Acute Cholecystitis Caused by Vancomycin-Resistant *Enterococcus faecium* in a Morbidly Obese Patient with Multiple Co-Morbidities

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Abstract

Background: Vancomycin-resistant *Enterococcus faecium* (VRE) is a low virulent pathogen. It can cause a variety of infections most commonly in immunosuppressed patients and those with previous exposure to broad-spectrum antibiotics.

Case Presentation: A morbidly obese male with multiple comorbidities presented with acute cholecystitis. Because of the high operative risk it was decided to treat the condition with antibiotics and ultrasound-guided percutaneous cholecystostomy tube placement. Cultures of bile revealed VRE and initial therapy consisted of daptomycin. Cultures on day seven after initiation of daptomycin showed continuing growth of VRE and therapy was changed to linezolid and the patient was able to clear VRE from bile and cholecystitis resolved. The tube was removed after six months and interval cholecystectomy was planned after appropriate weight loss.

Conclusions: We report the first case of VRE acute cholecystitis in North America. Only two additional cases have been reported thus far, both from Italy. One responded to daptomycin, which is in contrast to our experience. However, similar to the other reported case, our patient had a good response to linezolid, which may be the preferred agent to treat this condition.

ACUTE CHOLECYSTITIS is a common surgical condition. Depending on various factors, treatment may include antibiotics and interval cholecystectomy once the infection has resolved or immediate surgery [1]. Patient with various comorbidities such as diabetes mellitus (DM) and immunosuppressed individuals may progress to gangrenous cholecystitis with an increased risk for gallbladder perforation, in which case emergent surgery is indicated. In patients at high operative risk, gallbladder drainage is an option. Most centers prefer percutaneous ultrasound or computed tomography (CT) guided placement of a cholecystostomy tube [2]. Others, however, have used endoscopic retrograde cholangiopancreatogram (ERCP) guided gallbladder stents successfully [3].

Pathogens implicated in acute cholecystitis include *Escherichia coli* and other gram-negative bacilli, enterococci, streptococci, and various anaerobes including *Clostridium*

perfringens [4,5]. Multiple pathogens can be cultured from bile in cases of acute cholecystitis and/or gallbladder empyema [4]. The role of enterococci in biliary infections has been disputed.

Vancomycin-resistant enterococci (VRE) have emerged over the past 20 years as important hospital pathogens [6]. Most commonly VRE are found in patients with significant comorbidities, immunosuppressed individuals, those with prolonged hospitalization, and patients with previous exposure to broad-spectrum antibiotics. Vancomycin-resistant enterococci may cause a variety of infections such as bacteremia and endocarditis, peritonitis, urinary tract infection (UTI), and has also been isolated in cholangitis. In liver transplant recipients with cholangiopathy, VRE is one of the leading pathogens [7]. Linezolid, daptomycin, quinupristin-dalfopristin, and tigecycline are established treatment options but new agents are being developed [8,9]. Only two cases of

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FIG. 1. (A) Ultrasound showing gallbladder wall thickening. (B) Computed tomography scan showing large gallbladder with wall edema. (C) Ultrasound showing distended gallbladder, floating intra-luminal echogenicities, thickening of the gallbladder wall, and a peri-cholecystic fluid.

VRE acute cholecystitis have been published thus far [10,11]; both reports originated from Italy. We herein report the first case of VRE acute cholecystitis in the United States.

Case Presentation

A 64-year-old African American resident of a nursing care facility was transferred to an outside hospital with a four-day history of increasingly severe right upper quadrant pain and fever. Ultrasound and CT scans were consistent with acute cholecystitis with cholelithiasis (Figs. 1A, 1B, and 1C). The patient had an elevated white blood cell (WBC) count but liver enzymes were normal. He was morbidly obese with a body mass index (BMI) of 55.6 kg/m² accompanied by type 2 diabetes mellitus and hypertension. He also had a history of right below-knee amputation, chronic obstructive pulmonary disease (COPD), and obstructive sleep apnea. He had been recently hospitalized for hypercapnic respiratory failure and aspiration pneumonia and had been treated with various antibiotics.

At the hospital, he was initially treated with bowel rest and empiric intravenous piperacillin-tazobactam and vancomycin. Because of a worsening leucocytosis and persistent fever and abdominal pain, he was transferred to our hospital for possible surgical intervention. On physical examination he was febrile and was noted to have tenderness in the right upper quadrant with a positive Murphy sign, but there was no abdominal rebound. His peripheral WBC count on admission was $37.9 \times 10^3/\text{mm}^3$ and his bilirubin and liver enzymes were

within normal range. Ultrasonography of the right upper quadrant showed a distended gallbladder with many floating intra-luminal echogenicities, thickening of the gallbladder wall, and a pericholecystic fluid collection (Fig. 1C). The common bile duct was normal in size.

The patient was hemodynamically stable and because of his operative risk, the decision was made to continue non-operative management in an intensive care unit (ICU) with bowel rest, intravenous vancomycin, ertapenem, and fluconazole. Computed tomography-guided percutaneous cholecystostomy tube placement was attempted, however, because of his obesity he was unable to fit into our scanner with enough space to perform the intervention. Therefore, on hospital day three, he underwent ultrasound-guided percutaneous cholecystostomy at the bedside and thick turbid bilious fluid was evacuated. Culture of bile grew VRE and daptomycin at a dose of 650 mg/d was started. However, his respiratory status deteriorated with a PCO₂ of >80 mm Hg. He was intubated and placed on a ventilator. The patient's clinical condition slowly improved, the drain output became clearer, and his WBC count trended down. His condition continued to improve and on hospital day 11, the patient was extubated. Repeat culture of bile on hospital day 13 (treatment day seven) remained positive for VRE and thus daptomycin was switched to linezolid, 600 mg orally twice a day. The patient's clinical course continued to improve with no fever and the WBC count normalized. Bile drain output decreased from 300 mL/d to <30 mL/d. Liver enzymes and total bilirubin all were within normal limits. On hospital day 18, a

FIG. 2. Cholangiogram through cholecystostomy tube showing correct drain placement, patent cystic duct, and normal common bile duct with unremarkable intrahepatic biliary system.

TABLE 1. SUMMARY OF REPORTED CASES OF VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM*

#	Authors	Year	Origin	Age	Gender	Comorbidities	Therapy	Previous antibiotic exposure	Other infections	Antibiotic therapy	Duration of therapy	Comments	Outcome VRE cholecystitis	Patient outcome
1	Cremaschi et al.	2010	Parma, Italy	76	Male	Hepatic failure, acute kidney injury (on dialysis)	Cholecystostomy tube	Piperacillin-tazobactam, metronidazole, linezolid	None reported	Linezolid	7 d	Potentially high linezolid levels caused by hepatic and renal failure	Resolved, VRE from gallbladder	Death caused by arrhythmia
2	Tascini et al.	2011	Pisa, Italy	72	Male	COPD, dissecting AAA	Cholecystostomy tube	Teicoplanin	MRSA Bacteremia, hetero-VISA bacteremia	Daptomycin	60 d	Supra-therapeutic daptomycin levels caused by hepatic and renal failure	Resolved, VRE from gallbladder	Alive after 30 d
3	Current case		Nashville, Tennessee USA	64	Male	Morbid obesity, DM, HTN, right BKA, COPD, OSA	Cholecystostomy tube	Piperacillin-tazobactam, vancomycin, fluconazole	None reported	Daptomycin switch to Linezolid	14 d	Failure with daptomycin	Resolved, cleared VRE from gallbladder following switch to linezolid	Alive after 2 years; had ERCP for cholangitis due to CBD stones

VRE = vancomycin-resistant *Enterococcus faecium*; COPD = chronic obstructive pulmonary disease; AAA = abdominal aortic aneurysm; DM = diabetes mellitus; HTN = hypertension; BKA = below-knee amputation; OSA = obstructive sleep apnea; MRSA = methicillin-resistant *Staphylococcus aureus*; ERCP = endoscopic retrograde cholangiopancreatogram; VISA = vancomycin intermediate *Staphylococcus aureus*.

cholangiography through the cholecystostomy tube was performed (Fig. 2) and correct drain placement was confirmed; the cystic duct was patent, the common bile duct was of normal caliber with unremarkable intrahepatic biliary system; contrast promptly entered the duodenum. The patient was discharged to a nursing care facility on hospital day 19. Antibiotics were continued for a total of 14 d from the initiation of daptomycin. Cholecystectomy was planned after substantial weight loss and control of the comorbid conditions. The patient was ultimately discharged home from a nursing facility but did not lose any weight. The cholecystostomy tube was accidentally removed after six months and not replaced because the patient had no signs of cholecystitis. Two years later, he had an episode of cholangitis and an ERCP was done with extraction of multiple common bile duct stones. Because of the high operative risk no cholecystectomy was done.

Discussion

We report the first case of VRE acute cholecystitis in the United States. This pathogen should be considered in patients with this condition who had previous exposure to antibiotics. In light of the recent emergence of various multi-drug-resistant organisms such as community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), extended spectrum β -lactamase (ESBL), and *Klebsiella pneumoniae* carbapenemase (KPC)-producing gram-negative bacilli and VRE, it seems reasonable to recommend culturing bile from drains at least in subsets of patients. This may add critical information not only for optimizing treatment for the patient but also in order to protect health care workers and other patients.

Residents of long-term care facilities appear to be a reservoir for VRE and other multi-drug-resistant organisms. In a prospective cohort study, 45% of patients admitted to an acute care hospital from a long-term care facility had rectal colonization with VRE [12]; risk factors included prior use of antibiotics and the presence of a decubitus ulcer. Identification of VRE in biliary tract infection is rare with the important exception of liver transplant recipients with cholangiopathy [13]. This patient population is prone to become colonized with VRE; in fact VRE is an important pathogen causing cholangitis in this patient population [7].

The decision to manage this patient with a cholecystostomy tube and not perform surgery was based on his morbid obesity and his extensive comorbidities. Temporizing acute cholecystitis by drainage has been shown to be safe and feasible particularly in patient with extensive peri-operative risk [14]. In fact it is unclear if cholecystectomy is necessary and it has not been determined when this should be done [15,16]. Antibiotics alone may be able to treat acute cholecystitis appropriately [1], however, our patient most likely would not have received an agent active against VRE if no microbiologic data were available. As placement of a cholecystostomy tube is a relative simple procedure, this strategy may be more widely used in the setting of acute cholecystitis.

Our literature search revealed two additional cases of VRE cholecystitis; both were identified in Italy [10,11]. Table 1 summarizes our case and the two published cases. All three patients were critically ill and all had been exposed to broad-spectrum antibiotics prior to VRE cholecystitis. Both patients from Italy had renal and hepatic failure and therefore high levels of antibiotics were achieved. In contrast, our patient was

morbidly obese and neither for linezolid nor daptomycin good pharmacologic data in this patient population are available. Linezolid shows good penetration into bile [10,13]; in the reported patients with renal and liver failure daptomycin was recovered from bile, however, this was associated with high plasma levels. We had no capacity to do pharmacologic studies in our patient; in addition we have no reported minimum inhibitory concentrations (MICs) for our VRE isolate. The fact that daptomycin could not clear the pathogen from bile made us speculate that inadequate drug levels were achieved. In contrast linezolid was able to clear VRE from the patient's bile.

To summarize, VRE may cause acute cholecystitis in subsets of patients and best antimicrobial treatment has not yet been defined. In patients with high peri-operative risk, a cholecystostomy tube is a safe strategy to treat acute cholecystitis with the advantage of enabling microbiologic diagnosis and directed therapy of the causing organism.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

BMI = body mass index
COPD = chronic obstructive pulmonary disease
CT = computed tomography
DM = diabetes mellitus
ERCP = endoscopic retrograde
          cholangiopancreatogram
ESBL = extended spectrum β -lactamase
ICU = intensive care unit
KPC = *Klebsiella pneumoniae* carbapenemase
MICs = minimum inhibitory concentrations
UTI = urinary tract infection
WBC = white blood cell
VRE = vancomycin-resistant *Enterococcus*
          faecium

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