Pediatric Infectious Disease Society of the Philippines Journal
Vol 24 No 2, pp. 64-74 July-December 2023
Calimlim-Samson AL, delos Reyes CA, Gregorio GEV. Clinical Profile and Treatment Outcomes Of Acute Cholangitis in Children in a Tertiary Government Hospital in the Philippines: A Five-Year Retrospective Study.
https://doi.org/10.56964/pidspj20232402008

ORIGINAL ARTICLE

CLINICAL PROFILE AND TREATMENT OUTCOMES OF ACUTE CHOLANGITIS IN CHILDREN IN A TERTIARY GOVERNMENT HOSPITAL IN THE PHILIPPINES: A FIVE-YEAR RETROSPECTIVE STUDY

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ABSTRACT

Background: Acute cholangitis (AC) in children is a rare but life-threatening infection. Symptoms vary from mild to severe disease. There are no local published data on pediatric AC.

Objective: To determine the clinical, biochemical, ultrasonographic, microbiologic features, and treatment outcome of pediatric patients with definite AC.

Methodology: Cross-sectional study using medical records of pediatric patients diagnosed with definite AC based on the Modified Tokyo Guidelines of 2018 admitted from January 2016 to June 2021.

Results: Twenty-seven patients aged 0 to 18 years old (10.06 $\pm$ 7.34), predominantly male (51.85%) were included. Choledocholithiasis (22%) and post-Kasai biliary atresia (22%) were the common underlying biliary conditions. Fever (88.89%) was the most frequent presenting symptom. Majority were classified as moderate AC (40.74%). Leukocytosis (mean $16x10^9$/L), elevated inflammatory markers (93.33% with CRP >12mg/L and 100% with serum procalcitonin >0.25ng/mL), hyperbilirubinemia (total bilirubin 192.54±126.87umol/L) and elevated alanine transferases (mean 59 IU/L) were noted. Twenty-one out of 27 cases (87%) had a negative blood culture. Only 4 patients underwent bile culture, of which two (50%) grew *Klebsiella pneumoniae* resistant to empiric antibiotics. Dilated biliary ducts were observed on abdominal ultrasound in 92.59% of patients. Ampicillin-sulbactam (29.63%) was the most commonly utilized antibiotic. Discharge rate was high (88.89%).

Conclusions: AC affects all pediatric age groups but clinical presentations vary. Drug resistant organisms are a significant concern but despite this, favorable outcomes have been documented.

KEYWORDS: *Cholangitis, Children, Choledocholithiasis*

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INTRODUCTION

Acute cholangitis (AC), also known as ascending cholangitis, is a life-threatening disease affecting the biliary tree caused by a bacterial infection. The diagnosis is described by clinical presentation, laboratory results, and imaging studies implying infection and biliary obstruction.[1] In children, acute cholangitis is rare. Symptoms may be mild like fever, abdominal pain or jaundice to severe forms like shock. It occurs most often with specific diseases such as biliary atresia, biliary obstructions, or a sequela of previous biliary surgeries.[2] Severe AC may be a result of delayed diagnosis and treatment, significantly increasing mortality and morbidity rates. The leading causes of death are septic shock and multiple organ failure. Mortality rate of AC in children may reach 10-30%.[3]

Standard criteria for diagnosing and treating acute cholangitis in pediatrics have not been well established and only derived from a draft of the Tokyo Guidelines, an international consensus meeting of specialists for the management of acute cholecystitis and cholangitis held in Tokyo, Japan in the year 2006. The criteria for diagnosis and severity grading of AC were amended and reintroduced in 2013. Its validation through application in clinical practice was established in 2018. The updated guidelines determined the conditions that should be present to identify acute cholangitis in patients, which includes evidence of systemic inflammation, presence of cholestasis, and occurrence of biliary disorder based on history, histology or imaging.

As of this writing, no substantial description of demographic and clinical profile of pediatric acute cholangitis is available in the country. This study can initiate a local database on this condition and help identify further gaps in knowledge that can be addressed in future researches. The clinical and laboratory profile can inform clinicians on how acute cholangitis presents among pediatric patients and increase early recognition and thus early treatment as well, for improved outcomes. Ultimately, providing quality healthcare for Filipino children.

MATERIALS AND METHODOLOGY

Study Design

This was a retrospective, cross-sectional institution-based study conducted at the Philippine General Hospital, Department of Pediatrics, Divisions of Pediatric Gastroenterology, Hepatology and Nutrition and Infectious and Tropical Diseases .

Study Population and Setting

All pediatric patients 0 to 18 years old with a diagnosis of definite or recurrent acute cholangitis and severity classification as defined using the Modified Tokyo Guidelines 2018 (Table 1 and 2) admitted from January 1, 2016 to June 30, 2021 were included in this study. Suspected cases of acute cholangitis or cases that did not satisfy the diagnostic criteria were excluded.

Table 1. Diagnostic Criteria for Acute Cholangitis in Children (Modified from Tokyo Guidelines 2018)

A. Systemic inflammation
Persistent fever with no other focus of infection with laboratory data demonstrating evidence of any of the following laboratory response:
A-1. Increased white blood cell count
A-2. Increased quantitative C-reactive protein
B. Cholestasis
B-1. Appearance of jaundice or Increased intensity of jaundice in a child who is previously icteric
B-2. Presence of pale or acholic stools in a child with previously normal colored stool
B-3. Laboratory data: abnormal liver function tests (increased bilirubin and ALT levels) or deterioration in the levels of liver function tests
C. Biliary disorder based on history, histology or imaging (ultrasound of liver and hepatobiliary tree, CT scan of abdomen, magnetic resonance cholangiopancreatography)
C-1. History of biliary surgery
C-2. Evidence of biliary pathology on liver biopsy
C-3. Biliary dilatation on imaging
C-4. Evidence of the etiology on imaging (bile sludge, stricture, stone, mass, etc.)
Diagnosis
Suspected diagnosis: 1 item in A + 1 item in either B or C
Definite diagnosis: 1 item each in A, B and C
Recurrent Cholangitis: occurrence of 1 or more episodes of acute cholangitis within a 6-month period

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Table 2. Severity Assessment Criteria for Acute Cholangitis in Children (Modified from Tokyo Guidelines 2018)

Mild Acute Cholangitis
If the acute cholangitis does not meet the criteria of Severe or Moderate acute cholangitis at initial diagnosis
Moderate Acute Cholangitis
If associated with at least any three of the following conditions: 1. High grade fever (T>39C) with no other focus of infection 2. Abnormal white blood cell count for age[a] 3. Appearance of jaundice (TB > 5mg/dl) or increased in intensity of jaundice in a child who was previously icteric 4. Presence of irritability
Severe Acute Cholangitis
If the patient fulfills criteria for moderate acute cholangitis AND ANY of the following signs of organ dysfunction 1. Cardiovascular dysfunction: hypotension <5th percentile for age or systolic BP < 2 SD below normal for age) despite administration of isotonic intravenous fluid bolus ≥ 60ml/kg in 1 hour and/or inotropic support (dopamine or dobutamine >5ug/kg/min, or epinephrine or norepinephrine at any dose) 2. Neurological dysfunction: disturbance of consciousness (Glascow coma scale ≤11 or acute change in mental status with a decrease in GCS ≥3 points from abnormal baseline) 3. Respiratory dysfunction: PaO2/FiO2 < 300 in the absence of cyanotic heart disease or preexisting lung disease, or need for >50% FiO2 to maintain saturation ≥ 92% 4. Renal dysfunction: Serum creatinine ≥ 2 times upper limit of normal for age or 2-fold increase in baseline creatinine 5. Hepatic dysfunction: PT-INR >1.5 unresponsive to Vitamin K 6. Hematological dysfunction: platelet count <100,000/mm

[a]1 to 23 months >14,000/mm^3, 2 to 9 years >12,000/mm^3, 10 to 18 years >10,500/mm^3

Data Collection

The list of all pediatric patients who fulfilled the inclusion criteria was generated from the database of the pediatric divisions of gastroenterology and infectious disease of all patients diagnosed with acute cholangitis or ascending cholangitis from January 1, 2016 to June 30, 2021.

Using a standardized data collection sheet, the patient's age and sex were logged in the demographic profile. Their clinical manifestations, onset of symptoms, severity classification, recurrence of infection, and use of prophylaxis were noted in the clinical profile. Predisposing condition, underlying biliary diseases, as well as previous biliary procedures were documented. Determination of biochemical features included white blood cell count, inflammatory markers such as C-reactive protein and serum procalcitonin, serum bilirubin, and alanine transaminase. Isolates from blood and bile cultures were noted. Imaging findings, specifically dilatation of bile duct, presence of bile duct stones or calculi, strictures, obstructive lesions and stenosis, from abdominal ultrasound, abdominal computed tomography (CT) scan, abdominal magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound were noted. The antibiotics used as well as the outcome of the patients were documented. Clinical outcomes identified include the following: discharged, mortality, with complications (morbidity), and home against medical advice.

Statistical Analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption were summarized using mean and standard deviation (SD), while those that did not, were described using median and range. All valid data were included in the analysis. Missing data were neither replaced nor estimated. The null hypothesis was rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

Ethical Considerations

This study was approved by the Philippine General Hospital Expanded Hospital Research Office (EHRO) Technical Review Panel and the University of the Philippines Manila Research Ethics Board (UPMREB) prior to data collection. This study adhered to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, World Health organization

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guidelines, International Conference on Harmonization-Good Clinical Practice, Data Privacy Act of 2012, and National Ethics Guidelines for Health Research.

A waiver of informed consent was requested from the Ethical Panel since the research presents no more than minimal risk and the waiver or alteration will not severely affect the rights and welfare of the participants. In accordance with the National Ethical Guidelines of Health and Health-related Research 2017, the research cannot be carried out without the waiver and the review of medical records and its anonymity will be maintained. Since this is a retrospective study using medical records, it is prudent to state that a written informed consent was obtained from the parents/guardian upon admission. Data was solely collected by the primary investigator. All subject information was anonymized via identification code numbers and kept confidential. A master list linking the code number and subject identity was kept separately from the research data. Only members of the research team have access to the list. Computerized study information were stored on a secured network with password access and saved in a USB storage device. This and the data collection forms were kept in filing cabinets under lock and key and accessed only by the investigator. The data will be securely stored for at least five years from the date of final publication and will be destroyed thereafter. The risk to privacy is minimal in this study, however in case of a breach, the matter will be forwarded immediately to the Philippine General Hospital data privacy officer.

The investigators declare that there is no conflict of interest nor were they associated with any sponsor or compensation in the conduct of this study.

RESULTS

Table 3. Demographic and clinical profile of patients with AC (n=27)

	All (n=27)	<5 years old (n=9)	≥5 years old (n=18)
Age, years (Mean ± SD)	10.06±7.34	-	-
Sex (Frequency [%])			
Male	14 (51.85)	4 (44.44)	10 (55.56)
Female	13 (48.15)	5 (55.56)	8 (44.44)
Clinical manifestation			
Fever	24 (88.89)	9 (100)	15 (83.33)
Jaundice	23 (85.19)	8 (88.89)	15 (83.33)
Abdominal Pain	18 (66.67)	1 (11.11)	17 (94.44)
Pale/acholic stool	8 (29.63)	7 (77.78)	1 (5.56)
Lethargy	7 (25.93)	2 (22.22)	5 (27.78)
Irritability	5 (18.52)	4 (44.44)	1 (5.56)
Chills/Rigor	1 (3.70)	0	1 (5.56)
Confusion	1 (3.70)	0	1 (5.56)
Abdominal pain, fever, and jaundice	12 (44.44)	1 (11.11)	11 (61.11)
Cardiovascular dysfunction			
Hypotension despite intravenous fluid bolus and/or inotropic support	3 (11.11)	0	3 (16.67)
Neurologic dysfunction			
GCS<11	1 (3.70)	0	1 (5.56)
Acute change in mental status with a decrease in GCS ≥3 points from abnormal baseline	1 (3.70)	0	1 (5.56)
Respiratory dysfunction			
PaO2/FiO2 < 300 in the absence of cyanotic heart disease or preexisting lung disease	0	0	0
Need for >50% FiO2 to maintain saturation ≥ 92%	1 (3.70)	0	1 (5.56)
Renal dysfunction			
Serum creatinine ≥ 2 times upper limit of normal for age	2 (7.41)	2 (22.22)	0
2-fold increase in baseline creatinine	2 (7.41)	2 (22.22)	0
Hepatic dysfunction			
(PT-INR >1.5 unresponsive to Vitamin K)	4 (14.81)	2 (22.22)	2 (11.11)
Hematologic dysfunction			
(Platelet count <100,000/mm)	4 (14.81)	2 (22.22)	2 (11.11)
Onset of symptom			
≤1 week	6 (22.22)	4 (44.44)	2 (11.11)
>1 week	21 (77.78)	5 (55.56)	16 (88.89)
AC severity on admission			
Mild	10 (37.04)	5 (55.56)	5 (27.78)
Moderate	11 (40.74)	2 (22.22)	9 (50)
Severe	6 (22.22)	2 (22.22)	4 (22.22)
Recurrent acute cholangitis	2 (7.41)	1 (11.11)	1 (5.56)
Prophylaxis[b]	1 (3.70)	1 (11.11)	0

[b]Cotrimoxazole prophylaxis was given to only one patient out of two with a recurrent episode of acute cholangitis

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Twenty-seven pediatric patients with definite acute cholangitis were included in the analysis and divided into two groups: < 5 years old (n=9) and ≥ 5 years old (n=18) (Table 3). The youngest was 17 days old and the oldest was 18 years old. The average age of the patients was 10.06 ± 7.34 years. Patients were predominantly male (51.9% vs 48.2%). Overall, the three most common clinical manifestations were fever (88.89%), jaundice (85.19%), and abdominal pain (66.67%). Acholic stools were seen in eight (29.63%) patients. Other clinical manifestations seen were lethargy, irritability, chills/rigor and confusion. Multiorgan dysfunction such as cardiovascular, respiratory, renal, hepatic, and hematologic signs were also noted. The onset of symptoms was over a week from admission in 78% of the patients. Severity of AC in these patients varied from mild (37.04%), moderate (40.74%), to severe (22.22%). Two patients with biliary atresia and disseminated tuberculosis had recurrent AC, one of whom received prophylaxis with cotrimoxazole.

Table 4. Predisposing conditions of patients with AC (n=27)

	All (n=27)	<5 years old (n=10)	≥5 years old (n=17)
	Frequency (%)		
Conditions			
Choledocholithiasis	6 (22.22)	0	6 (35.29)
Post Kasai in Biliary Atresia*	6 (22.22)	5 (50)	1 (5.88)
Cholelithiasis	4 (14.81)	0	4 (23.53)
Choledochal cyst	3 (11.11)	1 (10)	2 (11.76)
Hepatobiliary tuberculosis	3 (11.11)	0	3 (17.65)
Biliary Atresia with no surgery	2 (7.41)	2 (20)	0
Gallbladder hydrops	1 (3.70)	1 (10)	0
Biliary ascariasis	1 (3.70)	0	1 (5.88)
Necrotizing enterocolitis	1 (3.70)	1 (10)	0
History of biliary disease			
Acute cholecystitis	2 (7.41)	1 (11.11)	1 (5.56)
Acute pancreatitis	0	0	0
Previous biliary procedures			
Kasai**	4 (14.81)	3 (33.33)	1 (5.56)
Open tube cholecystostomy	1 (3.70)	0	1 (5.56)
Roux-en-Y choledochocystojejunostomy	1 (3.70)	0	1 (5.56)
Cholecystectomy	0	0	0
Biliary stent placement	0	0	0

*Post Kasai procedure during the time of AC diagnosis and admission
**Previous Kasai procedure months or years prior to the time of AC diagnosis and admission

Of the 27 patients, there were six who had choledocholithiasis; six biliary atresia patients who had Kasai portoenterostomy procedure during the AC diagnosis and admission; four with cholelithiasis; three with choledochal cyst; three with hepatobiliary tuberculosis; two biliary atresia patients with no surgical intervention; and one patient for each case of gallbladder hydrops, biliary ascariasis, and sepsis from necrotizing enterocolitis (Table 4). Two patients also had a history of acute cholecystitis. Previous biliary procedures included four patients who had Kasai portoenterostomy months/years prior to AC diagnosis, one with open tube cholecystostomy and one with Roux-en-Y choledochocystojejunostomy.

Table 5. Biochemical and Microbiologic features of patients with AC (n=27)

	All (n=27)	<5 years old (n=9)	≥5 years old (n=18)
WBC [n=27]	Mean ± SD; Median (Range)		
10^9/L	16 (2.4-46.6)	15 (2.4-46.6)	16.55 (10.75-35.4)
CRP mg/L (n=13)	Frequency (%)		
<6	1 (6.67)	1 (20)	0
>12	12 (93.33)	4 (80)	8 (100)
Procalcitonin ng/mL (n=12)	Frequency (%)		
>0.25	12 (100)	5 (100)	7 (100)
ALT (n=27)	Mean ± SD; Median (Range)		
IU/L	59 (13-402)	53 (16-402)	74.5 (13-240)
Bilirubin umol/L (n=27)	Mean ± SD		
Total	192.54±126.87	201.46±151.97	188.57±118.78
Direct	163.58±116.92	167.49±141.89	161.85±108.65
Indirect	28.95±17.81	33.98±21.02	26.72±16.36
Blood culture done	24 (88.89)	9 (100)	15 (83.33)
No isolates	21 (87.50)	7 (77.78)	14 (93.33)
With positive isolates	3 (12.50)	2 (22.22)	1 (6.67)
Salmonella B sp.	1 (33.33)	1 (50)	0
Gram negative bacilli	1 (33.33)	0	1 (100)
Acinetobacter baumannii	1 (33.33)	1 (50)	0
Serratia marcescens	1 (33.33)	1 (50)	0
Bile culture done	4 (14.81)	0	4 (22.22)
No isolates	2 (50)	-	2 (50)
With positive isolates	2 (50)	-	2 (50)
Klebsiella pneumoniae	2 (100)		2 (100)

The average white blood cell count for those <5 years old was 15x10^9/L while for those >5 years old was 16.55x10^9/L. These values were particularly high based on the subjects' age. Meanwhile, the average

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serum alanine transferase for all patients was likewise elevated at 59 IU/L. Increased level of C-reactive protein (>12mg/L) was likewise seen in all 13 subjects requested with the biomarker except for one patient aged less than 5 years old. Procalcitonin was requested amongst 12 subjects and all showed elevated levels >0.25ng/ml. The mean values of total (192.54±126.87 umol/L), direct (163.58±116.92 umol/L) and indirect (28.95±17.81 umol/L) bilirubin were all elevated in both age groups. Laboratory data indicative of inflammation (e.g., leukocytosis and an elevated C-reactive protein [CRP] level), and evidence of biliary stasis (e.g., hyperbilirubinemia, elevation of biliary enzymes and liver enzymes) are frequently seen in patients with acute cholangitis, and such laboratory findings support the diagnosis.

All patients had blood culture requested on their chart, but only 24 were found to have results available on record. Only three patients were identified to have isolates. One patient had a mixed growth of *Serratia marcescens* and *Acinetobacter baumannii*, another with a *Salmonella B sp.* and unspecified gram-negative bacilli.

On the other hand, all patients with bile cultures were >5 years old, of whom, two had positive isolate of *Klebsiella pneumoniae*. Both empiric antibiotics used for these isolates were resistant based on their sensitivity pattern.

Table 6. Radiologic findings in patients with AC (n=27)

	All (n=27)	<5 years old (n=9)	≥5 years old (n=18)
	Frequency (%)		
Abdominal Ultrasound done	25 (92.59)	8 (88.89)	17 (94.44)
No findings	3 (12)	2 (25)	1 (5.88)
Dilation of the bile duct	13 (52)	3 (37.50)	10 (58.82)
Bile duct stones	2 (8)	0	2 (11.76)
Others	7 (28)	3 (37.50)	4 (23.53)
Abdominal CT Scan done	9 (33.33)	1 (11.11)	8 (44.44)
No findings	0	0	0
Dilation of the bile duct	9 (100)	1 (100)	8 (100)
MRC cholangiopancreatography done	2 (7.41)	0	2 (11.11)
No findings	0	-	0
Low-diameter strictures	2 (100)	-	2 (100)
Large common bile duct stones	0	-	0
Others	2 (100)	-	2 (100)

Table 6 continued. Radiologic findings in patients with AC (n=27)

	All (n=27)	<5 years old (n=9)	≥5 years old (n=18)
	Frequency (%)		
Abdominal MRI done	0	0	0
ERC done	6 (22.22)	0	6 (33.33)
No findings	0	-	0
Asymmetrical dilation of bile ducts	2 (33.33)	-	2 (33.33)
Presence of calculi	2 (33.33)	-	2 (33.33)
Presence of obstructive lesions and stenosis	1 (16.67)	-	1 (16.67)
Others	1 (16.67)	-	1 (16.67)
Endoscopic Ultrasound done	1 (3.70)	0	1 (5.56)
No findings	0	-	0
Biliary duct dilation	0	-	0
Small stones	0	-	0
Malignancy	0	-	0
Pseudocyst	1 (100)	-	1 (100)

Only 25 subjects underwent abdominal ultrasound while the remaining two subjects had no abdominal imaging requested. Amongst the 25 subjects with abdominal ultrasound (92.59%), 52% had dilatation of the bile duct and 12% had bile duct stones. Among the nine (33.33%) patients who underwent abdominal CT scan, all were found to have dilatation of the bile duct but none with high-attenuated nodules. Only two (7.41%) underwent MRCP with low-diameter strictures noted for both. Only one (3.7%) patient had endoscopic ultrasound and was found to have pseudocyst; while there were six (22.22%) who underwent ERCP and their findings included asymmetrical dilatation of the bile ducts (33.33%), presence of calculi (33.33%), and obstructive lesions and stenosis (16.67%) [Table 6].

Table 7. Antibiotics given to patients with AC (n=27)

Antibiotics	Frequency (%)
Ampicillin-Sulbactam	7 (25.93)
Ceftriaxone and Metronidazole	6 (22.22)
Cefoxitin and Metronidazole	4 (14.81)
Meropenem	4 (14.81)
Piperacillin-Tazobactam	4 (14.81)
Ampicillin-Sulbactam, shifted to Meropenem	1 (3.70)
Ampicillin-Sulbactam, shifted to Piperacillin-Tazobactam	1 (3.70)
Cefoxitin	1 (3.70)
Cefoxitin and Metronidazole, shifted to Ceftazidime and Metronidazole	1 (3.70)
Ceftriaxone	1 (3.70)
Colistin and Gentamycin	1 (3.70)
Oxacillin and Metronidazole	1 (3.70)

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The most common antibiotic given to patients was ampicillin-sulbactam (25.93%), followed by a combination of ceftriaxone and metronidazole (22.22%) [Table 7]. Depending on the course of the patient's hospital stay, initial antibiotics given could have been shifted to much broader coverage, thus some may have been on 1 or more antibiotics throughout their hospital stay. Average duration of antibiotic use was 4 to 7 days.

Most (88.89%) of the patients were discharged improved after treatment. There were two mortalities who were both classified as severe AC. The causes of death included multiorgan dysfunction and septic shock, respectively. One patient went home per request.

DISCUSSION

In 2007, the Tokyo guidelines defined acute cholangitis as an unusual type of biliary infection among children. In fact, acute cholangitis in the pediatric population has only about 0.13-0.22% incidence compared with the adults. Standards for diagnosis and treatment were only draft guidelines. [3] In this study, the clinical profile and treatment outcome of acute cholangitis in children were presented.

The clinical profile was disaggregated by age groups < 5 years and > 5 years based on the causes of AC depending on the age predilection. Cholangitis mostly occurs in children with specific diseases such as biliary atresia, pancreaticobiliary malfunction, or previous biliary surgeries like post Kasai procedure. [3] In this study, cholangitis from obstructive biliary conditions were higher in children >5 years old (66.6%) compared to cholangitis from biliary atresia and post-operative biliary procedures in children <5 years old (33.3%). This was consistent with the review of 693 cases conducted by Friesen and Roberts in which pediatric cholangitis are distributed to ages as follows: 9.8% (1 year old or younger), 4.5% (1–5 years old), 14.5% (6–10 years old), and 71.5% (age, 11–20 years). [4]

Clinical diagnosis of acute cholangitis is classically based on the Charcot triad of fever, jaundice, and abdominal pain. However, its excellent specificity is counteracted by its poor sensitivity. [5] In a summary of literature by Kiriyama, et al, fever and abdominal pain are the most frequently observed clinical manifestations of cholangitis involving adults. [6] In our study, fever was reliably the most common symptom while jaundice was observed more frequently than abdominal pain due to the usual causes of AC amongst the subjects. Pale or acholic stools, lethargy and irritability were also habitually noted for similar reasons.

The incidence of Charcot's triad is reported in not more than 72% of adult patients with acute cholangitis. On the other hand, more severe form such as Reynolds' pentad is extremely rare, about only 3.5%–7.7% of this population. [6] Our study likewise showed the same results having 44% children presenting with the triad of fever, abdominal pain, and jaundice while an average of 1 to 3 patients had multiple organ dysfunction. By severity of AC upon admission, mild and moderate AC predominate our study population compared to severe or recurrent forms of AC typically from post-Kasai procedures.

Laboratory findings supporting the diagnosis of AC typically indicate inflammation and evidence of biliary stasis.[6] Several published studies reported that in acute cholangitis despite its cause, evident leukocytosis, elevated levels of biomarkers such as C-reactive protein and serum procalcitonin, hyperbilirubinemia and elevation of biliary and liver enzymes were noted.[7-11] In this study, most of the children with AC regardless of its severity had increased white blood cell count, C-reactive protein, serum procalcitonin, serum alanine transferase and with direct hyperbilirubinemia.

The two key microbiological tests for acute cholangitis are hemoculture and bile culture. [6] Blood cultures usually show a low positive rate. [2] Wang et al. reported only 17% yield among 150 hemocultures of adult patients with biliary tract infections. [12] Specifically for episodes of AC due to biliary stent

obstruction in adults, a recent retrospective multicenter series showed 40% positive hemocultures. [13] On the other hand, Zhang et al. in 2018 illustrated only 11% positive blood cultures among 27 pediatric patients with definite AC of which, *Escherichia coli* and *Klebsiella pneumoniae* were the primary isolates. These data mentioned are consistent with the present study's low yield of 12.5% positive hemocultures. However, culture-negative result predominates our patient population at 88.89%. Varied gram-negative bacteria were isolated such as *Acinetobacter baumannii, Serratia marcescens,* and *Salmonella B sp.*

Studies have shown that cultures of bile collected through the duodenum have a high positive rate. This diagnostic is superior to blood cultures and can provide valuable evidence for clinical diagnosis of AC. [2] Yu et al. 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. [14] Among the four pediatric patients with AC in our study that underwent bile culture, two children showed no isolates while the other two subjects yielded *Klebsiella pneumoniae.* This finding is consistent with the 2018 Tokyo guidelines identifying *Escherichia coli* and Klebsiella spp. as the two main bacteria in bile which are responsible for most cases of acute cholangitis.[15] Although the isolates of *Klebsiella pneumoniae* from bile culture collected in this study were resistant to the empiric antibiotics started, the outcome of these patients remained to be favorable especially after targeted therapy was initiated. Of note, bile collection is an invasive procedure for children which could be the reason of its limitation of use in this study.

Highlighting biliary tract dilatation or an obstruction in the biliary tract is a key diagnostic element in AC. Several imaging modalities may be requested: abdominal ultrasound, abdominal computerized tomography (CT), abdominal magnetic resonance imaging (MRI) with or without endoscopic retrograde cholangiopancreatography (ERCP). Ultrasound is the primary imaging modality for assessment of patients with suspected acute cholangitis. It is often the first-line diagnostic test, as it facilitates search for biliary tract dilatation. [16] This study clearly showed that abdominal ultrasound was the common initial diagnostic imaging requested: 25 patients out of the 27 pediatric subjects. Majority of the findings showed dilatation of the bile duct followed by presence of bile duct stones. But while the results are relatively simple to visualize in abdominal ultrasound, findings may be inadequate in the event of acute obstruction. According to a meta-analysis conducted in 2015, abdominal ultrasound has low sensitivity (73%) for the detection of common bile duct stones. And as regards obstacles other than choledocholithiasis, its performances have been even less impressive. [17]

Abdominal and pelvic CT with and without contrast injection presents several advantages. It is more sensitive and specific than ultrasound in AC diagnosis regardless of the cause. Moreover, it facilitates search for complications and excludes alternative etiologies of abdominal pain. [18] Out of the 25 patients in our study, 9 subjects underwent abdominal CT scan and demonstrated bile duct dilatation. No dynamic CT imaging was done among these patients, as was emphasized as a need in the revised Tokyo guidelines. That is, in patients with acute cholangitis, a temporary uneven deep staining is frequently observed in the arterial phase of dynamic CT for the liver; furthermore, this deep staining disappears with improvement of the cholangitis. [6]

Magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sonography (EUS) are the most sensitive techniques to correctly determine the underlying cause and level of biliary obstruction in patients with acute cholangitis. [19] In this study, patients who underwent MRCP, ERCP and EUS showed strictures, presence of calculi and stenosis as well as findings of pseudocyst were noted respectively. By discovering these

abnormalities in the biliary tract, AC may be diagnosed by imaging.

The primary goal of antimicrobial therapy in acute cholangitis is to limit both the systemic septic response and local inflammation and to prevent complications like intrahepatic abscess formation. While drainage of the obstructed biliary trees has been recognized as the mainstay of management for patients with AC, antimicrobial therapy may allow patients to have elective source control procedures rather than emergency operation. [20] Antibiotic choice for coverage should be according to local ecology and resistance, subjective conditions of the patient (renal and hepatic functions, allergies) as well as the severity of the specific case of AC. [16] Based on the Tokyo guidelines 2018, agents appropriate for use can be grounded on antimicrobial class definitions. As regards community-acquired forms of AC without severity grade, the schema is based on 3rd-generation cephalosporin (ceftriaxone, cefotaxime) associated with an anaerobic agent (metronidazole); penicillin-based therapy with ampicillin-sulbactam if with <20% local resistance rate; carbapenem-based therapy with ertapenem or fluoroquinolone-based therapy such as ciprofloxacin and levofloxacin with an anaerobic agent (metronidazole) in cases involving biliary-enteric anastomosis. [20] In our study with majority of mild to moderate case severity of AC, monotherapy ampicillin-sulbactam predominated as the most started antibiotic. This was followed by ceftriaxone/cefoxitin with metronidazole as frequently used antimicrobials. Interestingly, several patients were shifted from initial ampicillin-sulbactam to broader carbapenems or penicillin-based therapy. These cases could be attributed to non-improving status of the subjects or a probable healthcare-associated AC.

In initially severe, healthcare-associated forms of AC, preferred antimicrobial treatments include broad-spectrum cephalosporin (cefepime) with an anaerobic agent; an association piperacillin + tazobactam; carbapenem-based therapy using meropenem or ertapenem; monobactam-based therapy with aztreonam with metronidazole. [20] Our study featured patients started with piperacillin + tazobactam or meropenem antibiotic regimens which could be attributable to severe or recurrent forms of AC. A study by Wong et al. in 2004 reported that patients with post- Kasai cholangitis prompted the use of wider coverage, higher generation antibiotics such as meropenem due to the challenge of antibiotic resistance. [21]

The duration of antimicrobial therapy is controversial. The 2018 Tokyo Guidelines suggested 4 to 7 days after identification of the source of infection. [20] On the other hand, the French Infectious Disease Society (SPILF) has proposed a reduction of antimicrobial therapy duration to 3 days. [22] In 2011, Kogure, et al conducted a study testing the cessation of antimicrobial therapy for AC once body temperature has been lower than 37°C for 24h after bile duct drainage. It concluded that the median duration of therapy was 3 days without relapse over the following 4 weeks. [23] Duration of 5 days antimicrobial therapy following drainage appears sufficient according to Sokal, et al in 2019. [16] For our study, average of 4-7 days antibiotic duration was recorded with no note of relapse. There were two recurrent cases of AC of which only one was given prophylactic cotrimoxazole. A systematic review done by Decharun, et al in 2016 showed contradictory recommendations for the use of prophylactic antibiotics to reduce incidence of AC in patients of post-Kasai procedure. [24]

The prognosis for AC depends on the timing of biliary drainage, administration of antibiotics, comorbidities of the patient and severity of the case. The overall mortality rate of AC is less than 10% after biliary drainage. In the pre-ERCP era, severe acute cholangitis was associated with a mortality of more than 50%. [25] Based on a study in 2013, poor prognostic factors include old age, high fever, leukocytosis, hyperbilirubinemia and hypoalbuminemia. Patients with comorbidities like malignancy, liver abscess and coagulopathy also carry greater risk. [26] For our study, 88.89% of the patients had good outcomes. Reasons may be largely because

most of the subjects are young, no comorbidities and only had mild to moderate cases of AC. Antibiotic coverage and duration of therapy were adequately given. And although invasive, ERCP was performed in very few cases for biliary drainage.

Procalcitonin has been proposed by some authors as a predictive indicator of severity and therefore of urgent biliary decompression. A value greater than 0.5 has an 18% mortality rate. [27] However, in our series, procalcitonin determination did not stand out as a strong prognostic factor and needs to be validated by more studies.

Out of the 6 severe forms of AC, two subjects succumbed to death due to multiorgan dysfunction and septic shock which could be attributable to absence of an emergent biliary drainage. The causes of death for these patients are in congruence with the report of Tokyo guidelines identifying multiple organ failure with irreversible shock as the major basis of mortality.[5]

This study had certain limitations as this involved data collection through chart review. It has a small sample size done in a single-center retrospective design. Sources of bias may be present due to varying ways of documentation. A number of patients were excluded in the data analysis owing to incomplete or missing charts. Suspected cases of AC were not included in the study as well.

CONCLUSION

Acute cholangitis in children remains to be unusual with only few studies describing the disease and its outcome. It is different from adult investigations due to the varied causes of pediatric biliary tract infections and anomalies. In this study, AC cases in children are mostly mild to moderate in severity, favorably responded to empiric antibiotics but possibly of better conclusion especially if adequately managed with prompt biliary drainage. However, generally, the subjects had good treatment outcome.

RECOMMENDATION

Existing studies about AC in children remain to be inadequate as of this writing. It is important to conduct further studies with multidisciplinary approach. Collaboration between gastroenterologists, infectious disease specialists, and surgeons is essential. Subsequent prospective clinical study with a larger population may be advisable to yield additional information and to eliminate the confounders encountered in this study.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Alizadeh MAH. Cholangitis: Diagnosis, Treatment and Prognosis. J Clin Transl Hepatol. 2017;5(4):404-413.
2. Zhang T, Zhou T, Deng Z, et al. Clinical Characteristics and Effectiveness of Anti-infective Therapy of Acute Cholangitis in Children. Int J Clin Exp Med. 2018;11(4):4114-4119.
3. Yasuda H, Takada T, Kawarada Y, et al. Unusual cases of acute cholecystitis and cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14(1):98-113.
4. Friesen C, Roberts C. Cholelithiasis: clinical characteristics in children. *Clin Pediatr.* 1989; 28:194–298.
5. Kimura Y, Takada T, Kawarada Y, Nimura Y, Hirata K, Sekimoto M, Yoshida M, Mayumi T, Wada K, Miura F, Yasuda H, Yamashita Y, Nagino M, Hirota M, Tanaka A, Tsuyuguchi T, Strasberg SM, Gadacz TR. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14(1):15-26.
6. Kiriyama S, Kozaka K, Takada T, Strasberg SM, Pitt HA, Gabata T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci. 2018;25(1):17–30.
7. Gigot JF, Leese T, Dereme T, Coutinho J, Castaing D, Bismuth H. Acute cholangitis: Multivariate analysis of risk factors. Ann Surg. 1989; 209:435-438
8. Boey JH, Way LW. Acute cholangitis. Ann Surg. 1980; 191:264-270
9. Saharia PC, Cameron JL, Clinical management of acute cholangitis. Surg Gynecol Obstet. 1976; 142:369-372
10. Ker CG, Chen JS, Lee KT, Sheen PC, Wu CC. Assessment of serum and bile levels of CA19-9 and CA125 in cholangitis and bile duct carcinoma. J Gastroenterol Hepatol. 1991; 6:505-508
11. Silangcruz K, Nishimura Y, Czech T, Kimura N, Yess J. Procalcitonin to Predict Severity of Acute Cholangitis and Need for Urgent Biliary Decompression: Systematic Scoping Review. *Journal of Clinical Medicine*. 2022; 11(5):1155
12. Wang PX, Zhou XY, Chen J, Lou JG. Analysis of 150 cases of biliary tract infection in children. Zhejiang Prev Med. 2007;

16:60
13. Gomi H, Takada T, Hwang T-L et al. Updated comprehensive epidemiology, microbiology, and outcomes among patients with acute cholangitis. J Hepato-Biliary-Pancreat Sci 2017; 24:310–318
14. Yu MN, Liu G, Huang LM, Wang W, Zhang HL, Qin SL, Duan L, Zhang J, Yu F. Recurrent cholangitis after hepatico-portoenterostomy for biliary atresia: analysis of bacterial spectrum and sensitive antibiotics. J Clin Pediatr Surg. 2012; 11:187-189
15. Gomi H, Solomkin JS, Schlossberg D et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepato-Biliary-Pancreat Sci 2018; 25:3–16
16. Sokal A, Sauvanet A, Fantin B, et al. Acute cholangitis: Diagnosis and management. Journal of Visceral Surgery. 2019; 156:515 - 525
17. Gurusamy KS, Giljaca V, Takwoingi Y et al. Ultrasound versus liver function tests for diagnosis of common bile duct stones. Cochrane Database Syst Rev 2015:CD011548
18. Kim SW, Shin HC, Kim HC. Diagnostic performance of multidetector CT for acute cholangitis: evaluation of a CT scoring method. Br J Radiol 2012; 85:770–777
19. Gallix BP, Aufort S, Pierredon MA, Garibaldi F, Bruel JM. Acute cholangitis: imaging diagnosis and management. J Radiol. 2006; 87:430-440
20. Gomi H, Solomkin JS, Schlossberg D et al. Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepato-Biliary-Pancreat Sci 2018; 25:3–16
21. Wong KK, Fan AH, Lan LC, Lin SC and Tam PK. Effective antibiotic regime for postoperative acute cholangitis in biliary atresia-an evolving scene. J Pediatr Surg 2004; 39: 1800-1802
22. Wintenberger C, Guery B, Bonnet E, Castan B, Cohen R, Diamantis S, et al. Proposal for shorter antibiotic therapies. Médecine Mal Infect 2017; 47:92–141
23. Kogure H, Tsujino T, Yamamoto K et al. Fever-based antibiotic therapy for acute cholangitis following successful endoscopic biliary drainage. J Gastroenterol 2011; 46:1411–1417
24. Decharun K, Leys CM, West KW, Finnell SM. Prophylactic Antibiotics for Prevention of Cholangitis in Patients with Biliary Atresia Status Post-Kasai Portoenterostomy: A Systematic Review. Clinical Pediatrics 2016; 55(1):66-72
25. Zhang WZ, Chen YS, Wang JW, Chen XR. Early diagnosis and treatment of severe acute cholangitis. World J Gastroenterol 2002; 8:150–152
26. Buyukasik K, Toros AB, Bektas H, Ari A, Deniz MM. Diagnostic and therapeutic value of ERCP in acute cholangitis. ISRN Gastroenterol 2013; 2013:191729
27. Suwa Y, Matsuyama R, Goto K, Kadokura T, Sato M, Mori R, Kumamoto T, Taguri M, Miyasho T, Endo I. IL-7 and procalcitonin are useful biomarkers in the comprehensive evaluation of the severity of acute cholangitis. J Hepatobiliary Pancreat Sci. 2017; 24(2):81-88