Clinical Vignettes

Treatment Considerations for Recurrent MRSA Bacteremia Leading to Cholecystitis

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ABSTRACT

We present an end-stage renal disease patient with acute cholecystitis caused by a recurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. Timely antibiotic therapy with vancomycin did not eradicate the patient's infection. In this patient, the minimum inhibitory concentration (MIC) of the organism for vancomycin was at the upper limit of susceptibility. The ability to thoroughly understand and interpret mean inhibitory concentrations is crucial in antibiotic selection. For high-risk patients with *Staphylococcus aureus* infection with reduced susceptibility to vancomycin as demonstrated by an MIC of 2 mg/L or greater, we suggest further investigation into linezolid as an alternative antibiotic to vancomycin therapy. Compared to vancomycin, linezolid has similar effectiveness in patients with MRSA bacteremia as well as improved penetration, particularly in bile.

KEY WORDS: *Staphylococcus aureus*; Cholecystitis; Minimum inhibitory concentration; Vancomycin; Linezolid.

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INTRODUCTION

Acute calculous cholecystitis results from obstruction of the cystic duct. As the gallbladder becomes distended, blood flow and lymphatic drainage are compromised, leading to mucosal ischemia and necrosis¹. The biliary tract is sterile in normal individuals; however, 20% to 50% of patients with chronic cholecystitis and 40% to 75% of patients with acute cholecystitis have positive bile cultures. The mechanisms responsible for infection are ascending infection due to reflux of duodenal contents, spread from blood-borne infection, and spread through portal-venous channels². The organisms most commonly isolated in biliary tract infections are *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus* spp, and *Klebsiella* spp³.

Staphylococci are usually associated with infections of the skin and soft tissues and are rarely reported as biliary patho-

gens, as the gastrointestinal tract does not harbor *Staphylococcus aureus* (*S. aureus*) as normal flora². *S. aureus* is also a common pathogen in nosocomial infections with increased prevalence in patients on hemodialysis due to frequent vascular access. *S. aureus* is the leading pathogen responsible for 27% to 39% of severe infections in dialysis patients including sepsis, distant infections, and acute infective endocarditis. The mortality rate for *S. aureus* bacteremia in dialysis patients is 8%⁴.

CASE REPORT

A 67-year-old woman presented to the emergency room with a three-day history of malaise and abdominal pain. She reported right mid-quadrant pain with chills, occasional nausea, and multiple episodes of non-bilious emesis. Review of systems was otherwise negative. Her past medical history was significant for end-stage renal disease (ESRD) on hemodialysis, hypertension, hyperlipidemia, and diet controlled diabetes. The patient's surgical history was significant only for AV fistula creation. No dermatologic changes were noted prior to this admission. The patient had been hospitalized six months prior for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia associated with healthcare-acquired pneumonia. The pathogen's minimum inhibitory concentration (MIC) for selected antibiotics at the prior hospitalization are seen in the table. The infection was treated for 2 weeks with intravenous vancomycin dosed during dialysis and maintained at therapeutic levels resulting in symptomatic resolution.

On admission, her temperature was 100.8°F in the emergency room after a measured temperature of 102°F taken in hemodialysis earlier that day. Her blood pressure was 106/60, pulse was 130 beats per minute, and respiratory rate was 20. The patient was alert and oriented throughout the exam. Her abdomen was tender in the right upper and right lower quadrants. Bowel sounds were present, though hypoactive. There was no guarding, rebound, or masses felt. A distant systolic ejection murmur was heard. Her arteriovenous fistula had a palpable thrill without erythema, warmth, or tenderness. Laboratory studies were significant for a white blood cell count of 34.5×10^3 cells/uL (normal $4.5\text{--}11.0 \times 10^3$ cells/uL) with 92% neutrophils and 7% bands. The patient's blood urea nitrogen was 27 mg/dL (normal 7–18 mg/dL) and creatinine was 7.8 mg/dL (normal 0.6–1.2 mg/dL). Total bilirubin was 0.6 mg/dL, ALT was 22 U/L, AST was 25 U/L and alkaline phosphatase was 130 U/L. The patient was started on intravenous vancomycin due to her previous infection and frequent hemodialysis and piperacillin-tazobactam because of concern for acute cholecystitis.

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Figure 1. CT scan of the abdomen showing two large stones (thick arrow) in the gallbladder (thin arrow) and evidence of thickening of the gallbladder wall.

A computerized tomography scan of the abdomen showed two large stones in the gallbladder and wall thickening suggesting cholecystitis (Fig. 1). A subsequent ultrasound of the abdomen showed two large impacted stones at the neck of the gallbladder, a 1.1 cm thick gallbladder wall, and a dilated common bile duct measuring 9 mm. Positive sonographic Murphy's sign was elicited. Blood cultures obtained on admission grew gram-positive cocci that were later identified as MRSA. The pathogen was found to have identical sensitivities to the previous MRSA infection (Table 1) and piperacillin-tazobactam was discontinued. Surgery consultation was obtained, however, due to the blood culture results and atypical presentation, investigation for alternate foci of infection was continued.

Despite continuation of vancomycin and subsequent negative blood cultures, the patient continued to experience abdominal pain and decreased appetite with an elevated white blood cell count of greater than 20×10^3 cells/uL. A transesophageal echocardiogram obtained to assess for acute infective endocarditis found mild aortic regurgitation with aortic annular calcifi-

cation, but no intracardiac vegetations or masses. On hospital day 8, the patient became tachycardic to a rate of 120–160 bpm and mildly febrile. Though a repeat abdominal exam failed to exhibit guarding or rebound tenderness, an exploration of the right upper quadrant and biliary tract was performed due to the patient's worsening clinical appearance.

Laparoscopic surgery was attempted to remove the gallbladder. Upon entering the abdomen, the gallbladder was cultured immediately by aspiration. Adhesions and local factors precluded a laparoscopic approach and an open cholecystectomy was performed. The gallbladder specimen showed acute suppurative and chronic cholecystitis with cholelithiasis (Fig. 2). The gallbladder serosa was tan-gray and exhibited an area of ulceration measuring 1.9 x 0.8 cm. The gallbladder was presumed to have perforated pre-operatively. The patient required no blood transfusion during surgery, and was extubated immediately following the cholecystectomy. Post-operatively, the patient was admitted to the intensive care unit for observation and was doing well for the first 8 hours. She suddenly became bradycardic with pulseless electrical activity followed by asystole. Despite resuscitative efforts, the patient expired. No autopsy was performed. Bile collected from the gallbladder at the time of surgery grew out *S. aureus*.

DISCUSSION

Repeated *S. aureus* bacteremia has been associated with an indwelling foreign body, vancomycin therapy, and hemodialysis dependency⁵. Further, a study at the National Taiwan University Hospital showed that patients with repeated bacteremia are more likely to have end-stage renal disease

Figure 2. Gallbladder sample showing acute on chronic inflammation. The arrow points to the gallbladder serosa, which is flattened and damaged. This is commonly seen in cholelithiasis.

Table 1. MIC* of Patient's Pathogen to Selected Antibiotics

Antibiotic	MIC of MRSA bacteremia associated with pneumonia (6 months prior to cholecystitis)	MIC of Cholecystitis associated MRSA bacteremia
Penicillin	>8	>8
Oxacillin	>2	>2
Erythromycin	>4	>4
Vancomycin	2	2
Tetracycline	<4	<4
Trimethoprim/Sulfamethoxazole	<0.5/9.5	<0.5/9.5

*MIC—mean inhibitory concentration

(45.8%), an arterio-venous fistula/graft (33.3%), and ultimately fatal disease (75%)⁶.

The most likely primary source of infection was hematogenous seeding of the gallbladder with the same MRSA pathogen from her healthcare-associated pneumonia six months prior. A less likely source of infection was ascending infection from the duodenum². Repeated MRSA bacteremia is not uncommon. While the infection typically recurs within 90 days, a recent study found the duration from completion of antibiotic treatment to recurrence of bacteremia can range from 35-854 days⁶. It is important for physicians to be aware of the possibility of a late recurrence, even in cases that appear to have clinically resolved.

Reviewing minimum inhibitory concentration (MIC) interpretation is necessary to determine if vancomycin was sufficient to treat this patient's MRSA bacteremia. The MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation. MIC determinations indicate the relative degree of susceptibility of a bacterial strain to a tested antibiotic, which is helpful in choosing the most effective and least toxic drug. The MIC results of each antibiotic against a specific strain of bacteria are classified into susceptible, intermediate and resistant categories. MIC breakpoints are the exact MIC concentrations that separate these three categories for an antibiotic. Bacteria with low MICs are categorized as "susceptible" to a given antibiotic, meaning that the bacteria will most likely be eradicated during treatment. Organisms that are "resistant" to an antibiotic display extremely high MICs; a poor clinical response would be expected even at maximal doses of an antibiotic⁷.

Previous treatment exposure to vancomycin may select for MRSA with increased resistance to antimicrobials⁸. Rising MICs within the "susceptible" range are being seen in this setting (MIC creep). The patient was treated with vancomycin with resolution of symptoms six months prior to this hospitalization. The Clinical Laboratory Standards Institute recommended upper limit of susceptibility for vancomycin's MIC is 2 mg/L, which was the MIC of the pathogen in both hospitalizations. This increases the likelihood that the infections were caused by a strain of MRSA with marginal vancomycin resistance⁹. Sensitivities of the intra-operative bile culture were not obtained, a limitation of the case report, but we presume that the sensitivities would have been identical to those of the previous pathogens. Treatment of the patient using vancomycin with an MIC at the upper limit of sensitivity may have led to continued colonization by isolates harboring virulence traits selected for by vancomycin, resulting in her bacteremia relapse.

As further evidence of this, a retrospective cohort study identified that in patients treated with vancomycin, those with vancomycin MIC values of ≥ 1.5 mg/liter had a 2.4 fold increase in treatment failure as compared to those with vancomycin MIC values of ≤ 1 mg/liter. Treatment failure was defined as a 30-day mortality, blood culture growing MRSA obtained 10 days after the initiation of vancomycin therapy and before completion of antimicrobial therapy, or recurrence of MRSA bacteremia within 60 days of the discontinuation of vancomycin therapy. The authors suggest that although the vancomycin MIC is within the CLSI defined susceptibility range, alternative anti-MRSA therapies should be considered for these patients¹⁰.

Another possible etiology for recurrence occurs in *S. aureus* strains with a vancomycin MIC of 1 to 2 ug/mL.

These strains may be heteroresistant intermediate *S. aureus* (hVISA). hVISA are isolates that contain subpopulations of cells, typically 1 in every 100,000 to 1,000,000 cells, for which the vancomycin MIC is 4ug/mL to 8 ug/mL. Because a standard broth microdilution test uses an inoculum of 2×10^5 CFU/mL, these resistant subpopulations go undetected, while the vancomycin MIC is in the susceptible range (less than or equal to 2ug/mL)¹¹. hVISA isolates resistant to vancomycin would continue to survive after therapy, possibly leading to recurrence after vancomycin therapy.

Mutations leading to inactivation of the Clp-C ATPase are a possible method for staphylococcal resistance. These mutants fail to enter the death phase and display enhanced survival in the stationary phase, which may explain how certain strains of bacteria can become senescent¹². While more exploration is needed, it is possible the patient's MRSA infection remained dormant in the gallbladder during the intervening period via a similar mechanism.

The patient in this case report was treated in a timely manner with therapeutic levels of vancomycin without clinical improvement. Although this patient ultimately needed surgical intervention, alternate antibiotic therapy should be investigated for patients previously treated with vancomycin and an MIC near the upper limit of susceptibility. Two treatment options are daptomycin, a cyclic lipopeptide, and linezolid, an oxazolidinone antibiotic that inhibits microbial protein synthesis¹³. In a recent meta-analysis, linezolid has been shown to have similar effectiveness to vancomycin in patients with MRSA, with improved penetration and 100% oral bioavailability¹⁴. In addition to the pathogen's decreased susceptibility to vancomycin, the limited concentration of vancomycin in bile may have permitted the continual presence of the infection¹⁵. Linezolid has recently been shown to penetrate bile at levels greater than serum concentrations in a small sample of liver transplant patients¹⁶. This is promising in the treatment of cholecystitis or cholangitis due to MRSA with possible heteroresistance (or MIC creep) to vancomycin and supports the possibility that linezolid may have provided this patient with a better clinical outcome.

CONCLUSION

Recurrent MRSA bacteremia leading to metastatic infection months after the initial episode is important to recognize when treating high-risk patients. This ESRD patient with cholecystitis had numerous risk factors for recurrent *S. aureus* bacteremia including diabetes and frequent hemodialysis. The MIC of the MRSA strain was at the upper limit of susceptibility for vancomycin, which may be a risk factor for recurrence and provide an early clue of a pathogen with marginal vancomycin resistance or heteroresistant strains. Timely vancomycin treatment was not successful at eradicating the infection in this patient. We suggest further investigation of linezolid as antibiotic therapy in patients who were previously treated with vancomycin with recurrence of MRSA infection and in patients with a vancomycin MIC of 2 mg/L with clinical deterioration. Continued investigation of adequate antimicrobial therapy in the face of growing resistance is necessary.

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