Failure of Cloxacinillin in Treatment of a Patient with Borderline Oxacillin-Resistant Staphylococcus aureus Endocarditis

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CASE REPORT

Borderline oxacillin-resistant Staphylococcus aureus (BORSA) isolates are characterized by MICs to oxacillin close to or just above resistance breakpoints (4). BORSA has been associated with various hospital- and community-acquired infections, including endocarditis (6, 8, 11). Although isolates of BORSA frequently display borderline resistance by accepted laboratory testing methods (4), previous reports have suggested that β-lactam therapy should still be successful in treating patients infected with BORSA and that clinical evidence for failure with β-lactam therapy is lacking (2, 3, 11). We describe a case of endocarditis caused by BORSA in a patient who failed therapy with high-dose cloxacillin.

A 43-year-old intravenous drug user with a history of diabetes, hepatitis C, cirrhosis, and chronic renal insufficiency presented with fever, nausea, and vomiting. Her past medical history included a previous tricuspid valve replacement with a bioprosthetic valve and pacemaker insertion for endocarditis 6 years earlier. The patient had four previous admissions over the previous 16 months for Staphylococcus aureus endocarditis and vertebral osteomyelitis but did not receive complete therapy at any of these admissions as the patient continued to leave the hospital against medical advice. Antibacterial therapy for three of these admissions was cloxacinillin and rifampin (rifampicin). Her most recent admission was 10 days prior to the current presentation, where she had been treated with cloxacinillin and rifampin for tricuspid valve endocarditis. All previous isolates of S. aureus were methicillin susceptible, with oxacillin MICs ranging from 0.25 to 0.5 μg/ml as determined on a Vitek2 (bioMerieux, Marcy l’Etoile, France) instrument.

On the current admission, she was started on 2 g of cloxacinillin intravenously every 4 hours and 600 mg of rifampin orally once daily, when initial blood cultures were identified as methicillin-susceptible S. aureus. A transthoracic echocardiogram revealed a 1.4-cm vegetation on a degenerated tricuspid valve, with vegetations present on the pacemaker wires in the right atrium. Chest X-ray, bone scan, and abdominal ultrasound were negative for emboli. Blood cultures were negative at 4 days; however, at 21 days, her fevers persisted, and repeat blood cultures again grew gram-positive cocci in clusters. The thermonuclease test, performed on an aliquot from the blood culture bottle, was negative at 4 hours and 24 h, and 24-hour growth on blood agar demonstrated poorly growing colonies. Colonies from the 24-hour blood agar plate were slide coagulase negative and tube coagulase negative at 4 and 24 h, and the Vitek2 could not identify the organism due to poor growth in the card. After 48 h of incubation, the colonies on blood agar had a golden appearance, the slide coagulase test was positive, the 4-hour tube coagulase test was negative, the 24-hour tube coagulase test was positive, and the organism was identified as S. aureus by the Vitek2. The organism was confirmed as S. aureus by PCR-based 16S rRNA gene sequencing (100% identity, BLAST search).

Vitek2 antimicrobial susceptibility testing of the isolate found the MIC to be ≥4 μg/ml. By Etest (AB Biodisk, Solna, Sweden) the isolate showed an MIC for oxacillin of 12 μg/ml and produced a zone of 6 mm (no zone) when tested by disk diffusion methodology (4). Each susceptibility test was performed in duplicate. The organism was also resistant to rifampin (4). The slide MecA latex agglutination test (MRSA-Screeen: Denka Seiken Company, Ltd., Tokyo, Japan) and mecA PCR (5) were negative, indicating the organism was a BORSA. The isolate was shown not to be a β-lactamase producer by the nitrocefin test (Cefinase; Becton Dickinson BBL, Sparks, MD). To confirm the absence of β-lactamase and to confirm β-lactamase hyperproduction as the mechanism responsible for the BORSA phenotype, the activity of clavulanic acid in combination with two β-lactam antimicrobial agents (cefotaxime and ceftazidime) was tested as previously demonstrated by others (11); disk diffusion testing was performed using cefotaxime (30 μg), ceftaxime-clavulanic acid (30 and 10 μg, respectively), ceftazidime (30 μg), and ceftazidime-clavulanic acid (30 and 10 μg, respectively) disks. The presence of clavulanic acid did not result in a significant change (≥5 mm) in cefotaxime or ceftazidime zone sizes. The mechanism
underlying the BORSA phenotype in this isolate of *S. aureus* remains unknown. Pulsed-field gel electrophoresis using five of the patient’s previous blood culture isolates of *S. aureus* and the current BORSA isolate showed that the BORSA isolate and four previous isolates were identical (no band differences) and that one isolate was closely related (one band difference compared to the BORSA isolate) (12). When the BORSA isolate was reported by the clinical microbiology laboratory, the patient was subsequently changed to vancomycin, resulting in resolution of her fevers and abdominal pain, and repeat blood cultures were negative 5 days later. She subsequently left against medical advice 7 days after initiating treatment with vancomycin.

BORSA isolates are *mecA* negative and have low-level resistance to oxacillin, with MICs between 1 and 8 μg/ml. Many BORSA isolates are phage type 94/96 and contain a plasmid that results in excess production of β-lactamase, thought to confer borderline oxacillin resistance (1). However, BORSA isolates have multiple genotypic and phenotypic characteristics contributing to resistance, including penicillin-binding protein (PBP) mutations (10) and methicillinase production (7). Previous in vitro and experimental animal models have suggested that β-lactams, including cloxacillin, can be used successfully to treat patients infected with BORSA and that the BORSA phenotype does not correlate with in vivo resistance; however, our case illustrates a failure of this strategy (6, 8, 11).

In one previously published case of endocarditis caused by a strain of BORSA, the patient had persistent fevers and hypotension while on vancomycin and defervesced only after antimicrobial therapy was changed to ampicillin-sulbactam (11). Our patient with endocarditis failed therapy, both clinically and microbiologically, with high-dose cloxacillin and ultimately required vancomycin for treatment. The different responses to antimicrobial therapy may be due to the heterogeneous nature of the bacteria exhibiting the BORSA phenotype. In a previously described case of endocarditis (11), the BORSA strain isolated was positive for β-lactamase by the nitrocefin test and MIC testing revealed a fourfold reduction in MIC with the addition of a β-lactamase inhibitor, whereas our strain did not exhibit a reduction in cefotaxime or ceftazidime MIC in the presence of clavulanic acid. This suggests that the mechanism of resistance in our case was likely due to one or more PBP mutations and that a β-lactam–β-lactamase inhibitor combination would be of no benefit for this serious infection. Although the use of a β-lactamase inhibitor may be of benefit if hyper-production of a β-lactamase was the only resistance mechanism, those isolates with mutations altering PBPs would not respond. Treating physicians must be extremely cautious when using a β-lactam alone for treatment of serious infections caused by BORSA, as inadequate therapy can lead to adverse outcomes.

In our patient, the multiple, inadequate courses of β-lactam therapy over the previous admissions led to the development of resistance and provide clear evidence of the risks of substandard antimicrobial therapy. The pulsed-field gel electrophoresis results for the blood isolates over the previous 6 months showed the isolates to be identical or closely related (12). This indicates that the development of resistance occurred due to mutations in the same strain rather than through reinfection. Patients who have had multiple courses of β-lactam therapy are at risk for the development of BORSA.

Of interest was that on the last set of blood cultures the organism was initially thermoneuclease and tube coagulase negative; further subculture produced the expected reactions for these two tests. The clinical appearance of the organism raised suspicion that it was *S. aureus*, and ultimately 16S ribosomal sequencing was required to confirm the diagnosis. Methicillin resistance can be associated with false-negative coagulase results (9) although it is highly unusual to have both negative coagulase and thermoneuclease testing. The most likely explanation is that the growth of the organism in the blood culture bottle was altered by the presence of antibiotics that may have affected the resulting phenotypic characteristics. This is of particular concern for the microbiology laboratory, which may misclassify *S. aureus* as coagulase-negative *Staphylococcus* on the basis of blood cultures of patients on antibiotics, as a single positive blood culture may not be evaluated further according to some laboratory protocols. This highlights the importance of technologists using their clinical suspicion based on colonial morphology and growth characteristics of gram-positive organisms.

In summary, we present a unique case of BORSA endocarditis that failed cloxacillin therapy. Recurrent inadequate courses of cloxacillin can lead to the development of the BORSA phenotype. In contrast to previous reports, β-lactam therapy is not a reliable treatment of serious infections caused by these organisms, and failures can occur. Given the heterogeneity of the BORSA phenotype, therapy should be guided by careful consideration of MICs of β-lactams with or without β-lactamase inhibitors and β-lactam–β-lactamase inhibitor combinations should be considered for therapy only for serious infections in which there is a confirmed significant decrease in the MIC (≥2 doubling dilutions) or increase in disk diffusion zone size (≥5 mm) with the addition of a β-lactamase inhibitor (4). Additionally, similar to those of methicillin-resistant *S. aureus*, BORSA growth characteristics can be affected by antibiotics, such as cloxacillin, resulting in negative thermoneuclease and coagulase tests, which may lead to false identification.

REFERENCES


