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Acute Acalculous Cholecystitis-Associated Bacteremia Has Worse Outcome

Javier E. Rincon, Rohit K. Rasane, Jose A. Aldana, Christina X. Zhang, Ricardo A. Fonseca, Qiao Zhang, Kelly M. Bochicchio, Obeid N. Ilahi, and Grant V. Bochicchio

Abstract

Background: Acute acalculous cholecystitis (AAC) is an inflammation of the gallbladder without gallstones in the setting of critical illness. It represents 2%–15% of acute cholecystitis (AC) cases. Bacteremia is associated with increased morbidity and mortality rates in patients in the intensive care unit (ICU). The incidence of bacteremia in acute calculous cholecystitis (ACC) has been described; however, the incidence of bacteremia in AAC has not been reported. We hypothesized that patients with AAC have higher bacteremia rates, leading to worse outcomes than in those with ACC.

Methods: A prospectively collected acute care surgery (ACS) institutional database of patients treated from 2008 through 2018 was queried for patients having ACC using International Classification of Diseases (ICD) 9 and 10 codes. Demographics, microbiology findings, and outcomes were extracted. Only patients with positive blood cultures were included in the study. We defined two cohorts: AAC with bacteremia and ACC with bacteremia. The Student t-test was used for continuous variables and the \( \chi^2 \) and Fisher exact tests for categorical variables. Multivariable regression was applied, and statistical significance was set at \( p < 0.05 \).

Results: Of 323 patients with AC, 57 (17.6%) had AAC and 266 (82.4%) had ACC. Of the 19 patients who had a blood culture, 11 (57.8%) were positive. Patients with positive blood cultures had a mean age of 56.7 ± 15.3 years and a mean Body Mass Index (BMI) of 26.7 ± 4.9. The incidence of bacteremia was significantly higher in AAC (\( n = 6; \) 10.5% versus \( n = 5; \) 1.9%; \( p = 0.005 \)), although the time between admission and diagnosis of bacteremia was similar in the two groups (1.2 ± 1.1 versus 0.2 ± 0.5 days; \( p = 0.128 \)). The patients with AAC and bacteremia were younger (53.8 ± 19.2 versus 60.2 ± 8 years; \( p = 0.021 \)) and had a longer ICU length of stay (LOS) (12.6 ± 7.2 versus 1.3 ± 2.1 days; \( p = 0.030 \)). However, there was no difference in the mortality rate in the groups (\( n = 2; \) 33.3% versus 1; 20.0%; \( p = 1.000 \)). After adjusting for age, gender, BMI, and Charlson Co-morbidity Index, bacteremia in AAC patients was found to be an independent variable for longer ICU LOS (odds ratio 8.8; 95% confidence interval 1.7–15.9; \( p = 0.024 \)).

Conclusions: The incidence of bacteremia in patients with AAC is five-fold higher and the ICU stay eight days longer than in patients with ACC.

Keywords: acalculous cholecystitis; bacteremia; calculous cholecystitis

Acute cholecystitis (AC) is defined as a sudden-onset inflammation of the gallbladder (GB) that causes severe right upper quadrant pain. This condition is responsible for approximately 3%–10% of all cases of abdominal pain [1]. According to the presence or absence of gallstones, this disease can be classified as acute calculous cholecystitis (ACC), which accounts for 90% of all cases of AC, and acute acalculous cholecystitis (AAC) [2]. The latter is an inflammatory condition of the GB wall in the absence of cholelithiasis, sludge, or cystic duct obstruction on diagnostic imaging and represents 2%–15% of total AC cases [3,4]. Although it is not well understood, the pathogenesis of AAC most likely is related to GB wall stasis, ischemia, and necrosis [5]. The acalculous condition commonly occurs in critically ill patients with multifactorial risk factors, such as major trauma, non-biliary operations, total parenteral nutrition (TPN) use, sepsis, acquired immunodeficiency syndrome, diabetes, malignant tumors, and bone marrow
transplantation [6–10]. Predisposing risk factors and use of invasive medical devices in the ICU setting increase the likelihood of bacteremia, which in turn is well known to increase morbidity and death [11]. The incidence of bacteremia in ACC has been described [12,13]; however, the incidence of bacteremia in AAC is not established. We hypothesized that patients with AAC have higher bacteremia rates and worse outcomes than patients with ACC.

Patients and Methods

A prospectively collected acute care surgery (ACS) institutional database from 2008 through 2018 was queried for patients having AC using the following International Classification of Diseases (ICD) codes: 9 (574.x, 574.1x, 574.3x, 574.4x, 574.6x, 574.7x, 575.x, 575.1x) and 10 (K80.00x, K80.01x, K80.18x, K80.19x, K80.40x, K80.41x, K80.42x, K80.43x, K80.60x, K80.61x, K80.62x, K80.63x, K81.0x, K81.9x, K82.A1x, K82.A2x). A total of 323 patients were found to have AC. All these patients had undergone cholecystectomy (laparoscopic or open surgery). The diagnosis of AAC was based on abdominal ultrasonography and intraoperative findings of the absence of stones or sludge in the GB. Also, surgical pathology reports confirmed the diagnosis of AAC in the absence of biliary calculi along with the acute inflammatory characteristics. Microbiology data including blood cultures were abstracted to identify the species, genus, and resistance markers in blood stream infections before initiating antibiotics using the Verigene gram-positive and gram-negative blood culture nucleic acid tests. Acquired bacteremia associated with AC was defined as a positive culture of a sample drawn in the ICU after the diagnosis of AC was established. Therefore, only patients with positive blood cultures were included in the study.

On the basis of the cultures, we established two cohorts: AAC with bacteremia and ACC with bacteremia. All the patients were started on empiric antibiotics after blood cultures were obtained. In order to have homogenous cohorts in terms of source control, we excluded patients who underwent percutaneous cholecystostomy (PC), as well as patients who were younger than 18 years, who had incomplete data without blood culture results, or those with negative blood cultures and with chronic cholecystitis. Demographic data such as age, gender, and Body Mass Index (BMI) were abstracted. We evaluated the following hospital outcomes: Length of stay (LOS), ICU LOS, and death. The Student t-test was used for continuous variables and the χ² and Fisher exact tests for categorical variables. Significant outcome differences between the two groups (AAC with bacteremia and ACC with bacteremia) were seen on univariable analysis, and linear regression was applied as appropriate. Statistical significance was set at p < 0.05. Statistical Package for the Social Sciences version 23.0 was used for data analysis.

Table 1. Incidence of Bacteremia in Patients with Acute Acalculous (AAC) and Acute Calculus (ACC) Cholecystitis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total n = 323 (%)</th>
<th>AAC (n = 57; 17.6%)</th>
<th>ACC (n = 266; 82.4%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture (+)</td>
<td>11 (3.40)</td>
<td>6 (10.5)</td>
<td>5 (1.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Blood culture (−)</td>
<td>312 (96.6)</td>
<td>51 (89.5)</td>
<td>261 (98.1)</td>
<td></td>
</tr>
</tbody>
</table>

Statistically significant differences are shown in bold.

Results

Of the total 323 patients with AC who underwent cholecystectomy, 57 (17.6%) had AAC and 266 (82.4%) had ACC. Of the 19 patients (5.9%) who had a blood culture performed, 11 (57.8%) were positive and were included in the study. The blood culture testing was done on average 3 days ±3 days after the diagnosis of AC was made.

The incidence of bacteremia was significantly higher in AAC (n = 6; 10.5% versus n = 5; 1.9%; p = 0.005) than the ACC group, as described in Table 1. Of the 11 patients included in the study, 7 (63.6%) were male (n = 4; 66.7% versus n = 3; 60.0%; p = 1.000), indicating a male predominance in both groups with a somewhat higher predominance in the AAC cohort. The mean age of the total series was 56.7 ±15.3 years; of these, the patients in the AAC group were significantly younger (53.8 ±19.2 versus 60.2 ±8 years; p = 0.021). The mean BMI of the total cohort was 26.7 ±4.9, and no significant difference was found between the groups. The time of diagnosis of bacteremia from admission was similar in both groups (1.2 ±1.1 versus 0.2 ±0.5 days; p = 0.128). No significant differences were found in the Charlson Comorbidity Index (4.7 ±3.1 versus 4.6 ±2; p = 0.791) or the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score (17.8 ±5.8 versus 11.8 ±4.3; p = 0.089). The source control was either open or laparoscopic cholecystectomy; no significant difference was found in the time between AAC and ACC diagnosis and source control (2.2 ±3.9 versus 5.6 ±2.7 hours; p = 0.130). The demographic data are listed in Table 2.

In unadjusted univariable analysis for hospital outcomes (Table 3), there was no difference in LOS between the groups (22.3 ±3.7 versus 15.7 ±12.6 days; p = 0.961). However, the AAC patients had a significantly longer ICU LOS (12.6 ±7.2 versus 1.3 ±2.1 days; p = 0.030). There was no difference in the mortality rate in the two cohorts (n = 2; 33.3% versus 1; 20.0%; p = 1.000). There were no correlations between the type of source control (open vs. laparoscopic cholecystectomy) and death (n = 3; 42.9% versus 0; p = 0.212) or between the time to source control and death (5.0 ±4.6 versus 3.25 ±1.3 days; p = 0.513).

We performed linear regression analysis to adjust for potential confounding factors using ICU LOS as the outcome. In this model, after adjusting for age, gender, BMI, and Charlson Comorbidity Index, bacteremia in AAC patients was found to have an independent variable for longer ICU LOS (odds ratio [OR] 8.8; 95% confidence interval [CI] 1.7–15.9 days; p = 0.024) as seen in Table 4.

The micro-organisms isolated from blood cultures of AAC patients were Staphylococcus spp., Streptococcus spp., Enterococcus spp., E. coli, Candida spp., and mold. In the ACC group, the micro-organisms were Staphylococcus spp., Propionibacterium spp., Corynebacterium spp., Enterococcus spp., and Peptostreptococcus spp.
spp., *Klebsiella* spp., *Enterobacter* spp., and *Candida* spp. The most common pathogen in both groups was *Staphylococcus* (AAC [n = 2; 28.5%] and AAC [n = 2; 25.0%]). No significant differences were found in the distribution of the micro-organisms (Tables 5 and 6).

### Discussion

Acute acalculous cholecystitis remains difficult to diagnose, likely because of the complicated clinical environments in which this disease develops. Notably, AAC is present in 0.2% to 0.4% of all critically ill patients [14], with predisposing multi-factorial risk factors including surgery, trauma, shock, burns, sepsis, and TPN use [6–10]. In our study, the suspected underlying cause of AAC was sepsis.

Percutaneous cholecystostomy is most commonly indicated in critically ill patients with AC with serious comorbidities who are at risk from major surgery or when there is no response to antibiotics, especially in patients with AAC.

### Table 2. Univariable Analysis of Demographic Data by Diagnosis in Patients with Positive Blood Cultures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n = 11</th>
<th>AAC (n = 6; 10.5%)</th>
<th>ACC (n = 5; 1.87%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ± SD</td>
<td>56.7 (± 15.3)</td>
<td><strong>53.8</strong> (± <strong>19.2</strong>)</td>
<td>60.2 (± 8.1)</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Male (%)</td>
<td>7 (63.6)</td>
<td>4 (66.7)</td>
<td>3 (60.0)</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>4 (36.4)</td>
<td>2 (33.3)</td>
<td>2 (40.0)</td>
<td></td>
</tr>
<tr>
<td>BMI ± SD</td>
<td>26.7 ± 4.9</td>
<td>26.8 ± 3.9</td>
<td>26.7 ± 6.6</td>
<td>0.074</td>
</tr>
<tr>
<td>CCI ± SD</td>
<td>4.6 ± 2.8</td>
<td>4.7 ± 3.1</td>
<td>4.6 ± 2.6</td>
<td>0.791</td>
</tr>
<tr>
<td>APACHE II Score ± SD</td>
<td>15.1 ± 5.9</td>
<td>17.8 ± 5.8</td>
<td>11.8 ± 4.3</td>
<td>0.089</td>
</tr>
<tr>
<td>Bacteremia diagnosis time from admission (d)</td>
<td>0.7 ± 0.9</td>
<td>1.2 ± 1.1</td>
<td>0.2 ± 0.5</td>
<td>0.128</td>
</tr>
<tr>
<td>AC diagnosis to source control (d)</td>
<td>3.7 ± 3.7</td>
<td>2.2 ± 3.9</td>
<td>5.6 ± 2.7</td>
<td>0.130</td>
</tr>
</tbody>
</table>

Statistically significant differences are shown in bold.

AAC = acute acalculous cholecystitis; AC = acute cholecystitis; ACC = acute calculous cholecystitis; APACHE = Acute Physiology, Age, and Chronic Health Evaluation; CCI = Charlson Comorbidity Index; SD = standard deviation.

### Table 3. Univariable Analysis of Hospital Outcomes (Intensive Care Unit [ICU] Length of Stay [LOS] [d]) in Patients with Acute Acalculous Cholecystitis (AAC) or Acute Calculous Cholecystitis (ACC) and Positive Blood Culture

<table>
<thead>
<tr>
<th>Hospital outcome</th>
<th>Total n = 11</th>
<th>AAC (n = 6; 10.5%)</th>
<th>ACC (n = 5; 1.9%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS</td>
<td>19.3 (± 13.0)</td>
<td>22.3 (± 3.7)</td>
<td>15.7 (± 12.6)</td>
<td>0.961</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>7.5 (± 7.9)</td>
<td><strong>12.6</strong> (± <strong>7.2</strong>)</td>
<td>1.3 (± 2.1)</td>
<td><strong>0.030</strong></td>
</tr>
<tr>
<td>Death (%)</td>
<td>3 (27.3)</td>
<td>2 (33.3)</td>
<td>1 (20)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Statistically significant differences are shown in bold.

ICU = intensive care unit; LOS = length of stay.

However, we included only patients with AC who were managed surgically (open or laparoscopy cholecystectomy) in order to have homogeneous cohorts in terms of source control. Similarly, Ganpathi et al. in 2007 [3] analyzed 133 patients with AC who had cholecystectomy (laparoscopic or open surgery), and they observed the de novo presentation of AAC in several of their patients.

Studies from Ganpathi et al. [3] and Kalliafas et al. in 1998 [15] demonstrated that the incidence of AAC ranges from 10%–14%. In our study population, the incidence of AAC was 17.6%, slightly higher than in these earlier reports.

Previous studies have shown the impact and epidemiology of bacteremia on outcomes for patients admitted to the ICU and also revealed that bacteremia is one of the major causes of morbidity and death in the ICU [11,16,17]. These studies further emphasized the importance of early diagnosis of bacteremia in critically ill patients along with the rapid initiation of antibiotics to improve clinical outcomes. The incidence of bacteremia has increased over time despite the availability of appropriate antibiotic therapy [18].

### Table 4. Linear Regression to Adjust for Confounding Factors Affecting Length of Stay in Intensive Care Unit

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAC vs. ACC</td>
<td><strong>8.83</strong></td>
<td>1.71–15.94</td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td>Age</td>
<td>-0.42</td>
<td>-0.78– -0.05</td>
<td><strong>0.031</strong></td>
</tr>
<tr>
<td>Gender</td>
<td>5.73</td>
<td>-3.14–14.62</td>
<td>0.151</td>
</tr>
<tr>
<td>BMI</td>
<td>0.31</td>
<td>-0.48–1.12</td>
<td>0.361</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1.61</td>
<td>-0.39–3.27</td>
<td>3.271</td>
</tr>
</tbody>
</table>

Statistically significant differences are shown in bold.

AAC = acute acalculous cholecystitis; AC = acute cholecystitis; ACC = acute calculous cholecystitis; BMI = Body Mass Index; CI = confidence interval.

### Table 5. Microorganisms Isolated from Patients with Acute Acalculous Cholecystitis

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive organisms</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>2 (28.5)</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp.</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Gram-negative organism</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Fungus</td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (14.3)</td>
</tr>
</tbody>
</table>
Blood cultures are the gold standard for the diagnosis of bacteremia. In a study done by Baitello et al. [12], the Bactec system was used to detect bacteremia in patients with ACC. In our institution, we used the Verigene nucleic acid tests to diagnose gram-positive and gram-negative bacteremia in patients with either AAC or ACC. The Verigene test is an automated and rapid diagnostic method that identifies the genus, species, and resistance patterns for a common set of gram-negative and gram-positive bacteria within approximately 2.5 hours of the gram stain, with high sensitivity and specificity [19–21].

Kuo et al. in 1995 [13] and Baitello et al. in 2004 [12] described the impact of bacteremia in patients with ACC, in which they observed the association of bacteremia with greater severity of complications and worse hospital outcomes such as longer LOS and higher mortality rates. However, these studies did not compare the outcomes of an AAC cohort. We found significantly higher rates of positive blood cultures in the patients with ACC, with the incidence of bacteremia being five times that in the ACC group. This is a unique finding that, to our knowledge, has not been described previously.

Kuo et al. [13] also observed that the most common organisms found in ACC-associated bacteremia were gram-negative Enterobacteriaceae such as E. coli and Klebsiella pneumoniae. Nevertheless, we found the most common microorganism grown from blood cultures in both groups to be Staphylococcus.

Antimicrobial susceptibility testing of bacterial isolates found high sensitivity to the antibiotics tested and guided the treatment for our patients, mostly as a monotherapy regimen. All the patients were started on empiric antibiotics after the blood culture was collected. Thus, antibiotic use did not influence the incidence of bacteremia. Vancomycin was the most common antibiotic used for gram-positive bacteria, followed by linezolid, piperacillin-tazobactam, and meropenem for gram-negative bacteria.

According to Laurila et al. [20], critically ill patients who developed AAC and underwent open cholecystectomy had longer ICU LOS (19 days) and a higher mortality rate. However, AAC was not associated with bacteremia. In contrast to the previous studies, we found that patients with AAC with bacteremia stayed in the ICU eight days longer than patients with ACC, which has not been described previously. Even though the mortality rate was high in both AAC (33%) and ACC (20%), no significant difference was found between the two cohorts. This study also noted that the time from admission to diagnosis of bacteremia was similar in the two cohorts, which demonstrates that there was no delay in diagnosis of bacteremia in our institution that could have caused the longer ICU LOS.

In the past, it has been seen that patients with AAC are more acutely ill than those with ACC because of various comorbidities and risk factors [6–10]. However, in our patients, no significant difference was found in the Charlson Comorbidity Index to support this previous result.

Although our study shows significant results, we were limited by the fact that it was a retrospective study confined to a single center. Another notable limitation was that a relatively small number of patients underwent blood cultures. Therefore, these findings should be analyzed prospectively to confirm the incidence data.

Conclusion

The incidence of bacteremia in patients with AAC was five times that in patients with ACC. The former group of patients stayed eight days longer in the ICU than those with ACC and bacteremia. Although the mortality rate was high in both AAC (33%) and ACC (20%) patients, there was no significant difference between the two groups. Further investigation to identify these high-risk patients earlier is warranted.

Author Disclosure Statement

No competing financial interests exist.

References

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