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Vancomycin plus nafcillin salvage for the treatment of persistent methicillin-resistant Staphylococcus aureus bacteremia following daptomycin failure: a case report and literature review

Paul O. Lewis, Regan E. Sevinsky, Paras D. Patel, Matthew R. Krolikowski and David B. Cluck

Abstract

Background: Evidence supporting beta-lactam plus vancomycin synergy for methicillin-resistant *Staphylococcus aureus* (MRSA) continues to grow. Current *in vivo* evidence demonstrates that combination therapy is associated with shorter time to blood sterilization than vancomycin monotherapy. However, this combination has not been reported as salvage therapy for persistent MRSA bacteremia.

Case report: We report a case of an 81-year-old male who was successfully treated with vancomycin plus nafcillin after failing vancomycin monotherapy, daptomycin monotherapy, and daptomycin plus gentamicin combination therapy. The patient originally presented with sepsis from a suspected urinary tract infection. Blood cultures drawn on days 1, 3, 5, 15, 19, 23, and 28 remained positive for MRSA despite multiple antimicrobial therapy changes. On day 29, therapy was changed to vancomycin plus nafcillin. Blood cultures drawn on day 32 remained negative. After 11 days, nafcillin was changed to piperacillin–tazobactam due to an infected decubitus ulcer. The combination was continued for 42 days after achieving blood sterility, 71 days after the patient originally presented. Evidence regarding salvage therapy for persistent bacteremia is sparse and is limited to case reports and case series.

Conclusion: This case report supports that vancomycin plus an anti-staphylococcal beta-lactam combination should be further studied as salvage therapy for persistent MRSA bacteremia.

Keywords: bacteremia, methicillin-resistant, nafcillin, salvage therapy, *Staphylococcus aureus*, vancomycin

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Correspondence to:
Paul O. Lewis
Department of Pharmacy, Johnson City Medical Center, 400 North State of Franklin Road Johnson City, TN 37604, USA.
plewis16@gmail.com

Paul O. Lewis
Department of Pharmacy, Johnson City Medical Center, Johnson City, TN, USA

Regan E. Sevinsky
Department of Pharmacy, Massachusetts General Hospital, Boston, MA, USA

Paras D. Patel
Matthew R. Krolikowski
Division of Infectious Diseases, Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA

David B. Cluck
Department of Pharmacy Practice, Bill Gatton College of Pharmacy, East Tennessee State University, Johnson City, TN, USA

Introduction

Staphylococcus aureus remains a long-standing challenge in healthcare due to resistance, metastatic complications, frequent treatment failures, and high mortality rates.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) first emerged in 1962, only 2 years after methicillin's approval in 1960.[1] In 2013, the Centers for Disease Control and Prevention (CDC)[1] highlighted MRSA as a serious drug-resistant threat citing over 80,000 severe infections leading to over 11,000 deaths each year in the United States. MRSA frequently enters the blood stream and metastasizes resulting in endocarditis and osteomyelitis. This represents a major burden on the healthcare system, with 30- and 90-day mortality rates as high as 30% and 50%, respectively.[2]

For treatment of MRSA bacteremia, the Infectious Diseases Society of America (IDSA)

MRSA guidelines recommend vancomycin or daptomycin.[3] Vancomycin is a glycopeptide that has historically been considered the workhorse for invasive MRSA infections. However, concerns have risen regarding slow bacterial killing, rising minimum inhibitory concentrations (MICs), variable tissue penetration, and the emergence of intermediate and resistant strains.[3] Daptomycin is a lipopeptide that often used as an alternative to vancomycin for bacteremia and other serious invasive infections.[3] However, daptomycin cannot be used for non-hematogenous pneumonia. In addition, vancomycin cross-resistance and the development of daptomycin nonsusceptible strains of *S. aureus* have emerged.[3]

IDSA MRSA guidelines define treatment failure as persistently positive blood cultures past 7 days of adequate therapy and recommend a salvage regimen of high-dose daptomycin (10 mg/kg/day) in combination with gentamicin, rifampin, linezolid, trimethoprim/sulfamethoxazole, or a beta-lactam antibiotic.[3] There are no recommended salvage regimens for daptomycin failure or any that include vancomycin combinations. To our knowledge, no clinical studies or case reports have been published to date describing the use of a beta-lactam plus vancomycin for the treatment of persistent MRSA bacteremia. Current literature describes shorter times to blood clearing but use as a salvage for persistent MRSA bacteremia is not well-described. Thus, we report our case of successful use of nafcillin/vancomycin combination salvage therapy for persistent MRSA bacteremia lasting longer than 4 weeks, after failing vancomycin monotherapy, daptomycin monotherapy, and daptomycin plus gentamicin combination.

Case report

We present the case of an 81-year-old male who presented from a skilled nursing facility with persistent fevers, confusion, and sepsis, secondary to a suspected urinary tract infection that failed to respond to outpatient levofloxacin. His past medical history included hypertension, cerebral hemorrhage, atrioventricular block, and benign prostatic hyperplasia. Pertinent vital signs and laboratories include heart rate of 94 beats per minute, respiratory rate of 23 breaths per minute, white blood cell (WBC) of 15.2 K/mcL, temperature of 100.7°F, and blood pressure of 128/70 mmHg. Medications on admission included tamsulosin, clonidine, and levofloxacin. He reported an allergy to sulfonamides. Blood and urine cultures were collected, levofloxacin was discontinued, and ceftriaxone 1 g intravenously (IV) every 24 h was subsequently initiated. A Foley catheter was in place but changed upon admission. An initial chest X-ray revealed no acute process.

On day 2 of admission, both blood and urine cultures were positive for *S. aureus, mecA* positive by polymerase chain reaction. Susceptibilities were performed by VITEK2 which demonstrated a vancomycin MIC $\leq$ 0.5 mg/L and a daptomycin MIC = 0.25 mg/L (see Table 1). Ceftriaxone was discontinued, and vancomycin was initiated at 15 mg/kg IV every 12 h. On day 3, a transthoracic echocardiogram (TTE) of adequate diagnostic quality found no evidence of endocarditis. Transesophageal echocardiogram was attempted on day 7 but was aborted due to complications. A repeat TTE was considered but not performed as it was unlikely to change the course of therapy. Vancomycin troughs were monitored twice weekly and maintained greater than 10 mg/L (range 10.2–12.2 mg/L). Subsequent blood cultures drawn on days 3, 5, and 15 remained positive. On day 17, a magnetic resonance imaging was performed to evaluate the lumbar spine, demonstrating no evidence of osteomyelitis, discitis, or abscess. On day 18, therapy was changed to daptomycin 6 mg/kg IV every 24 h. Creatinine phosphokinase was monitored weekly and remained within normal limits. Blood cultures on days 19 and 23 remained positive. On day 25, daptomycin was increased to 8 mg/kg IV every 24 h, and gentamicin 1 mg/kg IV every 8 h was added. Gentamicin levels were monitored to maintain peaks above 3 mg/L and troughs below 1 mg/L. In addition, a whole body indium-111 tagged WBC scan was performed and did not reveal any evidence metastatic infection.

Blood cultures were repeated on day 28 which subsequently turned positive on day 29. Hospice care was discussed with the patient and family due to his continued fevers, increasing confusion, declining clinical status, and overall poor prognosis. The family requested to continue care for an additional week. The infectious diseases service switched to the salvage regimen of vancomycin 15 mg/kg IV every 12 h plus nafcillin 2 g IV every 4 h. Vancomycin troughs ranged from 10.7 to 12.3 mg/L, similar to the previous course. Blood cultures drawn on day 32, 3 days after starting vancomycin and nafcillin, were negative. A

Table 1. Minimum inhibitory concentrations and interpretations for the patient's *Staphylococcus aureus* blood cultures.

	Oxacillin MIC[a], mg/L (interpretation)	Vancomycin MIC[a], mg/L (interpretation)	Daptomycin MIC[a], mg/L (interpretation)	Gentamicin MIC[a], mg/L (interpretation)
Day 1	⩾4 R	⩽0.5 S	0.5 S	⩽0.5 S
Day 3	⩾4 R	1 S	0.25 S	⩽0.5 S
Day 5	⩾4 R	⩽0.5 S	0.25 S	⩽0.5 S
Day 15	⩾4 R	⩽0.5 S	0.25 S	⩽0.5 S
Day 19	⩾4 R	⩽0.5 S	0.25 S	⩽0.5 S
Day 23	⩾4 R	⩽0.5 S	0.25 S	⩽0.5 S
Day 28	⩾4 R	⩽0.5 S and 1.5[b] S	0.25 S and 1[b] S	⩽0.5 S

MIC, minimum inhibitory concentration; R, resistant; S, susceptible.
[a]Susceptibility obtained from VITEK2 (bioMérieux Inc., Durham, NC) unless otherwise specified.
[b]Susceptibility testing obtained from manual E-test.

peripherally inserted central venous catheter was placed on day 16 which was removed with the tip sent for culture on day 33 which showed no evidence of growth. Local wound care had been continuously provided for an unstageable decubitus ulcer. A bedside debridement procedure was also performed on day 34, 2 days after the negative blood cultures. After 11 days, nafcillin was changed to piperacillin–tazobactam 3.375 g IV every 6 h, based on a culture of *Pseudomonas aeruginosa* growing from an infected decubitus ulcer. The patient continued to improve and was discharged on day 44 to a skilled nursing facility to continue vancomycin and piperacillin–tazobactam to complete 42 days of therapy following the negative blood culture, which was 71 days after the initial presentation. Renal function was monitored throughout therapy without any significant changes.

Discussion

Nafcillin/vancomycin combination demonstrated to be an effective salvage regimen in a patient previously failing multiple regimens for persistent MRSA bacteremia. This combination has gained notable attention in recent literature. At least 15 *in vitro* studies have found synergy between vancomycin and beta-lactams, with the greatest effect suggested with penicillinase-resistant penicillins, such as nafcillin.[4] Nafcillin/vancomycin combination has also been studied in animal models[5,6] and human models.[7–9] Results are summarized in Table 2. Based on the growing research, there is now a prospective, randomized controlled trial evaluating vancomycin or daptomycin alone or in combination with a beta-lactam.[4] Endpoints include 90 day all-cause mortality, persistent bacteremia at 5 days or longer, microbiological relapse, or microbiological failure. The trial is registered with clinicaltrials.gov (identifier NCT02365493) and is targeting an enrollment of 440 patients.[4] Efforts directed at the *in vivo* studies have only demonstrated reduced time to blood sterilization or a reduction in the number of treatment failure and have not evaluated salvage therapy for persistent bacteremia or daptomycin failure.

The exact mechanism for the synergy between vancomycin and anti-staphylococcal beta-lactams is unknown. One potential theory suggests that beta-lactams induce the potentiation of host defense peptides, such as cathelicidin lower limit (LL)-37.[10] Cathelicidins are a family of peptides prevalent in skin and neutrophils with a broad-spectrum antimicrobial activity, including MRSA.[9] Another theory describes a 'see-saw effect' in which increasing vancomycin resistance parallels decreasing beta-lactam resistance.[11] The distortion in the cell wall precursor pool results in reduced vancomycin susceptibility but appears to suppress methicillin resistance.[11] Furthermore, exposure to beta-lactams leads to upregulation of

Table 2. *In vivo* evidence supporting beta-lactam plus vancomycin combinations for *S. aureus*.

Study	Study type	Intervention	Outcomes
Climo and colleagues[5]	Rabbit endocarditis and renal abscess	Vancomycin or nafcillin alone and in combination for three strains of VISA	Therapy with either agent alone was ineffective. However, combination therapy resulted in a mean reduction of 4.52 CFU/g of aortic valvular vegetation compared to control. Combination therapy sterilized 89% of renal abscesses compared to 12.5% in monotherapy
Ribes and colleagues[6]	Murine peritonitis	Vancomycin, linezolid, or imipenem alone and in combination against 1 strain of VISA and 1 strain of hVISA	*In vitro*, vancomycin plus imipenem resulted in faster bacterial killing than vancomycin or imipenem alone in both strains tested. *In vivo*, linezolid plus imipenem achieved the highest rate of killing, followed by linezolid plus vancomycin
Dilworth and colleagues[7]	Retrospective human bacteremia	Vancomycin plus a beta-lactam combination ($n = 50$) compared to vancomycin monotherapy ($n = 30$) in MRSA bacteremia	Blood sterilization on the first blood culture after therapy initiation was achieved in 48/50 (96%) in the combination group compared to 24/30 (80%) in the monotherapy group ($p = 0.021$)
Davis and colleagues[8]	Prospective human bacteremia	Vancomycin monotherapy ($n = 30$) *versus* vancomycin plus flucloxacillin combination ($n = 30$) in MRSA bacteremia	Combination therapy reduced the duration of bacteremia by 35% compared to vancomycin monotherapy
Casapao and colleagues[9]	Retrospective human bacteremia	Vancomycin monotherapy ($n = 40$) *versus* vancomycin plus beta-lactam ($n = 57$) in MRSA bacteremia	Combination did not decrease clinical failure rates compared to monotherapy (24.6% *versus* 30%, $p = 0.552$) however did result in a 1-day reduction in time to blood sterilization. Combination was also inversely associated with treatment failure (adjusted odds ratio 0.237 (95% CI 0.057, 0.982); $p = 0.047$).

CFU; colony forming units; hVISA, hetero-resistant vancomycin intermediate *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; VISA, vancomycin intermediate *Staphylococcus aureus*.

the *mecA* gene and down-regulation of the accessory gene regulator (Agr) operon, ultimately promoting expression of cell wall surface proteins and repressing extracellular toxins.[12] These alterations to the cell wall and decreased toxin production then promote enhanced host complement-dependent attack and opsonophagocytic killing.[12] It should also be noted that daptomycin plus a beta-lactam has demonstrated similar synergistic killing, restoration of reduced daptomycin susceptibility, and increased daptomycin binding.[13]

For bacteremia, the 2009 IDSA vancomycin guidelines recommend doses of 15–20 mg/kg, given every 8–12 h and adjusted to a target trough of 15–20 mg/L and an area under the curve (AUC): MIC of greater than 400.[14] In our case, vancomycin doses were kept between 15–20 mg/kg; however, vancomycin trough levels were kept between 10–15 mg/L. The subtherapeutic treatment limitation warrants further discussion. Several studies have associated the higher troughs (15–20 mg/L) with increased rates of vancomycin-associated nephrotoxicity.[15–17] Other studies have been unable to find an association between higher troughs and improved outcomes.[18–20] Pharmacokinetic modeling studies further support attainment of AUC:MIC goals with lower troughs (10–14.9 mg/L) and less nephrotoxicity risk.[21,22] As noted in Table 1, the MIC for vancomycin was consistently 0.5 mg/L when tested *via* VITEK2, except for one culture noting an MIC of 1 mg/L. This means that total AUC must be maintained higher than 200 mg h/L, to achieve an AUC:MIC of 400. By calculation, troughs of 10–15 mg/L far exceed this goal. The target AUC:MIC goal has been brought into question. Original data defining the AUC:MIC goal of greater than 400 were based on broth microdilution, the gold standard for MIC testing. MICs determined by elipsometer (E)-tests tend to be consistently higher than automated testing methods, such as VITEK2.[23,24] Goal AUC:MIC may need to be redefined to specify testing method.[25,26] The limitations to MIC testing methodology have led many prescribers to return to evaluating effectiveness of therapy based on clinical response.[3] Patients not responding to current therapy should be evaluated for a therapeutic change despite the MIC. In this case, the original dose leading to treatment failure was reinitiated in combination with the nafcillin, suggesting the lack of efficacy was not dose dependent.

Another consideration is the dose of daptomycin, which was initially dosed at 6 mg/kg and later increased to 8 mg/kg when gentamicin was added. The IDSA MRSA guidelines recommend 6 mg/kg for uncomplicated bacteremia and 8–10 mg/kg for complicated bacteremia.[3] Furthermore, a daptomycin dose of 10 mg/kg is recommended for persistent MRSA bacteremia, in combination with another agent.[3] Daptomycin displays concentration-dependent killing and theoretically should have a better efficacy with higher doses. Bassetti and colleagues[27] conducted a retrospective review, which included uncomplicated and complicated bacteremia, and found higher clinical success rates in patients treated with 7–9 mg/kg/day than patients treated with 4–6 mg/kg/day. The study concluded that high-dose daptomycin (greater than 6 mg/kg/day) should be studied prospectively in a randomized controlled trial. Furthermore, in a randomized trial comparing daptomycin 6 mg/kg to gentamicin plus either vancomycin or an anti-staphylococcal penicillin, failure rates were high, 44.2% *versus* 41.7%, respectively.[28] Daptomycin failures were noted to have the emergence of reduced susceptibility to daptomycin in 6 of the 19 patients with microbiological failures.[28] Given the concentration-dependent killing, the favorable safety profile of higher doses, and observed clinical benefit, the dose should have been pushed to 10 mg/kg/day.[29,30]

Specifically related to salvage therapy for persistent MRSA bacteremia, there are a number of different therapeutic options other than beta-lactams plus vancomycin. Potential options include daptomycin plus a beta-lactam, ceftaroline alone or with vancomycin or daptomycin, linezolid alone or in combination with a carbapenem, quinupristin/dalfopristin, telavancin, trimethoprim/sulfamethoxazole alone or in combination with daptomycin or ceftaroline, and intravenous fosfomycin (not available in the United States) plus imipenem.[31] Given the lack of head-to-head clinical trials on persistent or treatment-refractory MRSA bacteremia, the optimal salvage regimen has not emerged. With the blood culture time to positivity decreasing, the decision was made for a complete regimen change rather than substituting one drug in a failing regimen.

Many different beta-lactams, including broad spectrum, have been studied *in vitro* and *in vivo* with positive results. The growing evidence for combination therapy may hinder antimicrobial

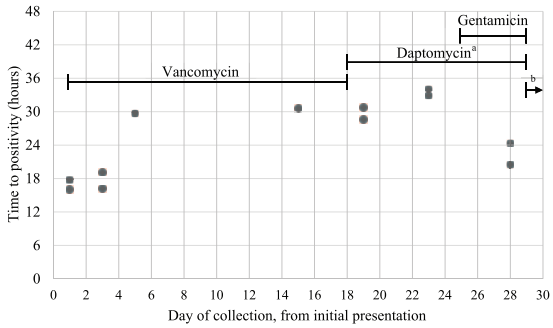

Figure 1. Antibiotic regimens and corresponding time to blood culture positivity, measured from collection to alarm on BacT/ALERT® 3D automated microbial detection system.
[a]On day 25, the dose of daptomycin was increased from 6 to 8 mg/kg daily.
[b]On day 29, daptomycin and gentamicin were discontinued and vancomycin plus nafcillin were initiated.

stewardship efforts that seek to de-escalate unnecessary broad-spectrum coverage when *S. aureus* is identified. In severe or life-threatening cases of bacteremia, continuation of a beta-lactam may ultimately be warranted until achieving negative blood cultures. A more practical solution might be de-escalating the broad-spectrum beta-lactam to a narrower spectrum beta-lactam when *S. aureus* is identified, a recommendation already proposed due to the superior activity of beta-lactams when susceptible.[32]

This report is limited to a single case. It is possible that the previous therapies needed more time to be effective. To account for this, we utilized blood culture time to positivity (TTP) as a marker of therapeutic response in persistent bacteremia. One case reported persistent MRSA bacteremia lasting greater than 30 days in which TTP did not change with appropriate antibiotics.[33] A subsequent study by the authors included 87 patients with persistent bacteremia and demonstrated that patients with repeat blood cultures with TTPs not increasing by at least 50% had worse outcomes.[34] Another study demonstrated that patients who had decreases in the TTPs on follow-up blood cultures experienced a higher 30-day mortality.[35] TTP *versus* the day of therapy in our case is plotted in Figure 1. While initially the TTP did increase (days 1 and 3 *versus* day 5), the TTP prior to the therapeutic change was decreasing (day 23 *versus* day 28), suggesting a lack of response prior to switching to nafcillin/vancomycin combination.

In addition to subtherapeutic dosing, other limitations include lack of an identified initial source and no test for hetero-resistant vancomycin intermediate *Staphylococcus aureus* (hVISA) or other resistance mutations. Recent and ongoing clinical trials have targeted initial combination therapy and measure time to blood culture negativity. It is unlikely that any robust clinical trials will ever be conducted for persistent MRSA bacteremia due to the infrequency and severity of cases. A prospective study seeking to compare salvage regimens would likely have to be an extensive collaboration of multiple large academic medical centers to obtain enough patients to draw any meaningful conclusions. Given the limitations in conducting prospective trials, case reports and case series are crucial in establishing a body of evidence regarding optimal treatment options.

Conclusion

Nafcillin/vancomycin combination resulted in clearance of persistent MRSA bacteremia within 3 days after initiation after failure of vancomycin monotherapy, daptomycin monotherapy, and daptomycin plus gentamicin combination therapy. Current literature demonstrates fewer treatment failures when combination therapy used initially. However, the optimal regimen for treatment failure, namely daptomycin failure, has yet to be determined. This case report supports the necessity for further *in vivo* research evaluating similar combinations as salvage therapy when standard treatment fails.

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Conflict of interest statement

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ORCID iD

Paul O. Lewis https://orcid.org/0000-0002-2626-7390

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