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MINIREVIEWS

Acute acalculous cholecystitis in children

Dimitri Poddighe, Vitaliy Sazonov

Dimitri Poddighe, Vitaliy Sazonov, Department of Medicine, School of Medicine, Nazarbayev University, Astana 010000, Kazakhstan

Vitaliy Sazonov, Pediatric Intensive Care Unit, UMC National Research Center for Mother and Child Health, Astana 010000, Kazakhstan

ORCID number: Dimitri Poddighe (0000-0001-6431-9334); Vitaliy Sazonov (0000-0003-0437-4694).

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Corresponding author to: Dimitri Poddighe, MD, MSc, Assistant Professor, Department of Medicine, School of Medicine, Nazarbayev University, Kerei-Zhanibek Str. 5/1, Astana 010000, Kazakhstan. dimitri.poddighe@nu.edu.kz
Telephone: +7-700-2679413

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Abstract

Acute acalculous cholecystitis (AAC) is the inflammatory disease of the gallbladder in the absence of gallstones. AAC is estimated to represent at least 50% to 70% of all cases of acute cholecystitis during childhood. Although this pathology was originally described in critically ill or post-surgical patients, most pediatric cases have been observed during several infectious diseases. In addition to cases caused by bacterial and parasitic infections, most pediatric reports after 2000 described children developing AAC during viral illnesses (such as Epstein-Barr virus and hepatitis A virus infections). Moreover, some pediatric cases have been associated with several underlying chronic diseases and, in particular, with immune-mediated disorders. Here, we review the epidemiological aspects of pediatric AAC, and we discuss etiology, pathophysiology and clinical management, according to the cases reported in the medical literature.

Key words: Acute acalculous cholecystitis; Children; Viral biliary disorders

Core tip: Acute acalculous cholecystitis (AAC) is the most frequent form of acute cholecystitis in children. In childhood, this disease has been described in critically ill or post-surgical patients, as it often occurs in adults, but most pediatric cases are actually caused by infectious diseases. In addition to bacterial and parasitic infections, most recent pediatric reports have described children developing AAC during viral illnesses, in particular, Epstein-Barr virus and hepatitis A virus infections. Moreover, some pediatric cases have been associated with non-infectious disorders, such as immune-mediated disorders. Therefore, the medical management presents significant differences compared to adult AAC.

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INTRODUCTION

Acute cholecystitis is an inflammatory condition of the gallbladder, which is most commonly associated with the presence of gallstones. These cases are referred to as acute calculous cholecystitis (ACC); here, the obstruction of the cystic duct from small- and medium-sized gallstones that migrate from the gallbladder or from large gallstones that intermittently obstruct the neck of the gallbladder, is considered the main pathogenic moment. However, several clinical and experimental evidences from human and animal studies strongly suggest that biliary obstruction due to gallstones represents only the final event of a more complex pathological process, where the development of acute inflammation is due to the progression from an underlying chronic injury. Very briefly, cholecystitis can develop in the presence of lithogenic bile with high cholesterol concentrations, diffusing through the gallbladder wall and permitting the hydrophobic bile salts to increase the levels of oxidative stress and to trigger the inflammatory process[1,2].

These pathogenic mechanisms may be implicated even in some cases of acute AAC where no gallstones can be identified, but only gallbladder bile sludge. However, most cases of AAC are not associated with any pre-existing biliary disease and/or factors suggesting the presence of lithogenic bile, especially in the pediatric population. Indeed, AAC is the most frequent form of acute cholecystitis in children, whereas in adults it accounts for only 5%-10% of all cases. AAC is estimated to represent at least 50% to 70% of all cases of acute cholecystitis during childhood; of course, the remaining portion is represented by ACC, which is usually associated with hemolytic diseases or intestinal diseases that affect the entero-hepatic recirculation of biliary salts[3,4].

AAC can develop in a variety of clinical settings, suggesting the existence of several pathogenic mechanisms, which may have different weights according to the specific situation. However, those mechanisms can be traced back to two main types of gallbladder injury. One is the chemical injury from bile stasis; however, unlike ACC, the harmful effect on the gallbladder in AAC actually derives from impaired gallbladder emptying rather than altered bile composition[5]. This is likely to be the main trigger in pediatric AAC cases due to some parasite infections obstructing the common bile duct (*e.g.*, *Ascaris lumbricoides* infestation) or in rare congenital malformations of the gallbladder (*e.g.*, multiseptated gallbladder, diaphragm of the gallbladder, choledochal cyst, *etc*). Moreover, bile stasis may be also a pathogenic component of AAC in children admitted to the pediatric intensive care unit (PICU) for different reasons. Indeed, the prolonged period of fasting (with oral feeding replaced by parenteral nutrition) and the use of opiates (inducing spasms and/or dyskinesia of the sphincter of Oddi) interferes with gallbladder emptying[6].

A second important mechanism of gallbladder injury is local ischemia[5,6]. The cystic artery is the chief source of blood supply to the gallbladder, in addition to the cystic duct, common hepatic duct and the upper part of the bile duct. The cystic artery can have different anatomical origins, but it usually arises from the right hepatic artery, which is one of the terminal branches of the proper hepatic artery[7]. Importantly, the cystic artery is a terminal artery, meaning that it is the only supply of oxygenated blood to gallbladder tissues, which explains its major susceptibility to ischemic conditions in the presence of several underlying or concomitant diseases. The remarkable importance of the ischemic mechanism in AAC was demonstrated through a fundamental study by Hakala *et al*[8], published in 1997. Briefly, these authors compared angiographic and histological aspects of patients affected with ACC and AAC. The main gallbladder micro-angiographic findings in AAC were clearly different from those in gallstone-associated cholecystitis. The latter revealed a florid and dilated microcirculation (related to inflammation), whereas an irregular arterial/capillary network with absent or minimal venous filling characterized AAC. Importantly, AAC patients presented quite different underlying diseases (cardiac infarction - treated with emergency coronary bypass -, staphylococcal septicemia, septic shock and hypovolemic shock), which highlighted the fact that ischemic factors and/or tissue hypoxia are the common and final pathogenic mechanisms of gallbladder injury. Further studies confirmed these pathological aspects, and they likely have a prominent role even in AAC cases arising outside the PICU, like patients suffering from vasculitis or previously healthy children developing ACC during a concomitant infectious disease[9,10].

EPIDEMIOLOGY AND RISK FACTORS

Gallbladder disease is a relatively rare condition in children. Before 2000s, Tsakayannis *et al*[3] estimated only 1.3 pediatric cases for every 1000 cases of adult gallbladder disease. Nevertheless, the incidence of cholecystitis in children has increased over the last 20 years. For example, a recent study from Canada reported that the incidence of pediatric cholecystectomy increased from 8.8 to 13.0 per 100000 person-years from 1993 to 2012, and cholecystitis accounted for 9.3% of all pediatric procedures of the biliary tract[4].

As previously mentioned, AAC represents the most common form of cholecystitis in children (50%-70%), and it can arise in different clinical settings. According to this observation, AAC can be grouped into three main categories: (1) AAC associated with critical medical conditions, (2) AAC associated with underlying (non-critical) diseases, and (3) AAC arising in previously healthy children.

Acute acalculous cholecystitis in children with critical medical conditions

AAC has been described as a complication of several types of surgery. In adults, most reports of post-operative AAC followed interventions of open abdominal

Table 1 Reported cases of non-infectious pediatric acute acalculous cholecystitis associated with immune-mediated disorders (2000-2018)

Ref.	Age (yr)	Sex	Comorbidity	Clinical manifestations
Basiratnia *et al*[13], 2006	10	M	Systemic lupus erythematosus	RUQ pain, fever, nausea, vomiting
Shin *et al*[14], 2007	5	M	Nephrotic syndrome	Abdominal pain, vomiting
Mendonca *et al*[15], 2009	12	F	Systemic lupus erythematosus	Abdominal pain, anorexia, weight loss, nausea, vomiting
Lee *et al*[16], 2014	N/A	N/A	Systemic lupus erythematosus (n = 2); nephrotic syndrome (n = 1)	N/A (patients were included in a large case series of pediatric AAC)
Sanches *et al*[17], 2014	11	F	Juvenile dermatomyositis	RUQ pain, nausea, vomiting
Ozkaya *et al*[18], 2016	7	M	Henoch-Shonlein purpura	Abdominal pain, jaundice
Yi *et al*[19], 2016	N/A	N/A	Kawasaki disease (n = 28)	N/A (patients were included in a large case series of pediatric AAC)

AAC: Acute acalculous cholecystitis; RUQ: Right upper quadrant.

aortic reconstruction and cardiac surgery (in particular, cardiac valve replacement with or without bypass)[5]. Of course, this is a very rare occurrence in childhood. Here, the development of AAC related to critical diseases is mostly due to medical conditions requiring prolonged or long-term parenteral feeding, extensive burns and shock syndromes (regardless of the hypovolemic or septic mechanism)[3]. Indeed, those situations are associated with bile stasis and gallbladder ischemia. Moreover, the concomitance and/or the superimposition of infectious factors might contribute to AAC pathogenesis. Finally, Imamoglu *et al*[11] reported several children developing AAC after appendectomy and blunt abdominal trauma, supporting a mechanism of direct traumatic injury in some pediatric cases. Anyway, post-traumatic AAC in children is very rare, and concomitant factors, such as shock or other comorbidities, may play a role[12].

Acute acalculous cholecystitis in children with non-critical medical conditions

This category includes those cases of AAC developing in patients with comorbidity, which is supposed to contribute to the occurrence of gallbladder disease. Indeed, there are many reports of AAC arising in the context of autoimmune/immune-mediated diseases, in particular vasculitis. Here, the systemic inflammation could also involve the gallbladder vasculature, leading to local ischemic injury[5]. In Table 1, we listed all of the case reports describing AAC in children affected with immune-mediated diseases since 2000[13-18].

Among these immunological conditions, Kawasaki disease received particular attention and detailed description. According to the large case series published by Yi *et al*[19], which included 131 children with AAC, 26.7% of patients were affected with a systemic (non-infectious) disease, and most had Kawasaki disease (28 cases). Interestingly, these authors found that the presence of AAC in the acute phase of Kawasaki disease was statistically associated with the development of coronary complications, in addition to more severe clinical presentations[20]. Previously, Chen *et al*[21] studied the occurrence of gallbladder abnormalities (including AAC or hydrops) in children with Kawasaki disease, and they found higher rates of intravenous immunoglobulin resistance.

Additional reports of AAC associated with systemic (non-infectious) illnesses included malignancies (*e.g.*, hemophagocytic lymphohistiocytosis, acute leukemias), renal diseases (*e.g.*, end-stage renal disease) and genetic diseases (*e.g.*, galactosemia, diabetes mellitus, cystic fibrosis)[16,19,22-24].

Acute acalculous cholecystitis in previously healthy children

Most cases of pediatric AAC have been described in children without life-threatening conditions or underlying comorbidities. In this group, a large variety of infectious agents have been implicated in the pathogenesis of AAC, including viruses, bacteria, yeasts and parasites. Before 2000, most reports of infectious AAC referred to intestinal parasites (*e.g.*, *Ascaris lumbricoides*), typhoid fever and leptospirosis[6]. AAC can be one of the clinical manifestations of hepatobiliary ascariasis, characterized by the passage of worms from the duodenum to the biliary tract, leading to bile flow obstruction[25]. Typhoid fever is a systemic infection caused by some *Salmonella* species, in particular *Salmonella typhi*. AAC in typhoid fever is usually a secondary complication depending on bacterial strain virulence or its resistance to treatment, especially in endemic areas. These bacteria reach the gallbladder through the blood stream and have been shown to have a tropism for the vesicular wall epithelium[26]. Leptospirosis is a zoonotic infection sustained by several species of the genus *Leptospira* and, again, AAC derives from the direct localization of these bacteria in the gallbladder[27].

However, after 2000 (probably due to the larger diffusion of the abdominal ultrasound), a multitude of publications have associated pediatric AAC with many types of infections, including several viral diseases. In Table 2, we listed all case reports or small case series describing infectious AAC in children, in whom a clear etiological diagnosis was achieved[28-60].

Among AAC cases due to viral infections, many

Table 2 Reported cases of pediatric acute acalculous cholecystitis associated with specific infections (2000-2018)

Ref.	Age (yr)	Sex	Comorbidity	Clinical manifestations
Ashley *et al*[28], 2000	4	M	*B. abortus*	RUQ pain, fever, constipation, anorexia
Ciftci *et al*[29], 2001	7	M	HAV	Abdominal pain, fever, jaundice
Lo *et al*[30], 2002	5	M	*Salmonella* group D	Abdominal pain, fever, vomiting, diarrhea
Batra *et al*[31], 2003	12	M	*S. aureus*	RUQ pain, fever, jaundice, maculopapular rash
Garel *et al*[32], 2003	4	M	*Salmonella spp.*	Abdominal pain, fever, vomiting, diarrhea
Saha *et al*[33], 2005	7	F	*P. falciparum*	RUQ pain, fever
Axelrod *et al*[44], 2007	3	F	*S. typhi*	Abdominal pain, fever, vomiting
Kuttiat *et al*[35], 2007	8 and 9	M	*P. falciparum* and *P. vivax*	RUQ pain, fever, vomiting (*P. vivax*)
Lagona *et al*[36], 2007	4	F	EBV	RUQ pain, fever, jaundice, vomiting, anorexia
Anthoine-Milhomme *et al*[37], 2007	7	F	*Plasmodium spp.*	Abdominal pain, fever, diarrhea, jaundice
Prassouli *et al*[38], 2007	13	F	EBV	Abdominal pain, fever, vomiting, jaundice
Gora-Gebka *et al*[39], 2008	9 and 4	F	EBV + CMV and EBV	RUQ pain, fever, jaundice, enlargement of liver and spleen
Kumar *et al*[40], 2008	3	F	*P. falciparum*	Abdominal pain, fever, vomiting
Bouyahia *et al*[41] 2008	14	M	HAV	Abdominal pain, vomiting, fever
Attilakos *et al*[42], 2009	5	M	EBV	Fever, jaundice, enlargement of liver and spleen
Sureshet *al*[43], 2009	2	F	HAV	Abdominal pain, fever, vomiting
Souza *et al*[44], 2009	16	M	HAV	Abdominal pain, fever, vomiting
Arroud *et al*[45], 2011	11	M	HAV	Abdominal pain, fever, vomiting, jaundice
Herek *et al*[46], 2011	9	M	HAV	Abdominal pain, fever, vomiting, jaundice
Prashanth *et al*[47], 2012	12	F	HAV	Abdominal pain, vomiting
Newcombe *et al*[48], 2013	9	M	*C. burnetii*	N/A
Gnassingbe *et al*[49], 2013	5-13	4 M, 2 F	*S. typhi*	Mainly abdominal pain, fever and vomiting
Poddighe *et al*[50], 2014	7	F	EBV	RUQ, fever, vomiting, jaundice, liver enlargement.
Kim *et al*[51], 2014	10	F	EBV	RUQ pain, fever, cervical lymphadenopathy
Fretzajas *et al*[52], 2014	11 and 12	F	EBV	Abdominal pain, fever, jaundice, hepatosplenomegaly
Strehle *et al*[53], 2014	14	F	EBV	Fever, RUQ pain, vomiting, anorexia, eyelid swelling
Suga K *et al*[54], 2014	6	F	EBV	Abdominal pain, epigastralgia
Alkoury *et al*[55], 2015	15	F	EBV	Abdominal pain, fever, vomiting
Pawlowska-Kamieniak *et al*[56], 2015	17	F	EBV	RUQ pain, fever, anorexia
Majdalani *et al*[56], 2016	16	F	EBV	Abdominal pain, fever, vomiting
Gomes *et al*[58], 2016	3	M	HHV-6	Abdominal pain, vomiting, generalized maculo-papular skin rash
Ismaili-Jaha *et al*[59], 2018	1, 2, 4, 10	F, F, F, M	*Ascaris lumbricoides*	Mainly fever, diarrhea, vomiting
Aguilera-Alonso *et al*[60], 2018	5	F	*P. falciparum*	Abdominal pain, fever, jaundice

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HAV: Hepatitis A virus; HHV: Human herpes virus; RUQ: Right upper quadrant.

have been associated with hepatitis A virus (HAV) and Epstein-Barr virus (EBV); however, only a minority of infected children develop AAC, which represents a rare complication.

As for EBV specifically, Yi *et al*[61] recently described 94 children affected by primary infection and undergoing abdominal ultrasonography. Around 25% of patients showed gallbladder abnormalities, particularly increased wall thickness; however, only a very small percentage (2%) fulfilled the diagnostic criteria for AAC. Interestingly, the authors noticed that EBV hepatitis seems to be more frequently associated with cholestasis abnormalities (*e.g.*, increase of γ-glutamyl transpeptidase) compared to infections sustained by other herpes viruses (*e.g.*, *Cytomegalovirus*)[62,63]. Unfortunately, the pathogenic mechanisms of viral AAC are not well known, but direct invasion or inflammation triggered by bile stasis may play a role. As for HAV, direct viral invasion of the gallbladder has been documented by Mourani *et al*[64] in a dated study. However, the local extension of the hepatic inflammatory process and/or elevated portal pressure (leading to edema of the gallbladder wall) have been speculated by some authors[65].

CLINICAL AND DIAGNOSTIC ASPECTS

In critically ill children who are not able to communicate appropriately, the diagnostic suspicion of AAC often derives from the onset of biochemical abnormalities suggesting cholestasis and liver dysfunction (*e.g.*, plasma bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase), in addition to fever and leukocytosis. Otherwise, the main clinical manifestation of AAC is abdominal pain (mild to severe), typically in the right upper quadrant, but sometimes diffuse. Fever, jaundice, vomiting and nausea can be variably present. Then, the clinical presentation is quite nonspecific, and the diagnosis can be challenging, especially when AAC is superimposed on acute hepatitis, whose laboratory findings can be similar because of concomitant intrahepatic cholestasis[6,66,67].

Therefore, AAC diagnosis necessarily relies on abdominal ultrasonography (US), which can reveal typical findings and diagnostic criteria, as follows: (1) Increased gallbladder wall thickness (> 3.5 mm); (2) pericholecystic fluid; (3) presence of mucosal membrane sludge; and (4) gallbladder distension. The presence

of at least two of these US criteria, in addition to the absence of gallstones, usually supports the diagnosis of AAC in the pediatric age[10]. Thickening of the gallbladder wall is the most reliable single criterion, with a specificity of 90% and 98.5% using the cut-off of 3.0 mm and 3.5-mm wall thickness, respectively; moreover, the sensitivity was 100% at 3.0 mm, but only 80% at 3.5 mm. Therefore, especially in the presence of suggestive clinical and laboratory findings, gallbladder wall thickness of 3.5 mm or more by itself is generally accepted to be diagnostic[5,68]. Among other imaging studies of the biliary tract, computerized tomography (CT) has been shown to be as accurate as US in the diagnosis of AAC, but it has some limitations due to radiological exposure, especially in the pediatric age. Moreover, CT is more expensive and cannot be performed bedside. However, CT should be used any time that other thoracic and/or abdominal diagnoses are under consideration and it is essential for the pre-operative assessment, if required (see below). The diagnostic criteria for AAC by CT are similar to those described for US[5,69,70]. Other imaging studies such as technetium-labeled scintigraphy are quite problematic in children and, importantly, could be of limited value in the critical setting because of potential false positive results, due to prolonged fasting and concomitant liver disease[5,71].

THERAPEUTIC MANAGEMENT

AAC therapy in adults is substantially surgical, namely cholecystectomy. Indeed, a substantial rate of complications (*e.g.*, empyema, perforation, gangrene) and the possibility of other underlying biliary diseases (malignancy, for instance) must be considered. Here, open or laparoscopic cholecystectomy provides both the possibility to review the gallbladder and the definitive treatment. Therefore, supportive therapy (*e.g.*, analgesic drugs, intravenous hydration, parenteral nutrition) and antibiotics do not substitute the surgical approach, although they represent an essential part[65,72,73].

However, the epidemiology and etiology of pediatric AAC is quite different from adults, as previously shown. Therefore, even the therapeutic management of AAC in children is different and, in particular, the frequency of the surgical approach is generally much lower than in adults or in children with ACC[6,74]. In Table 3, we reported the conservative or interventional management in all available pediatric reports and small (uniform by etiology) case series[13-15,17,28,30,31,33,35-39,41,43-48,50,51,53-56,75-80]. As already mentioned, this overview confirms that the management of AAC in children is often conservative. Most AAC children who finally required surgical management were affected with vasculitis or systemic bacterial infections or, interestingly, were patients who did not receive a final diagnosis, as the cause of AAC remained unknown.

In addition to all those case reports, there are some larger and/or heterogeneous case series that deserve to be discussed separately. Imagoglu *et al*[11] described 12 children that developed AAC after previous abdominal surgery, during severe systemic infections or because of blunted abdominal trauma. Three of them required cholecystectomy because of the deterioration of their clinical conditions and US findings. Previously, in 1975 Ternberg *et al*[27] reviewed 67 pediatric cases: 36 patients underwent cholecystectomy and 25 patients were treated by tube cholecystostomy; however, no analysis according to the etiology of AAC was provided in this study. Chirdan *et al*[81] (from Nigeria) and Gnassingbé *et al*[49] (form Togo) described two small case series of children developing AAC because of *S. typhi* infection, including sixteen (13 M, 3 F) and six (4 M, 2 F) patients, respectively. Interestingly, almost all children (except one in Chirdan's study) required cholecystectomy by laparotomy as a final treatment, in addition to antibiotics, which supports the previous observations about the medical management in children.

Unfortunately, very few pediatric case series described AAC in critically ill children, but conservative management is strongly pursued, because these patients may not be able to safely sustain surgical (and anesthesiology) procedures. Huang *et al*[82] retrospectively described their experience with 109 children with AAC (from 2000 to 2009) due to a variety of etiologies and highlighted some findings (including low platelet count, low hemoglobin value, presence of pericholecystic fluid/high sonographic score, hypofibrinogenemia and septic shock) as being predictive of poor outcome. However, all of their patients were treated non-operatively, including those affected with critical illnesses. They reported 15% mortality rate (16 patients), and most of them (11 patients) developed AAC during sepsis (presented by a total of 27 patients), who then died of shock and multi-organ failure. Of course, it is not possible to make any conclusion about the most correct therapeutic management in these cases, but a timely surgical approach might be considered in selected situations, whenever the clinical condition allows it and before irreversible clinical deterioration. More recently, in a retrospective study (from 2004 to 2014) by Yi *et al*[19] (including 131 children), only two patients (1.5%) underwent cholecystectomy. Interestingly, no patients were admitted to the intensive care unit or presented with septic shock, but the indication for shifting from the conservative to the surgical approach was not specified. On the contrary, Rijcken[83] performed cholecystectomy in all seven cases he described from his experience in a Malawi hospital, suggesting surgery as a preferential approach "in the African setting" and "in the very ill patient". Only one child died post-operatively because of complicated sepsis. Recently, Schaefer CM retrospectively described ten critically ill and immune-compromised children who underwent percutaneous cholecystostomy. All patients were admitted to the intensive care unit; four children were hemodynamically unstable, three had multi-organ system failure, three developed renal failure and one was in septic shock. No patient developed procedure-related complications, but four patients died because of concomitant multi-organ failure. The surviving children

Table 3 Main therapeutic approach in the reported cases of pediatric acute acalculous cholecystitis (2000-2018)

Author (etiology, yr, country)	Age (yr)/sex	Surgery	Antibiotic	Observations
Ashley *et al*[28] (*B. Abortus*, 2000, United States)	4-M	-	Cotrimoxazole rifampin	Diagnosis through blood culture (initial antibiotic therapy with ampicillin, metronidazole and gentamicin)
Croteau *et al*[75] (N/A, 2001, United States)	2-M	Laparoscopic cholecystectomy	Second-generation cephalosporin	Removal of gallbladder after AAC recurrence
Lo *et al*[30] (*Salmonella group D*, 2002, Taiwan)	5-M	Laparotomic cholecystectomy	Ceftriaxone	Removal of gallbladder for AAC complicated by empyema
Batra *et al*[31] (*S. Aureus*, 2003, United States)	12-M	Laparotomic cholecystectomy	Ampicillin/sulbactam Ceftriaxone, metronidazole	AAC developed for bacteriemia during osteomyelitis.
Saha *et al*[33] (*P. Falciparum*, 2005, India)	7-F	-	Ceftriaxone	Intravenous quinine as soon as definitive diagnosis was achieved
Basiratnia *et al*[13] (SLE, 2006, Iran)	10-M	Laparotomic cholecystectomy	Ceftriaxone, metronidazole	High-dose prednisolone for 3 d. Surgical approach due to poor response (not specified)
Kuttiat *et al*[35] (*P. falciparum* and *P. Vivax*, 2007, India)	8-M 9-M	-	Ceftriaxone	Intravenous quinine as soon as definitive diagnosis was achieved
Lagona *et al*[36] (EBV, 2007, Greece)	4-F	-	-	Only supportive therapy and close follow-up
Anthoine-Milhomme *et al*[37] (*Plasmodium spp.*, 2007, France/ Ivory Coast)	7-F	-	Amoxicillin triamphenicol	Halofantrin was started upon diagnosis
Prassouli *et al*[38] (EBV, 2007, Greece)	13-F	-	Cefotaxime, tobramicin, metronidazole	
Shin *et al*[14] (Nephrotic syndrome, 2007, South Korea)	5-M	-	Ampicillin, cefotaxime	Deflazacort 60 mg/m^2
Gora-Gebka*et al*[39] (EBV + CMV and EBV, 2008, Poland)	9-F, 4-F	-	Cefotaxime	
Bouyahia *et al*[41] (HAV, 2008, Tunisia)	14-M	-	Cefotaxime, gentamicin	
Suresh *et al*[43] (HAV, 2009, India)	2-F	-	-	
Souza *et al*[44] (HAV, 2009, Brazil)	16-M	-	-	
Mendonca *et al*[15], (SLE, 2009, Brazil)	12-F	-	-	Concomitant SNC vasculitis findings: treated with high-dose prednisolone for 3 d.
McNaughton *et al*[76] (N/A, 2010, United States)	14-M	Laparoscopic cholecystectomy	Antibiotics (not specified)	
Karkera *et al*[77] (N/A, 2010, India)	11-M	Laparotomic cholecystectomy	Antibiotics (not specified)	Both patients developed complicated (perforated) AAC
Arroud *et al*[45] (HAV, 2011, Morocco)	11-M	-	Amoxicillin-clavulanic acid, gentamicin	
Herek *et al*[46] (HAV, 2011, Turkey)	9-M	-	-	
Pal K[24], (Type I Diabetes mellitus, 2011, Saudi Arabia)	11-M	Laparoscopic cholecystectomy	Antibiotics (not specified)	Emphysematous AAC associated with secondary appendicitis. Bile bacteriology revealed E. Coli and Ebterococcus spp
Prashanth *et al*[47] (HAV, 2012, India)	12-F	-	-	
Newcombe *et al*[48] (*C. Burnetii*, 2013, Australia)	9-M	-	Ampicillin, gentamicin, metronidazole	AAC as probable complication of infection-associated anti-phospholipid syndrome
Shihabuddin *et al*[22] (Cystic fibrosis, 2013, United States)	10-F	-	Antibiotics (not specified)	
Poddighe *et al*[50] (EBV, 2014, Italy)	7-F	-	Cefotaxime	Patient coming from South-East Asia
Kim *et al*[51] (EBV, 2014, South Korea)	10-F	-	Antibiotics (not specified)	
Strehle *et al*[53] (EBV, 2014, United Kingdom)	14-F	-	Antibiotics (not specified)	
Sanches *et al*[17] (JDM, 2014, Portugal)	11-F	-	-	high-dose prednisolone for 3 d
Suga *et al*[54] (EBV, 2014, Japan)	6-F	-	-	Only supportive therapy
Alkoury *et al*[55] (EBV, 2015, United States)	15-F	-	N/A	
Pawlowska-Kamieniak *et al*[56] (EBV, 2015, Poland)	17-F	-	Antibiotics (not specified)	UDCA, analgesics, and relaxants
Muta *et al*[78] (N/A, 2015, Japan)	6-M	Laparoscopic cholecystectomy	N/A	Case of eosinophilic cholecysitis without evidence of other eosinophilic disease
Majdalani *et al*[57] (EBV, 2016, Lebanon)	16-F	-	Ciprofloxacin, metronidazole	
Rodà *et al*[79] (EBV, 2016, Spain)	2-M	-	Ceftriaxone	Concomitant nephrotic syndrome and EBV infection
Özkaya *et al*[18] (Henoch-Schonlein purpura, 2016, Turkey)	7-M	Laparotomic cholecystectomy	Antibiotics (not specified)	
Gomes *et al*[58] - (HHV-6, 2016, Portugal)	3-M	-	-	

Naselli *et al*[23] (ALL-T, 2017, United Kingdom)	12-M	-	Piperacillin-tazobactam, metronidazole	Neutropenia during chemotherapy (dexamethasone, daunorubicin, vincristine, PEG-asparaginase)
Aguilera-Alonso *et al*[60] (*Plasmodium falciparum*, 2018, Spain/Equatorial Guinea)	5-F	-	Clindamycin, cefotaxime, metronidazole	Intravenous quinine as soon as definitive diagnosis was achieved
Ismaili-Jaha *et al*[59] (*Ascaris lumbricoides*, Albania, 2018)	1-F, 2-F, 4-F, 10-M	-	Antibiotics (not specified)	Mebendazole
Ng *et al*[80] (N/A, *concomitant pneumonia*, 2018, Australia)	7-M	-	Ceftriaxone, metronidazole	

AAC: Acute acalculous cholecystitis; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; HAV: Hepatitis A virus; HHV: Human herpes virus; RUQ: Right upper quadrant; UDCA: Ursodeoxycholic acid.

benefited from percutaneous cholecystostomy, as three of them returned to normal gallbladder function, and this interventional procedure obviated cholecystectomy in the remaining three children until they were in such a clinical condition to endure it[84].

In summary, the current therapeutic management of AAC in children is mostly conservative, but hospital admission should be recommended in order to monitor the clinical and sonographic evolution in any individual case. Indeed, as mentioned previously, the study by Huang *et al*[82] reported a mortality rate of 15%, and more recently, Lu *et al*[85] showed that 29.25% of their pediatric patients needed the intensive care unit, and around 9.5% died. Again, concomitant sepsis was the main comorbidity in fatal AAC cases, but also other severe or lethal complications may develop[82,85].

Regardless of the etiology or the clinical condition, supportive therapy (analgesia, rehydration) is mandatory. Moreover, oral feeding is usually suspended until the amelioration in order to avoid stimulation of bile production, and the evacuation of gastric contents *via* nasogastric tube may be appropriate in some cases. Consequently, intravenous fluid replacement and parenteral nutrition is paramount[5,6]. Importantly, children must receive effective pain relief through nonsteroidal anti-inflammatory drugs, while opiates should be avoided. Finally, considering the frequent implication of infections in the development of AAC, antibiotic therapy should almost always be recommended and should include antibiotics against both gram-negative and anaerobic microorganisms, unless there is a different indication from the clinical situation and/or microbiological results. Antibiotic therapy is often prescribed even in AAC cases with a high suspicion of viral infection in order to prevent further complications, as described in Table 3. Most used antibiotics were a variable combination of a third generation cephalosporin, gentamicin and metronidazole[86,87]. Unfortunately, specific guidelines for pediatric cholecystitis are not available, and controlled studies are necessary to establish the most appropriate medical management of pediatric AAC.

CONCLUSION

AAC is a very heterogeneous disease, as it can arise in multiple clinical settings and can be sustained by different and/or overlapping pathogenic mechanisms. Importantly, the therapeutic management of pediatric AAC significantly differs from adults. Indeed, according to our literature review, most cases in children have been conservatively managed, while the surgical procedure (namely, laparotomic or laparoscopic cholecystectomy) was required in a minority of cases. Importantly, cholecystectomy was mostly performed in children developing AAC due to systemic bacterial infections or with no clear etiology. Indeed, those patients were more prone to complications (*e.g.*, empyema, perforation), which represents the main indication for surgery in children. Most pediatric AAC cases were associated with viral infections (in particular, HAV and EBV), which showed lower rates of complications. In these cases, supportive management (including appropriate rehydration, temporary suspension of oral feeding and analgesic therapy) was sufficient. However, in almost all cases, wide-spectrum antibiotic therapy has been implemented despite the viral etiology. It is not always possible to immediately achieve a conclusive etiologic diagnosis, and that may be the reason why antibiotics are often or initially used. Therefore, in the management of pediatric AAC, pediatricians should be aware that many cases have a good prognosis and are often due to viral illnesses; however, if or until the viral nature is not completely evident, it is still recommended to start an appropriate antibiotic therapy. Moreover, children with AAC should always be admitted to the hospital to provide a tight clinical and sonographic follow-up, which can allow for quick response after complications that require a surgical approach.

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