use could potentially lead to increased MRSA rates; this risk would appear greater if broad-spectrum cephalosporins and β-lactam/β-lactamase inhibitors were used instead of nafcillin and cefazolin [34, 35]. Broad-spectrum β-lactams would also provide unnecessary gram-negative activity. Additionally, experimental evidence suggests that methicillin and vancomycin resistance have an inverse relationship and that the combination of β-lactams and vancomycin may improve killing effect and limit resistance development [36–38]. The high risk of morbidity and mortality in staphylococcal bacteremia should be weighed against the risks of empirically adding nafcillin or cefazolin to vancomycin monotherapy.

ALTERNATIVES TO COMBINATION THERAPY: DAPTOMYCIN AND LINEZOLID

A possible alternative to discussing empirically combining vancomycin with nafcillin or cefazolin would be recommending linezolid or daptomycin for bacteremia. However, neither agent has definitively improved outcomes with staphylococcal bacteremia. Daptomycin was compared to vancomycin in a randomized controlled noninferiority trial of *S. aureus* (both MRSA and MSSA) bacteremia and endocarditis with similar treatment success (41.7% vs 44.2%, respectively; risk difference [RD], 2.4%; 95% CI, −10.2% to 15.1%) [39]. Linezolid was compared to vancomycin in a noninferiority trial for catheter-related bloodstream infections and demonstrated similar microbiologic cure rates for MSSA and MRSA bacteremia and mortality (82.1% vs 83.3%, respectively; RD, 1.2; 95% CI, −16.3 to 13.9) [40]. In both studies, vancomycin was de-escalated to an antistaphylococcal penicillin for MSSA. However, similar outcomes were reported for MSSA and MRSA, suggesting that daptomycin and linezolid therapy are not superior to de-escalation to a β-lactam but may be an alternative therapy if β-lactams are contraindicated (ie, allergy). In contrast, observational data suggest that combination therapy with a β-lactam and vancomycin results in improved bacteremia outcomes compared to de-escalation [6, 25]. The acquisition cost of daptomycin (80-kg patient, 6 mg/kg, US$362/day) and linezolid (600 mg intravenous twice daily, US $288/day) alone is also higher than vancomycin (1 g twice daily, US$10/day) and oxacillin (2 g every 4 hours, US$169/day) combined, although drug monitoring increases vancomycin costs [41]. Daptomycin and linezolid are noninferior compared to vancomycin therapy but do not appear to have superior clinical outcomes in *Staphylococcus aureus* infective endocarditis or catheter-related bloodstream infections.

A clinical trial for ceftaroline (cephalosporin with anti-MRSA activity) and MRSA bacteremia is ongoing (www.clinicaltrials.gov: NCT01701219) [42, 43]. Serial passages in subinhibitory concentrations of ceftobiprole, another cephalosporin with anti-MRSA activity, for 28 days did lead to resistance development in MRSA [44]. Ceftaroline may be an acceptable alternative but is not approved for bacteremia.

APPROPRIATE SETTING FOR USE OF COMBINATION THERAPY WITH VANCOMYCIN AND NAFCILLIN OR CEFAZOLIN

As a guiding principle, initiation of appropriate antimicrobial therapy is a critical predictor of outcome, especially in serious infections. In those institutions with a high prevalence of MRSA requiring empirical vancomycin therapy, combination of both vancomycin and nafcillin or cefazolin empirically could improve MSSA clinical outcomes. After susceptibility results are known, therapy can be de-escalated to the appropriate antibiotics to limit risk of toxicity. Patients at the highest risk of morbidity and mortality from *S. aureus* infection would gain the greatest benefit from receipt of initial combination therapy. The cohort studies demonstrating a benefit included patients with severe sepsis (signs of end-organ dysfunction or decreased tissue perfusion), complicated bacteremias (such as probable or proven infective endocarditis), or presence of a prosthetic device, intravascular device, or nonremovable foci of infection [6, 21].

One might argue that bacteremia with *S. aureus,* independent of host risk factors, carries sufficient risk of morbidity and mortality to support initial combination therapy.

CONCLUSIONS

Use of combination therapy in infectious disease practice has been used for life-threatening gram-negative infections with the rationale that improved treatment outcomes outweigh the risks of toxicity, promoting further antibiotic resistance and increased cost [45]. Similarly, treatment success rates can be <50% in *Staphylococcus aureus* bacteremia (both MSSA and MRSA), demonstrating a need for alternative treatment options [39]. Newer therapies such as daptomycin, linezolid, and ceftaroline have not yet demonstrated superiority to vancomycin alone for empirical treatment of bacteremia. A potential alternative to combination therapy is adoption of a rapid diagnostic test capable of discriminating MRSA and MSSA from positive blood cultures. Additional research focusing on early antimicrobial initiation (ie, time to antibiotic initiation with vancomycin vs other agents) in *Staphylococcus aureus* bacteremia and more adequately controlling for underlying risk factors for treatment failure would help solidify the current evidence. Although randomized trials are the highest level of evidence-based research, none are currently available. Current observational data provide evidence that empirical vancomycin therapy carries an increased risk of mortality in MSSA bacteremia even if therapy is de-escalated to nafcillin or cefazolin. A shift in focus to combining vancomycin and an antistaphylococcal penicillin or first-generation cephalosporin in *Staphylococcus aureus* bacteremia could potentially improve overall morbidity and mortality with this serious infection.

Notes

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