

# Daptomycin Resistance in Vancomycin-Intermediate Staphylococcus Aureus Isolate

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## Citation

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## Abstract

We describe a patient with methicillin-resistant Staphylococcus aureus (MRSA) who developed resistance to daptomycin, a new cyclic lipopeptide recently approved for the treatment of infections by gram-positive organisms. Development of resistance to daptomycin during prolonged use may occur with MRSA bacteremia

## INTRODUCTION

Daptomycin is a cyclic lipopeptide recently approved for the treatment of infections by gram-positive organisms, including infections with methicillin-resistant Staphylococcus aureus (MRSA). We describe a patient infected with MRSA who developed resistance to daptomycin after prolonged exposure, which resulted in clinical failure. Although daptomycin is an alternative agent for treatment of drug-resistant gram-positive bacterial infections, development of resistance during prolonged use may occur with MRSA bacteremia.

## CASE REPORT

A 61-year-old, African American man with a history of human immunodeficiency virus, hepatitis C, hypertension, diabetes mellitus, and end-stage renal disease was transferred from the dialysis unit to the hospital after being found to be bleeding from an arteriovenous shunt. Upon arrival, the patient started to complain of lower abdominal and suprapubic pain. The urine analysis showed white blood cells, with moderate amount of leukocyte esterase and positive nitrites. The patient received empirically vancomycin 1 gram intravenously (IV), gentamicin 80mg IV, cefepime 500 mg IV, and ciprofloxacin 200mg. All antibiotics were given for one dose.

Within 48 hours, the blood culture results revealed methicillin-resistant Staphylococcus aureus, sensitive to vancomycin. Urine cultures yielded Proteus mirabilis, sensitive to gentamicin. Vancomycin was continued at 500 mg intravenously every 48 hours, in addition to gentamicin

80 mg IV. But despite receiving vancomycin and gentamicin the patient continued to remain febrile and tachycardic. A transesophageal echocardiogram did not show valvular vegetations. Seven positive blood cultures for MRSA persisted despite therapeutic serum trough levels of vancomycin ranging from 8.4 – 12.4mg/l. Rifampin 600 mg orally once daily was initiated by day 7. Patient condition was worsening, he continued to be febrile, and gallium scan did not show any uptake. By day 14, the vancomycin (trough concentration 16.7 mg/ml) and gentamicin were discontinued. Daptomycin 6 mg/kg IV every 48 hours was initiated in addition to the rifampin. After fourteen days of daptomycin therapy and twenty-six days of rifampin therapy, 2 sets of blood cultures grew vancomycin–intermediate Staphylococcus aureus (VISA) resistant to daptomycin with (MIC of 4 µg/ml).

Linezolid 600 mg IV q12h was started 2 days before the cultures returned. Automated susceptibility testing by Kirby-Bauer zone size revealed resistance to daptomycin with a mean inhibitory concentration (MIC) of 4 mcg/ml. Results were confirmed by the Department of Health. At this time, the patient was restarted on vancomycin with a loading dose of 1250 mg, in addition to 600 mg of quinupristin/dalfopristin 7.5 mg/kg IV every 8 hours and continued linezolid. After 10 days of treatment four negative blood cultures came back after starting this treatment regimen.

This patient had a prolonged hospital stay, developed upper gastrointestinal bleeding, shock and eventually expired.

## DISCUSSION

We report a case of VISA infection resistant to daptomycin that was successfully treated with vancomycin, linezolid, and quinupristin/dalfopristin. In 1997, the first clinical isolate of *S. aureus*, which had intermediate resistance to vancomycin, was reported from Japan in a child who developed a nosocomial surgical site infection with MRSA. Since then, many *S. aureus* isolates with reduced susceptibility to glycopeptides have been reported from around the world. Amongst six cases of VISA in New York City in 2007, resistance to daptomycin was present in 3 isolates. According to the Centers for Disease Control and Prevention (CDC), sixteen cases of VISA (through January 2006) and seven cases of VRSA (through September 2007) have been reported in the US.

In 2006, after reviewing data regarding treatment failure of vancomycin against *S. aureus*, the Clinical and Laboratory Standards Institute revised the vancomycin MIC breakpoints for *S. aureus*. Susceptibility was redefined as MIC  $\leq$  2.0  $\mu\text{g/ml}$ ; intermediate resistance as 4.0-8.0  $\mu\text{g/ml}$  and resistance as  $\geq$  16.0  $\mu\text{g/ml}$ . Based on these changes the CDC came up with testing algorithm.

Heteroresistant VISA (hVISA) is probable precursor of VISA, these strains susceptible to vancomycin (MIC  $<$ 4 mg/mL); though, they contain subpopulations of organisms for which the MIC of vancomycin is in the intermediate range.

Risk factors determined from case reports were prolonged vancomycin use, indwelling foreign bodies and hemodialysis dependence [1]. But one study of 19 patients did not show that dialysis exposure is a predictor [2]. Colonization of health-care workers or family members associated with the case patients has not been reported. Patients with infections that have high bacteria loads (endocarditis), longer duration of fever, time until clearance of bacteremia, length of hospitalization; and failure of vancomycin treatment are prone to hVISA.

Howden et al. confirmed that isolates of *S. aureus* with reduced glycopeptide susceptibility developed during failed therapy and arose from fully susceptible Vancomycin-susceptible *S. aureus* isolates [3].

The primary factor that causes reduced susceptibility to vancomycin among VISA isolates is the presence of a thickened cell wall with several more peptidoglycan layers, compared with non-VISA isolates. Cui et al. showed in his

study of 16 clinical VISA strains from 7 countries and demonstrated that the mean cell-wall thickness of the VISA strains was significantly greater than that of control strains and that the MIC of vancomycin correlated with cell wall thickness [4]. Vancomycin binds to the many d-alanine-d-alanine residues within the additional peptidoglycan layers and never reaches the surface of the cytoplasmic membrane to exert an effect on the synthesis of peptidoglycan [1]. The mean cell-wall thickness of the VISA strains was significantly greater than that of control strains and that the MIC of vancomycin correlated with cell wall thickness [5]. Even though daptomycin does not bind peptidoglycan to form subsequent physical barriers within the cell wall, it might be hard for daptomycin, with a molecular weight over 1,620, to smoothly penetrate the cell wall when the cell wall becomes as thick as that of VISA [4,5]. The *vanA*, *vanB*, and *vanC* genes that mediate vancomycin resistance in enterococci were not found in VISA strains. However, the 2 reported clinical isolates of VRSA in the United States have contained the *vanA* gene, which is believed to confer true vancomycin resistance [6,7]. The following features were suggested to imply the possibility of VISA or hVISA: ongoing positive blood cultures for MRSA after 7 days of glycopeptide therapy, positive normally sterile site isolates for MRSA after 21 days of glycopeptide therapy, persistent signs of infection, after a period of glycopeptide therapy which would normally be expected to be associated with clinical improvement. And finally relapse of infection caused by MRSA after completion of a course of glycopeptide therapy that would normally be expected to eradicate the infection [8].

VISA strains are slow growers and may not appear on the primary culture plate until 2 days of incubation. In addition, colonies may initially appear pinpoint and may have variable—even atypical—morphologies. Loss of typical phenotypic characteristics, such as  $\beta$ -hemolysis and thermostable nuclease activity, has been observed as isolates develop increasing MICs to vancomycin [1]. It is recommended that primary testing of *S. aureus* will require 24 h of incubation with confirmation of VISA/VRSA by using CDC recommended algorithm.

Currently there are no published treatment recommendations for VISA. Vancomycin monotherapy has been associated with treatment failure in VISA infections. Removal of infected indwelling hardware and debridement of infected sites is of extreme importance and must be considered for every patient. Until 2002 all of the VISA isolates identified

in the US have been susceptible to trimethoprim-sulfamethoxazole (TMP-SMX) and tetracycline. These agents have been used in various combinations with other agents for the treatment of some VISA infections. But efficacy of TMP-SMX in these patients has been difficult to determine because of previous and concomitant therapies. The addition of rifampin to therapy can also be considered if the isolate is drug susceptible.

Both linezolid and quinupristin-dalfopristin have in vitro activity against 3 of the VISA strains and the Michigan and Pennsylvania VRSA strains, although both linezolid and quinupristin-dalfopristin were bacteriostatic against the Pennsylvania strain.

The in vitro activity of daptomycin against MRSA, penicillin-resistant *S. pneumoniae*, and VRE species is 2–4-fold superior to that of vancomycin. The mechanism of action is the disruption of the bacterial membrane through the formation of transmembrane channels. These channels cause leakage of intracellular ions leading to depolarizing the cellular membrane and inhibition of macromolecular synthesis. And more recently, in vitro studies have documented daptomycin activity against MRSA and VRE comparable to that of linezolid.

Treatment may include daptomycin if there is a strong possibility, based on local microbiological data or a recent history of vancomycin treatment, that the isolates have a vancomycin MIC of  $> 1$  mg/mL [9]. If daptomycin is administered, daptomycin MICs should be tested for all *S. aureus* isolates recovered from blood or deep tissue specimens.

There is an emergence of daptomycin resistance in *S. aureus* with first report of daptomycin-resistant *S. aureus* in a patient with VISA in 2005, followed by several cases in 2006 [10,11,12]. As it was mentioned above the most likely explanation for that is the thickening of cell wall, acting as a barrier to daptomycin and vancomycin penetration.

Development of new antimicrobial therapy agents, probably with smaller molecular sizes will be a new approach to

overcome vancomycin- and daptomycin-resistance of *S. aureus* infections and it will continue to challenge researchers and clinicians.

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