

Daptomycin For Intravenous Access-Related MRSA Septicemia: A Case Report

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Citation

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Abstract

A 32-year-old black man receiving hemodialysis presented with intravenous access-related methicillin-resistant *Staphylococcus aureus* (possibly heterogenous vancomycin-intermediate *S. aureus*). He was successfully treated with daptomycin (minimum inhibitory concentration = 2 µg/mL) in spite of data from three laboratories suggesting the isolates were not susceptible to daptomycin.

INTRODUCTION

Dialysis patients have a 100-fold higher risk for invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections than the general population [1]. Resistant vancomycin-intermediate *S. aureus* (VISA) and heterogenous (h)VISA have been shown to be selected for by vancomycin exposure in patients with significant underlying illness, particularly chronic renal failure [2]. This case illustrates the limitations of current laboratory antibiotic susceptibility testing for MRSA with regard to the choice of effective therapy (figure).

CASE PRESENTATION

The patient, a 32-year-old black male, was admitted to our hospital August 13, 2008, with confusion, fever, and swelling of the upper right extremity. Septicemia from a right subclavian hemodialysis catheter was suspected. He had had the catheter since May 2008 and was on hemodialysis 3 times per week. Since July 2007, he had had recurrent vancomycin-susceptible *S. aureus* bacteremia and vascular access infections. His medical history included longstanding type 1 diabetes mellitus, a left below-the-knee amputation due to peripheral vascular disease, renal failure, hepatitis C, and AIDS (CD4 = 186 cells/µL). He had refused highly active antiretroviral therapy. In March 2008, he had had a subtotal gastrectomy due to a bleeding peptic ulcer.

An ultrasound of the right upper extremity showed a deep venous thrombosis of the subclavian, axillary, and cephalic veins. Blood cultures from the hospital laboratory on August 13, 2008, grew a vancomycin-susceptible MRSA with a

vancomycin minimum inhibitory concentration (MIC) of 2 µg/mL. He was started on vancomycin on August 13 at doses between 0.75 g and 1 g on hemodialysis. The subclavian catheter was removed on August 15, 2008, and replaced with a right femoral catheter. Cultures of the catheter tip and venipuncture blood cultures done the same day grew MRSA susceptible to vancomycin and linezolid, both with an MIC = 2 µg/mL. Daptomycin was not tested. He had received the 2 doses of vancomycin before repeat blood cultures (1 from venipuncture and 1 from the new femoral catheter) were obtained on August 20, 2008, which remained positive for MRSA. The local lab (Willis Knighton) referred the cultures to a reference lab (Focus) and the Centers for Disease Control (CDC) for daptomycin susceptibility testing. The results are given in table 1. He also received gentamicin at a dose of 80 mg on August 20 and 22, on hemodialysis.

On August 20, 2008, while still on vancomycin, the patient was started on daptomycin at a dose of 6 mg/kg every 48 hours. On August 25, 2008, when the first daptomycin susceptibility results became available, the daptomycin MIC was 2 µg/mL, defined as non-susceptible, so linezolid was added to daptomycin. However, blood cultures from August 21 and 23, 2008, were both negative after 1 day of treatment with daptomycin and before the addition of linezolid. The patient was discharged from the hospital on September 3, 2008, and continued on both daptomycin and linezolid given after dialysis. He was readmitted to the hospital on September 8, 2008, with thrombocytopenia attributed to linezolid, which was discontinued. He remained on

daptomycin as an inpatient on dialysis from September 10, 2008, through September 21, 2008.

Figure. Summary of the treatment course and vancomycin and daptomycin minimum inhibitory concentrations (MICs) for methicillin-resistant *Streptococcus aureus* (MRSA) bloodstream and/or catheter tip isolates. +RFC, right femoral catheter inserted; -SCC, infected subclavian catheter removed, TCP, thrombocytopenia develops. Note: for August 20, 2008 susceptibility results, see table 1.

Figure 1

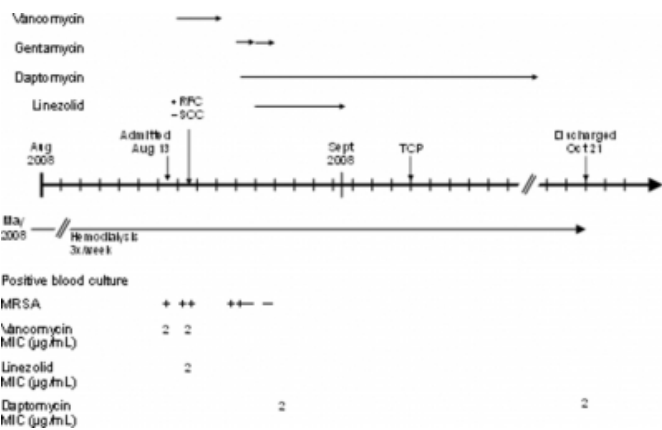


Figure 2

Table 1. Antibiotic susceptibility results of August 20, 2008, blood cultures, positive for methicillin-resistant by drug, test, and testing laboratory.

Drug/test	Willis Knighton lab: MIC result (ug/mL)	Interpretation	Daptomycin reference lab: MIC result (ug/mL)	Interpretation	CDC: MIC result (ug/mL)	Interpretation
Vancomycin/BMD	4	I	2	S	2	S
Daptomycin/BMD	2	NS	2	NS	2	NS
Daptomycin/Etest			2	NS		Not done
Vancomycin/Etest					3	See note
Linezolid/BMD					2	S

I, intermediate susceptibility; NS, nonsusceptible; S, susceptible.

NOTE: The Centers for Disease Control (CDC) has provided no interpretation, because breakpoints for the Etest are under investigation. The vancomycin minimum inhibitory concentration (MIC) by broth microdilution method (BMD) and the Etest are within a single doubling dilution. Since the BMD is the reference method, the isolate is considered susceptible to vancomycin. The elevated BMD and Etest MICs suggest that the isolate is developing reduced susceptibility to vancomycin.

DISCUSSION

This case illustrates the difficulties of treating MRSA infections in the age of VISA and hVISA. Results from 2 different laboratories reported vancomycin (MIC = 2 µg/mL) as sensitive, although bacteremia was still present after 7 days of treatment. The same laboratories found daptomycin to be nonsusceptible at an MIC = 2 µg/mL, although in vivo, it sterilized blood cultures within 1 day, indicating rapid bactericidal activity.

The US Renal Disease System reported that 369,000 patients were receiving hemodialysis therapy at the end of 2007 [3]. From 1993 through 2006, hospitalization rates of infection for end-stage renal disease (ESRD) rose 31% for sepsis/bacteremia and 20.3% for cellulitis, and rates of vascular access infections in hemodialysis patients rose 105% [4]. Rates for infectious admissions reached their highest point in 2005 — nearly 37% higher than in 1993. While they have since fallen, in 2007 they remained 25.8 % greater than in 1993 [3].

In 2005, the Active Bacterial Core surveillance estimated the overall incidence of invasive MRSA infections among dialysis patients to be 45.2 cases per 1000 dialysis population [1]. Approximately 85% of dialysis patients had indwelling catheters or other devices at the time of their infections, with approximately 90% requiring hospitalization, resulting in a 17% mortality rate [1].

As defined by MIC, clinical response, and the Etest, this may have been a case of hVISA. VISA and hVISA are defined by MICs = 4–8 µg/mL and MICs = 1–2 µg/mL, respectively, and a lack of response to vancomycin [5]. In this case, the heteroresistant *S. aureus* was likely a subpopulation with reduced sensitivities to vancomycin that existed within a larger population of fully vancomycin-susceptible *S. aureus* and may represent a step toward the development of a uniform VISA population [6].

hVISA is not detected by standard susceptibility testing methods, such as the broth microdilution method, because resistant subpopulations (vancomycin MICs of 8–16 µg/mL) are typically represented at frequencies ≤1 in 10⁵ to 1 in 10⁶ colony forming units (CFUs), while standard MIC tests, which use 5 x 10⁴ CFU/well fail to detect them [6]. Three Detroit area hospitals using the Etest found that the proportion of MRSA harboring hVISA increased from 2.2% during 1986–1993 to 8.3% during 2003–2007 [8].

Daptomycin is the first cyclic lipopeptide available in the United States and is clinically effective against aerobic Gram-positive bacteria, including Gram-positive bacteria resistant to methicillin, vancomycin, and linezolid. The lipophilic tail of daptomycin may be responsible for the drug's rapid bactericidal action through its insertion into the bacterial cytoplasmic membrane, with consequent destruction of the ion-concentration gradient, thereby inhibiting protein, DNA, and RNA synthesis, without causing cell lysis, and with a significant post-antibiotic effect. [9, 10].

Daptomycin is primarily excreted by the kidney and has convenient dosing in dialysis patients [8] The recommended dose for *S. aureus* bloodstream infections in dialysis patients is 6 mg/kg every 48 hours [9].

Until methods to reliably detect reduced susceptibility to vancomycin become widely available in clinical microbiology laboratories, the use of vancomycin for MRSA infections caused by isolates with vancomycin MIC >1µg/mL should be undertaken cautiously [5]. Rybak et al. recommend that MRSA infections with MICs ≥2µg/mL should not be treated with vancomycin [11]. Daptomycin offers a valuable alternative for the treatment of infections related to vascular access in dialysis patients.

COMPETING INTERESTS

The author is a member of the Cubist Pharmaceuticals visiting Speaker's Bureau.

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