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MEDICAL REVIEW

Staphylococcus aureus Cholecystitis: A Report of Three Cases with Review of the Literature

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Infection of the hepatobiliary system is most commonly due to enteric bacteria. We report three unusual cases of acute cholecystitis in which Staphylococcus aureus *was the primary pathogen. Infection of the gallbladder with this organism has been rarely described and may be associated with gallstones and obstructive disease as well as acalculous cholecystitis in the setting of staphylococcal bacteremia and endocarditis. Two of our patients had multiple chronic medical conditions and were infected with oxacillin-resistant* S. aureus *(ORSA) suggesting nosocomial acquisition. Including our cases with a review of the literature, three of nine reports of* S. aureus *cholecystitis were associated with infectious endocarditis. Thus, the finding of* S. aureus *cholecystitis with bacteremia is rare and should prompt an investigation for a possible endovascular focus of infection.*

INTRODUCTION

Acute cholecystitis is most commonly associated with obstruction of the cystic duct leading to ischemia and inflammation [1]. In normal individuals the biliary tract is sterile, however, 20 to 50 percent of patients with chronic cholecystitis and 40 to 75 percent of patients with acute cholecystitis have positive bile cultures [2, 3]. Several modes of infection have been postulated, including ascending infection due to reflux of duodenal contents, blood-borne infection and infection spread through the portal-venous channels [4]. Ascending infection from the duodenum is felt to be the primary mechanism by which bacteria enter the bile. The organisms most commonly isolated in biliary tract infections are *Escherichia coli*, *Klebsiella* species (sp.)[d], *Enterococcus* sp. and anaerobes [5, 6]. Staphylococci are usually associated with infections of the skin and soft tissues and are rarely reported as pathogens in diseases of the gallbladder. In this report, we describe three patients with *Staphylococcus aureus* acute cholecystitis seen over a two-year period and summarize the published English literature on staphylococcal infections of the gallbladder.

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[d]*Abbreviations:* CT, computed tomography; IV, intravenous; NIDDM, non-insulin dependent diabetes mellitus; ORSA, oxacillin-resistant S. aureus; sp., species; TEE, transesophageal echocardiogram; WBC, white blood cell.
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METHODS

S. aureus was isolated from blood or bile cultures by the Rochester General Hospital Clinical Microbiology Laboratory. Identification of staphylococci was initially based on colony morphology and Gram stain with confirmation by positive catalase reaction. Suspected *S. aureus* isolates were confirmed by positive coagulase tube test. Antibiotic susceptibility was performed with the Vitek automated system (bioMerieux Vitek Inc., Hazelwood, Missouri). Oxacillin resistance was confirmed by growth of the isolate on Mueller-Hinton agar plates containing 6 μg/ml of oxacillin.

CASE REPORTS

Patient one was a 64-year-old woman admitted with right upper quadrant pain, fever and nausea for 48 hours. Her history was significant for cholelithiasis, hypertension, hypothyroidism, and pernicious anemia. She had no history of diabetes mellitus, recent infections, skin disorders, or antibiotic use. On admission her temperature was 101.4°F and her abdomen was tender in the right upper quadrant. No cardiac murmur was heard. White blood cell (WBC) count was 17.4×10^9 cells/L and liver function tests (serum bilirubin, alkaline phosphatase and transaminases) were with in normal limits. Abdominal ultrasound showed a distended gall bladder with pericholic fluid. Despite intravenous (IV) fluids and ampicillin-sulbactam, she remained symptomatic and underwent cholecystectomy on hospital day two. The gallbladder contained many stones, and histopathologic evaluation showed acute and chronic inflammation. Tissue Gram stain was not done. The postoperative course was complicated by delirium and high fever. Admission blood cultures grew oxacillin-sensitive *S. aureus* in one of four bottles, and culture of the gallbladder was positive for 3+ *S. aureus* and 3+ alpha-hemolytic streptococci. On hospital day five, nafcillin was given and previous antibiotics were discontinued. By hospital day eight, the patient became afebrile, abdominal tenderness resolved and the WBC count returned to normal. Trans-esophageal echocardiogram (TEE) revealed normal cardiac valves. She was discharged on a three-week course of nafcillin and did well.

Patient two was a 73-year-old female admitted to the hospital with one day of severe epigastric pain, melena, and nausea. She had an extensive past medical history that included diverticular bleeding, coronary artery disease, aortic valve replacement, hypertension, atrial fibrillation, meningioma, psoriasis, and non-insulin dependent diabetes mellitus (NIDDM). She had a recent prolonged hospital admission for gastrointestinal bleeding and a hip fracture. During that time she had no *S. aureus* infections or active skin problems.

On admission she was afebrile. Cardiac exam revealed a 3/6 systolic murmur, and her abdomen was tender in the epigastrium and left upper quadrant. Because of poor venous access, a central venous catheter was placed. She was treated with IV fluids and antibiotics. Endoscopy on hospital day two showed no evidence of bleeding. Her initial hospital course was complicated by *Clostridium difficile* colitis that responded to oral metronidazole. Blood cultures at that time were sterile. On hospital day 13, her IV catheter site was noted to be purulent and the central line was removed. The catheter tip grew *S. aureus* resistant to oxacillin, clindamycin, erythromycin, and quinolones. The following day, the patient became febrile and lethargic, and she was begun on IV vancomycin. She required intubation and transfer to the medical intensive care unit on hospital day 15. Two sets of blood cultures grew ORSA with the same antibiogram as the catheter tip. A TEE revealed a normal mechanical valve and no vegetations. Blood cultures were persistently positive one week after removal of the catheter, and gentamicin and rifampin were added. Gradually, the patient improved and by hospital day 20 fevers resolved and blood cul-

tures became sterile. On hospital day 22, she developed fever, right upper quadrant tenderness, elevated levels of serum alkaline phosphatase (225 U/L [39-117, normal]) and gammaglutamyl transpeptidase (212 U/L [1-64 normal]) and WBC of 14.0 $\times$ 10^9 cells/L. Abdominal computed tomography (CT) revealed a distended, thick-walled gallbladder, pericholic fluid, and a calculus in the cystic duct. Under ultrasound guidance, a percutaneous cholecystomy tube was placed, and thick fluid with several stones was drained. Gram stain of the bile showed many Gram-positive cocci in clusters and cultures grew 4+ ORSA. Blood cultures at the time of the procedure were negative. After drainage, fever and abdominal tenderness resolved. Gentamicin was discontinued after two weeks, and she completed six weeks of vancomycin and rifampin for presumed endovascular infection given her prolonged bacteremia. On hospital day 70, the gallbladder drain was dislodged. Over the next two months, the patient developed progressive azotemia requiring hemodialysis. In her fifth month of hospitalization, she again developed right upper quadrant tenderness and blood cultures grew ORSA. Abdominal ultrasound did not reveal stones or obstruction. She was re-started on antibiotics, however, her family decided against aggressive treatment and she died on hospital day 150, from multiple organ failure. An autopsy was not performed.

Patient three was a 48-year-old man admitted because of severe right upper quadrant pain and vomiting. One week prior to admission he had an episode of mild epigastric and right-upper quadrant pain that resolved spontaneously. Severe pain radiating to the back returned on the day of admission. He had no fevers or chills. The patient had a history of alcoholic cirrhosis with esophageal varices, hepatitis C, hypertension, and NIDDM. He denied intravenous drug use. The patient had two previous episodes of cholecystitis and pancreatitis presumed to be secondary to passage of gallstones and that were managed medically. During an episode of pancreatitis three months earlier, he underwent endoscopic retrograde cholangio-pancreatography with sphincterotomy. He had no history of staphylococcal infections or skin problems during previous admissions.

On admission, the patient appeared uncomfortable and had mild icterus. He was afebrile. The abdomen was tender in the right upper quadrant. The remainder of the exam was unremarkable. Total bilirubin was 2.1 mg/dL (0-1.0, normal range), alkaline phosphatase was 165 U/L (39-117), and SGOT was 107 U/L (7-37). Abdominal ultrasound revealed a distended, thick walled gallbladder with stones and sludge. The patient was started on ampicillin-sulbactam and ciprofloxacin. He was felt to be high risk for surgery, and medical management was undertaken. On hospital day two, admission blood cultures grew Gram-positive cocci in clusters, and IV vancomycin was added. The organism was subsequently identified as ORSA with resistance to erythromycin, clindamycin, and quinolones. Transthoracic echocardiogram showed no vegetations, and TEE was not performed because of esophageal varices. Abdominal CT confirmed a distended gallbladder with pericholecystic fluid. The liver was enlarged and irregular consistent with cirrhosis, but no abscess was identified. Despite antibiotics his pain continued and a percutaneous cholecystostomy tube was placed under ultrasound guidance on hospital day six. The bile contained several small stones and grew 3+ ORSA. His symptoms improved significantly and broad-spectrum antibiotics were discontinued on hospital day eight. Vancomycin was continued for four weeks. The patient underwent a transjugular intrahepatic porto-systemic shunting procedure after finishing the course of vancomycin. Two weeks later, he had an uneventful laproscopic cholecystectomy. Blood cultures were negative at the time of surgery, and the patient made a full recovery.

DISCUSSION

Staphylococcal infections are typically associated with skin and soft tissue infections, pneumonia, osteomyelitis, septic arthritis, and infective endocarditis. The usual portal of entry for the organism is through a break in the skin or aspiration into the lungs. Hence, the presence of *S. aureus* in the gallbladder is surprising, since the gastrointestinal tract does not usually harbor *S. aureus* as normal flora. In our three patients, *S. aureus* grew from both blood and bile indicating that it was the primary pathogen. Although the usual enteric bacteria associated with cholecystitis were not found in our patients, suppression of other organisms by broad-spectrum antibiotics cannot be entirely ruled out.

A review of the English literature revealed only six cases of cholecystitis in which *S. aureus* was cultured from the gallbladder or bile [7-12]. Five of the six cases involved acalculous cholecystitis and were associated with bacteremia.

The first case, from 1966, is the only report of *S. aureus*-associated cholelithiasis and was similar to our first patient [10]. A healthy 26-year-old woman with a history of biliary colic was admitted with four days of severe right upper quadrant pain, fever, and leukocytosis. She underwent cholecystectomy, and the gallbladder was found to contain 25 stones and 150 cc. of purulent material that grew *S. aureus* in pure culture. She received antibiotics and made a full recovery.

In 1970, a case series of post-operative acalculous cholecystitis was reported in twelve casualties from the Vietnam War. One soldier had *S. aureus* isolated from his wound, blood, and gallbladder, but details of the case were not provided [8].

The third case report, from 1981, describes a 19-year old man with an asymptomatic ventricular septal defect who presented to the hospital with a four-day history of hip pain, malaise, fever, and a loud cardiac murmur. Prior to admission he received an oral antibiotic, which was discontinued, and the patient underwent a battery of diagnostic tests and cultures. After ten days his blood cultures were negative, his condition improved, and he was discharged without a diagnosis. He was readmitted two days later with similar symptoms and blood cultures grew *S. aureus*. Several days later he developed severe right upper quadrant pain and at laparotomy was found to have a necrotic gallbladder without stones which grew *S. aureus* [7]. He was treated with antibiotics and recovered.

In 1990, a case of *S. aureus* empyema of the gallbladder in a patient with HIV infection was reported [11]. The clinical presentation was notable for indolent symptoms.

The fifth case, reported in 1993, was an 11-year-old boy who had *S. aureus* aortic valve endocarditis, pneumonia, and osteomyelitis. His course was complicated by a splenic abscess and acute cholecystitis after two days of appropriate antibiotic therapy [9]. Cholecystectomy was required and a gangrenous gallbladder was removed and was sterile. The patient received six weeks of antibiotics.

Lastly, a 71-year-old Japanese man with diabetes and renal cell carcinoma who presented with staphylococcal scalded skin syndrome was found to have ORSA bacteremia and cholecystitis [12]. He recovered after cholecystomy and antibiotics.

In addition to these six case reports, a review of the literature revealed six studies in which *S. aureus* was rarely isolated from bile or gallbladder of patients with biliary disease (Table 1) [1, 4, 6, 13-15]. In all reviewed studies, the percentage of *S. aureus* was very low with only 16 of 2611 (0.6 percent) positive cultures. No information was given as to whether the *S. aureus* was isolated as a single organism or in combination with other bacteria. Several studies identified coagulase-negative staphylococci in a substantial number of bile specimens [4, 13, 16, 17]. A report by

Table 1. Series of gallbladder and bile cultures from patients with biliary tract diseases.*

Author	Flemma [1]	Fukunaga [4]	Chaitin [13]	Haff [14]	Lou [15]	Brook [6]	Mason [16] Pitt [17]	Various [2, 3, 5, 18, 19]
Year	1967	1973	1973	1976	1977	1989	1968,1982	1976-1983
Patients with positive cultures/Total tested	32/75	234/501	75/150	2/18	16/74	123/145	300/487	359/1161
Organisms**								
E. coli	25	75	25	1	2	71	71	195
Klebsiella sp.	0	33	7	0	6	29	37	85
Other GNR	13	23	18	0	6	57	58	135
Streptococcal sp.	5	37	11	0	4	51	50	70
Anaerobes	2	25	0	0	1	70	28	36
S. aureus	1	7	5	1	1	1	0	0
CNS	0	52	20	0	0	6	24	0
Miscellaneous	1	35	3	0	0	0	19	7

*Biliary tract diseases included acute and chronic cholecystitis, cholangitis, malignancy, and parasitic liver disease.
**The total number of individual organisms isolated is greater than the total number of patients with a positive culture since many patients had more than one organism isolated from the gallbladder wall or its contents.
E. Coli = *Escherichia Coli*; sp = species; GNR = Gram-negative rods, CNS = Coagulase-negative staphylococci

Nielson et al. described recovery of staphylococcal species from gallbladder contents only when cultures were obtained at the end of surgery but not immediately after incision, suggesting these organisms were contaminants introduced during surgery [2]. Although several studies have demonstrated staphylococcal species in the bile, in five large studies that included over 1100 subjects, investigators never isolated staphylococci [2, 3, 5, 18, 19].

There did not appear to be a common risk factor or pathologic process linking our three patients. Patients two and three had multiple medical problems which placed them at higher risk for infections in general, however, patient one was relatively healthy and had no obvious risk factors for developing invasive staphylococcal disease. Her history was consistent with a typical case of acute cholecystitis associated with cholelithiasis. The anterior nares are reservoirs for *S. aureus* [20]. Approximately 20 percent of healthy people consistently carry a strain of *S. aureus*, and 60 percent harbor staphylococci intermittently [20]. It seems plausible that her duodenum may have become contaminated with staphylococci if she were a naspharyngeal carrier. Patient three had an endoscopic sphincterotomy three months prior to admission that may have allowed reflux of duodenal bacteria into the biliary tract and may have become colonized with ORSA during previous hospitalizations. Unfortunately, cultures of the anterior nares were not done to investigate this possibility in either of these patients. Although *S. aureus* is not a common isolate from the duodenal flora, it can occasionally be recovered. Keighley et al. isolated *S. aureus* from the duodenum in four out of 47 patients undergoing biliary tract procedures [21]. However, none had *S. aureus* recovered from their bile fluid. It has been postulated that

bile is bacteriastatic against Gram-positive cocci making isolation of staphylococci from the bile difficult [21, 22].

Patient two was presumed to have prosthetic valve endocarditis despite a normal echocardiogram given her prolonged bacteremia following removal of her infected IV catheter. It seems most likely that she either seeded her gallbladder with *S. aureus* during her initial high-grade bacteremia or had a septic embolus to the gallbladder later in her course. Secondary infection of the gallbladder from bacteremia was felt to be the mechanism of infection in two of the previously described case reports of *S. aureus* cholecystitis. One patient had confirmed endocarditis and another with a VSD and bacteremia likely had cardiac involvement. Thus, in three of the nine cases of *S. aureus* cholecystitis cases reported to date, endocarditis with metastatic involvement of the gallbladder was the most likely mechanism of infection.

Two of our patients were infected with ORSA, which is relatively uncommon in community-acquired staphylococcal infections. The antibiogram in both patients revealed a broadly resistant staphylococci suggesting that acquisition of the organism was nosocomial [23]. Community-acquired strains of ORSA isolated from patients without additional risk factors are more commonly susceptible to other antibiotics compared to nosocomial strains. In our series, patient two clearly had a nosocomial infection due to an infected IV catheter; however, the source of patient three's infection was less certain. Although he was not previously documented to be a colonized with ORSA, it seems likely that he acquired ORSA carriage during a prior hospital admission given the resistant antibiogram of his staphyloccal isolate.

In summary, we report three patients with *S. aureus* infection of the gallbladder, a condition that has rarely been described. These cases expand the already broad range of serious infections that can be caused by staphylococci. Given the infrequency of this organism in the biliary tract, empiric coverage for acute cholecystitis should be directed at common enteric bacteria and therapy adjusted according to the culture results. However, if *S. aureus* is isolated, it should not be dismissed as a contaminant. In addition, in view of the rarity of this condition and the fact that 33 percent of the reported cases were associated with probable endocarditis, an evaluation for an endovascular focus should be done in bacteremic cases.

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