Clinical characteristics and effectiveness of anti-infective therapy on acute cholangitis in children

Tianao Zhang1,*, Tao Zhou2, Zhaohui Deng1, Lirong Jiang1, Bin Zhang1, Yazhen Xu1

1Department of Pediatric Digestive, Shanghai Children’s Medical Center, Shanghai, China; 2Department of Liver Surgery and Liver Transplantation, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China. *Equal contributors.

Received August 5, 2017; Accepted February 14, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: Objective: Although pediatric acute cholangitis (AC) in children is a rare disease, delayed diagnosis and treatment may lead to septic shock and multiple organ failure. However, the characteristics, diagnostic criteria, and treatment of pediatric AC need further exploration. This study aimed to investigate the clinical characteristics and effectiveness of anti-infective therapy on AC in children. Method: The clinical characteristics of children diagnosed with AC at the Shanghai Children’s Medical Center, Shanghai, China, between March 2007 and April 2016 were retrospectively reviewed. Twenty-seven patients with AC were divided into a surgery-related AC group (SR) and surgery-unrelated AC group (SUR). Clinical manifestations, laboratory findings, ultrasonography, and treatments were compared between the two groups. Results: The SR was comprised of 19 (70.4%) patients (10 boys and 9 girls; average age 7.82 ± 4.68 months). The SUR was comprised of 8 (29.6%) patients (5 boys and 3 girls; average age 5.75 ± 3.49 years). Fever was reported in both groups (100%). Jaundice and mental fatigue were more apparent in SR than in SUR. Also, abdominal pain was more apparent in SR than in SUR. Positive rates in ultrasonography and blood culture were higher in SUR than in SR. SR was less sensitive to cefoperazone compared with SUR. The median duration of anti-infective therapy was 18 days in SUR and 11 days in SR. Twenty-seven patients were discharged after the infection was controlled. Conclusions: Although the treatment of SR is more difficult than that of SUR, anti-infective therapy is effective for treating AC in children.

Keywords: Acute cholangitis, antibiotics, children, clinical manifestation

Introduction

Acute cholangitis (AC) is a rare disease in children. The symptoms of AC in children range from mild symptoms such as fever, abdominal pain, and jaundice to septic shock. Delayed diagnosis and treatment of AC can result in severe AC, significantly increasing mortality and morbidity rates. The leading causes of death are septic shock and multiple organ failure and the mortality of AC is 10%-30% [1]. In children, AC occurs most often with specific diseases such as biliary atresia and pancreaticobiliary maljunction or after liver transplantation. Moreover, it has been reported during the course of infectious diseases such as septicemia, typhoid fever, gastroenteritis, pneumonia, and giardiasis. Different causes of AC may be associated with different clinical characteristics and therapeutic effects. However, accurate criteria for diagnosing and treating AC in children have not been established because AC is such a rare disease in children. Although the Tokyo Guidelines were available for managing and treating AC in children, it was only a draft of the guidelines and, therefore, its effectiveness needs to be verified. Therefore, a retrospective review of AC in children at the Shanghai Children’s Medical Center, Shanghai, China, was conducted and the findings were reported.

On the basis of different causes, patients with AC were divided into a surgery-related AC group (SR) and surgery-unrelated AC group (SUR). The aim of the study was to (1) compare clinical manifestations, laboratory findings, ultrasonog-
Acute cholangitis in children

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>SR</th>
<th>SUR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>27</td>
<td>19 (70.4%)</td>
<td>8 (29.6%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>/</td>
<td>7.82 ± 4.68 months</td>
<td>5.75 ± 3.49 years</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>9 (47.4%)</td>
<td>3 (37.5%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Fever</td>
<td>27</td>
<td>19 (100%)</td>
<td>8 (100%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Jaundice</td>
<td>17</td>
<td>15 (78.9%)</td>
<td>2 (25%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9</td>
<td>2 (10.5%)</td>
<td>7 (87.5%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>19</td>
<td>18 (94.7%)</td>
<td>1 (12.5%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Increase in C-reactive protein</td>
<td>27</td>
<td>19 (100%)</td>
<td>8 (100%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Increase in white blood cell count</td>
<td>27</td>
<td>19 (100%)</td>
<td>8 (100%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Positive in blood culture</td>
<td>3</td>
<td>0 (0%)</td>
<td>3 (37.5%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Cytomegalovirus/Epstein-Barr virus DNA positive</td>
<td>3 (11.1%)</td>
<td>3 (15.8%)</td>
<td>0 (0%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Positive in ultrasonography</td>
<td>11</td>
<td>3 (15.8%)</td>
<td>8 (100%)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Median duration of anti-infection (days)</td>
<td>14</td>
<td>18</td>
<td>11</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Sensitive to cefoperazone</td>
<td>9</td>
<td>2 (10.5%)</td>
<td>7 (87.5%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sensitive to menopenem</td>
<td>18</td>
<td>17 (89.5%)</td>
<td>1 (12.5%)</td>
<td></td>
</tr>
</tbody>
</table>

raphy, and treatments between the two groups and summarize the clinical characteristics of AC; (2) compare the response of antibacterial therapy between the two groups; and (3) discuss the characteristics, treatment, and prognoses of AC in children.

**Materials and methods**

**Clinical information**

A retrospective review of all patients with AC admitted to the GI department at the Shanghai Children's Medical Center was carried out for the period of 2007 to 2016. This study was permitted by the Ethics Committee of the Shanghai Children's Medical Center (SCMCIRB-W2017-007). According to the draft diagnostic criteria for pediatric AC included in the Tokyo Guidelines in 2007 [1], a total of 27 children whose ages ranged from 3 months to 13 years were involved. Inclusion criteria for the study were as follows: (1) children, after an operation for biliary atresia, who had a fever of 38°C or higher were diagnosed as having suspected acute biliary tract infection; (2) children, after a biliary atresia operation or after liver transplantation, who had a fever of 38°C or higher and an increased white blood cell count or increased C-reactive protein, and/or increased transaminase level were diagnosed as having AC. The study included 15 males and 12 females divided into a surgery-related AC group (SR) (n = 19) and surgery-unrelated AC group (SUR) (n = 8) (Table 1). The average age was 7.82 ± 4.68 months in SR and 5.75 ± 3.49 years in SUR. Acquired clinical information included gender, age, clinical manifestations, laboratory examination, findings of ultrasonography, treatment, and prognosis from the medical records room in the hospital.

**Clinical characteristics and laboratory findings**

All of the patients had repeated episodes of fever and the mean peak body temperature was 39.34 ± 0.62°C. Jaundice was found in 17 patients (15 in SR and 2 in SUR). Abdominal pain was observed in 9 patients (2 in SR and 7 in SUR). Mental fatigue was noted in 19 patients (18 in SR and 1 in SUR).

Increase in blood levels of C-reactive protein (CRP, normal value < 8 mg L) and white blood cells (WBC, normal value 4-15 × 10⁹/L) were found in 27 patients. Blood culture for bacteria showed positive results in 3 patients in SUR (Klebsiella pneumoniae: n = 1; Escherichia coli: n = 2). None in SR had a positive blood culture but one patient was positive for Epstein-Barr virus DNA and two were positive for cytomegalovirus DNA. Eight patients in SUR and three patients in SR showed characteristics of cholangitis during abdominal ultrasonography.
Acute cholangitis in children

Therapy

Anti-infective therapy was administered to all 27 patients. Initial anti-infective therapy was based on third-generation cephalosporins such as cefoperazone (a dose of 25 mg/kg 8 hourly for 2 weeks according to the protocol). The response to antibiotic treatment was monitored twice weekly. Meropenem was used at a dose of 20 mg/kg 8 hourly for a further 2 weeks if no response to treatment with cefoperazone was observed. A clinical response was defined as resolution of fever, decrease in CRP or WBC count, and improvement in liver function after 5 days of antibiotic treatment. Ganciclovir was used for antiviral therapy. Gamma globulin was administered to 5 patients. The median duration of anti-infective therapy was 18 days in SUR and 11 days in SR.

Prognosis

Twenty-seven patients were discharged after infections were controlled. They were followed up 2 months later. Patients did not have an infection again, except for two patients who underwent Kasai operation for biliary atresia and had recurrent AC.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc. IL, USA). Categorical data were expressed as numbers with percentages, continuous data with normal distributions were expressed as mean ± standard deviation with a range, and data with non-normal distributions were expressed as median with a range. Fisher’s exact test was used to compare clinical data of the two groups since the sample number was only 27, far less than 40 and the minimum frequency was 0, less than 5. Mann-Whitney U test was used to compare the anti-infection duration of the two groups for data with non-normal distributions. P values less than 0.05 were considered to indicate a statistical significance.

Results

Causes and clinical characteristics of AC in children

Clinical manifestations of AC vary among individuals and arise from different causes (Tables 3 and 4). Fever was reported in both groups (100%). Moreover, abdominal pain was found in most patients in SUR (SR vs. SUR, 10.5% vs. 87.5%, respectively; $P = 0.003 < 0.01$) but most patients in SR had jaundice (SR vs. SUR, 78.9% vs. 25%, respectively; $P = 0.014 < 0.05$) and mental fatigue (SR vs. SUR, 94.7% vs. 12.5%, respectively; $P < 0.01$). Inflammatory parameters such as CRP and WBC counts increased significantly in both groups. Blood cultures for bacteria showed a low positive rate ($n = 3$, 11.1%). The positive rate of blood culture was 0% in SR and 37.5% in SUR, showing a significant difference between the groups (SR vs. SUR, 0% vs. 37.5%, respectively; $P = 0.019 < 0.05$).

Positive ultrasonographic findings were detected in all of the patients in SUR and this proportion was markedly higher than that in SR (SR vs. SUR, 15.8% vs. 100%, respectively; $P < 0.01$) (Table 5).

Therapies and prognosis

SUR was sensitive to third-generation cefoperazone and only one patient with SUR received
Acute cholangitis in children

Table 4. Laboratory examination of patients with AC

<table>
<thead>
<tr>
<th>Group</th>
<th>Increase in CRP (&gt; 8 mg/L)</th>
<th>Increase in WBC count (&gt; 15 × 10⁹/L)</th>
<th>Positive blood culture</th>
<th>Cytomegalovirus/Epstein-Barr virus DNA positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR (n = 19)</td>
<td>19 (100%)</td>
<td>19 (100%)</td>
<td>0 (0%)</td>
<td>3 (2/1) (15.8%)</td>
</tr>
<tr>
<td>SUR (n = 8)</td>
<td>8 (100%)</td>
<td>8 (100%)</td>
<td>3 (37.5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 5. Findings of AC in ultrasonography

<table>
<thead>
<tr>
<th>Group</th>
<th>Stones (0%)</th>
<th>Sludge (15.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR (n = 19)</td>
<td>0</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>SUR (n = 8)</td>
<td>2 (25%)</td>
<td>6 (75%)</td>
</tr>
</tbody>
</table>

meropenem after failing to respond to treatment with cefoperazone. SR was less sensitive to third-generation cefoperazone compared with SUR (SR vs. SUR, 10.5% vs. 87.5%, respectively; \(P = 0.003 < 0.01\)). SR showed a successful response to meropenem (89.5%). The duration of anti-infective therapy in SR was longer than that in SUR (SR vs. SUR, 18 d vs. 11 d, respectively; \(u = 48.5 < u_{0.05}\) (Table 6).

Therapeutic efficacy was favorable in 27 patients and they were discharged after the infection was under control.

Discussion

The incidence of AC in children is about 0.13%-0.22% [1], which is lower than that in adults. Thus, the Tokyo Guidelines for treating acute cholangitis and cholecystitis in 2007 defined AC in children as unusual types of biliary tract infection. Also, the guideline for diagnosis and treatment of AC in children was a draft guideline. In China, a few reports have discussed the clinical characteristics of AC in children. This novel study summarized the characteristics, treatment, and prognoses of AC in children according to different causes. Different causes of AC in children were associated with different clinical characteristics and different responses to antibiotic treatment.

Theoretically, fever, abdominal pain, and jaundice are the typical features of Charcot’s triad with AC. Not all children with AC presented with the typical Charcot’s triad in our present study. Fever was the common finding observed in all of the patients. Abdominal pain was found mainly in SUR and patients in SR presented mainly with jaundice and mental fatigue. Clinical manifestations were atypical in children, which might be ascribed to differences in the causes of AC.

Thus, the Tokyo Guidelines emphasized other laboratory examinations such as CRP level, WBC count, and especially ultrasonography of the liver and gallbladder, which have been helpful in early diagnosis of AC [2-4]. Ultrasonography of the liver and gallbladder identified AC in all of the patients in SUR in the present study. Cholangitis was a major cause of fever after operation for biliary atresia in SR and increases in CRP level and WBC count were indicative of cholangitis but ultrasonography was not necessary for diagnosing AC in SUR.

Blood cultures usually show a low positive rate in cases of cholangitis. For example, Wang et al. [5] reported that the rate of positive blood culture was only 17% among 150 patients with biliary tract infections. Rate of positive blood culture was only 11% in the present study. The rate of positive blood culture was lower in SR than in SUR, which might be ascribed to anti-infective therapy before admission and prophylactic anti-infective therapy after surgery. However, evidence has shown that cultures of bile collected through the duodenum have a high positive rate. This method is superior to blood cultures and can provide valuable evidence for clinical diagnosis of AC [6-9]. Yu et al. [10] analyzed 128 patients with recurrent cholangitis after operation for biliary atresia and results showed that the positive identification rate was only 34.3% for blood culture but was as high as 100% for bile culture. Of note, bile collection is an invasive procedure which significantly limits its wide application in children in China.

Antibiotics are an important component in treating AC. Early treatment with a sufficient dose of antibiotics for a sufficient duration is crucial for anti-infective therapy. Gram-negative bacteria such as E. coli are the most common pathogens that cause AC, [6, 11] followed by K pneumoniae, Enterococcus, and Streptococcus. Thus, cefoperazone is routinely used in AC.
Acute cholangitis in children

The present results showed that SUR was sensitive to cefoperazone but SR was insensitive to cefoperazone. Hence, meropenem was administered. Wong et al. [14] also reported that among 40 patients with post-Kasai cholangitis, efficacy of cefoperazone was 75% and meropenem was used for complete response in unresponsive episodes. Antibiotic resistance has been the major challenge in treating cholangitis after Kasai procedures and liver transplantations and has prompted the wider use of higher-generation antibiotics [10, 14-16]. Furthermore, the duration of anti-infective therapy in SR was longer compared with SUR. The prognoses of AC were good, except for two patients in SR having recurrent cholangitis 2 months later.

Although positive findings were relatively few in blood culture and bile collection was not feasible in SR, meropenem was efficient for treating AC (89.5%) because of its broad spectrum with good biliary concentration, having been shown to be effective against many different organisms including anaerobes. Besides anti-infective therapy, symptomatic therapy such as administration of gamma globulins is also helpful in improving patient condition.

In conclusion, characteristics and treatments have varied among children with AC of different causes. Meropenem is more effective than cephalosporins for treating cholangitis after Kasai procedures and liver transplantations. Although the therapy for cholangitis after operation is difficult and long term, active anti-infective and symptomatic therapy can achieve favorable efficacy in children. However, the problem of antimicrobial resistance in this study still needs attention. Strict hospital guidelines in antibiotic use, adoption of an antibiotic rotation policy, and use of a combination of antibiotics as the first-line treatment should be advocated in an attempt to reduce the problem of antimicrobial resistance. Our present study had certain limitations such as the small sample size, a single-center retrospective design, and short-term follow up. A future prospective clinical study could yield a more definitive conclusion.

Acknowledgements

The authors would like to thank Professor Yunfang Zhou of Shanghai Children’s Hospital in China for his skilled assistance and valuable cooperation.

Disclosure of conflict of interest

None.

Address correspondence to: Zhaohui Deng and Lirong Jiang, Department of Pediatric Digestive, Shanghai Children’s Medical Center, School of Medicine, Shanghai Jiao Tong University, No 1678 Dongfang Road, Pudong District, Shanghai 200127, China. Tel: +86-21-38626161-5600; Fax: +86-21-50891405; E-mail: dengzhaohui@scmc.com.cn (ZHD); Tel: +86-21-38626161-5600; Fax: +86-21-50891405; E-mail: jiangli_rong@aliyun.com (LRJ)

References


Table 6. Therapy of AC

<table>
<thead>
<tr>
<th>Group</th>
<th>Median duration of anti-infective therapy (days)</th>
<th>Sensitivity to cefoperazone</th>
<th>Sensitivity to meropenem</th>
<th>Ganciclovir</th>
<th>Gamma globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR (n = 19)</td>
<td>18</td>
<td>2 (10.5%)</td>
<td>17 (89.5%)</td>
<td>3 (15.8%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>SUR (n = 8)</td>
<td>11</td>
<td>7 (87.5%)</td>
<td>1 (12.5%)</td>
<td>0 (0%)</td>
<td>1 (12.5%)</td>
</tr>
</tbody>
</table>
Acute cholangitis in children


