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**Acute acalculous cholecystitis in children**

Poddighe D *et al*.Pediatric acute acalculous cholecystitis

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**Abstract**

Acute acalculous cholecystitis (AAC) is the inflammatory disease of the gallbladder in 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, actually most pediatric cases have been observed during several infectious diseases: In addition to those 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 to several underlying chronic diseases and, in particular, to immune-mediated disorders. Here, we reviewed the epidemiological aspects of pediatric AAC and we discussed the general aspects of the medical management, according to the cases reported in the medical literature.

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

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**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 have been actually caused by infectious diseases: In addition to bacterial and parasitic infections, recently most pediatric reports 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 to the presence of gallstones. These cases are referred 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 they 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 suggested that the biliary obstruction due to the gallstones represents only the final event of a more complex pathological process, where the development of acute inflammation would be due to the progression from an underlying chronic process. Very briefly, the cholecystitis can develop in the presence of lithogenic bile with high cholesterol concentrations, diffusing through the gallbladder wall and permitting to 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 demonstrated, but only gallbladder bile sludge, sometimes. 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 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 to hemolytic diseases or intestinal diseases affecting the entero-hepatic recirculation of biliary salts[3,4].

Actually, AAC can develop in a variety of clinical settings, suggesting the implication of several pathogenic mechanisms, which may have different weight, according to the specific situation. However, those mechanisms may be basically traced back to two main types of gallbladder injury. One is the chemical injury from bile stasis: However, unlike the ACC, in AAC the harmful effect on the gallbladder would actually derive from the impaired emptying of gallbladder, rather than the altered bile composition[5].Probably, this could be the main trigger in pediatric cases of AAC due to some parasite infections obstructing the common bile duct (*e.g.*, *Ascaris lumbricoides* infestation) or in those 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 those cases of AAC developing 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 the emptying of the gallbladder[6].

A second important mechanism of gallbladder injury is the local ischemia[5,6]. The cystic artery is the chief source of blood supply to gallbladder, in addition to cystic duct, common hepatic duct and the upper part of the bile duct. The cystic artery may 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, cystic artery is a terminal artery, meaning that it is the only supply of oxygenated blood to the gallbladder tissues, which explains its major susceptibility to the ischemic conditions, in presence of several underlying or concomitant diseases. The remarkable importance of the ischemic mechanism in AAC was demonstrated by the 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 the inflammation), whereas irregular arterial/capillary network with absent or minimal venous filling characterized patients with AAC. Importantly, AAC patients presented quite different underlying diseases (cardiac infarction, treated with emergency coronary bypassing, staphylococcal septicemia, septic shock and hypovolemic shock), which highlighted that the ischemic factor and/or tissue hypoxia is the common and final pathogenic mechanism of gallbladder injury. Further studies confirmed these pathological aspects and, probably, they may have a prominent role even in AAC cases arising outside PICU, like patients suffering from vasculitis or some previously healthy children developing ACC during a concomitant infectious disease[9,10].

**EPIDEMIOLOGY AND RISK FACTORS**

The gallbladder disease is a relatively rare condition in children: For every 1000 cases of adult gallbladder disease, there are only 1.3 pediatric cases[3]. Nevertheless, the incidence of cholecystitis in children has increased over the last 20 years. For example, a very 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 on the biliary tract[4].

As previously mentioned, AAC represents the most common form of cholecystitis in children (50%-70%) and it can arise in very different clinical settings. Schematically, according to this observation, AAC could be grouped in three main categories: (1) AAC associated to critical medical conditions; (2) AAC associated to not critical underlying diseases; (3) AAC arising in previously healthy children.

***Acute acalculous cholecystitic 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 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, both situations are at risk for AAC, because of bile stasis and gallbladder ischemia, respectively. Moreover, the concomitance and/or the superimposition of infectious factors might contribute to AAC pathogenesis, as well. Finally, Imamoglu *et al*[11]. reported several children developing AAC after appendicectomy and blunt abdominal trauma, supporting also a mechanism of direct traumatic injury in some pediatric cases. Anyway, post-traumatic AAC in children is very rare and, probably, concomitant factors (such as a shock or other comorbidities) may play a role[12].

***Acute acalculous cholecystitic in children with not critical medical conditions***

This category includes those cases of AAC developing in patients with comorbidity, which is supposed to contribute to the occurrence of the 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 involve also the gallbladder vasculature, leading to local ischemic injury[5]. In Table 1, we listed all 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], including 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 resulted to be statistically associated with the development of coronary complications, in addition to more severe clinical presentations[20]. Previously, even 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 were about 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 resulted to be 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*. The AAC in typhoid fever is usually a secondary complication depending on bacterial strain virulence or its resistance to the treatment, especially in endemic areas. These bacteria are supposed to reach the gallbladder through the blood stream and have been proved to have a tropism for the epithelium of the vesicular wall[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 associated pediatric AAC with many types of infections, including several viral diseases, can be retrieved. 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 have been associated of hepatitis A virus (HAV) and Epstein-Barr virus (EBV); however, only a minority of infected children developed AAC, which represents a rare complication.

As for EBV specifically, recently Yi *et al*[61] described 94 children affected by the primary infection and undergoing abdominal ultrasonography: Around 25% of patients showed gallbladder abnormalities, in particular increased wall thickness; however, only a very small percentage (2%) fulfilled the diagnostic criteria for AAC. Interestingly, some 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: Direct invasion or inflammation triggered by the bile stasis may play a role. As for HAV, the direct invasion of the gallbladder by the virus has been documented by Mourani *et al*[64] in a dated study. However, the local extension of the hepatic inflammatory process and/or an 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 the abdominal pain (mild to severe), typically at the right upper quadrant, but diffuse sometimes. Fever, jaundice, vomiting and nausea can be variably present. Then, the clinical presentation is quite unspecific and the diagnosis can be challenging, especially whenever AAC is superimposed to an acute hepatitis, whose laboratory findings can be similar, because of the concomitant intrahepatic cholestasis[6,66,67].

Therefore, the diagnosis of AAC necessarily relies on abdominal ultrasonography (US), which can reveal the typical findings and diagnostic criteria: (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]. Anyway, 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 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 tracts, computerized tomography (CT) resulted to be as accurate as US in the diagnosis of AAC, but it has some limitations due to the radiological exposure, especially in the pediatric age; moreover, CT is more expensive and cannot be performed at 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 later). The diagnostic criteria for AAC by CT are similar to those described for US[5,69,70]. Other imaging studies, such as labeled technetium scintigraphy, are quite problematic in children and, importantly, could be of limited value in the critical setting, because of the potential false positive results, due to prolonged fasting and concomitant liver disease[5,71].

**THERAPEUTIC MANAGEMENT**

The therapy of AAC 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, the supportive therapy (*e.g.*, analgesic drugs, intravenous hydration, parenteral nutrition) and the antibiotics do not substitute the surgical approach, although they represent an essential part[65,72,73].

However, the epidemiology and the etiology of pediatric AAC is quite different from adults, as previously showed. 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 a surgical management, were affected with vasculitis or systemic bacterial infections or, interestingly, were patients who actually 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 developing 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 at that time 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 16 (13 M, 3 F) and 6 (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 the conservative management is strongly pursued, even because these patients may not be able to sustain surgical (and anesthesiology) procedures safely. 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 aspects (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 their patients were treated non-operatively and, then, even those affected with critical illnesses: Actually, they reported 15% mortality rate (namely, 16 patients) and most of them (11 patients) developed AAC during sepsis (presented by a total of 27 patients) and, 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 situation, whenever the clinical condition should allow it and before the irreversible clinical deterioration. More recently, in the retrospective study (from 2004 to 2014) by Yi *et al*[19](including 131 children), only 2 patients (1.5%) underwent cholecystectomy; interestingly, none was admitted to the intensive care unit or presented 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’s 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. Very recently, Schaefer CM retrospectively described 10 critically ill and immune-compromised children who underwent percutaneous cholecystostomy. All patients were admitted to the intensive care unit: 4 children were hemodynamically unstable, 3 had multiorgan system failure, 3 developed renal failure and 1 was in septic shock. No patient developed procedure-related complications, but 4 patients died because of the concomitant multiorgan failure. The surviving children benefited from percutaneous cholecystostomy, as 3 of them returned to normal gallbladder function and, in the remaining 3 children, this interventional procedure obviated the cholecystectomy until they were in condition to endure it[84].

In summary, the current therapeutic management of AAC in children is mostly conservative, but the 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 SC reported a mortality rate of 15% and, more recently, Lu *et al* showed that 29.25% of their pediatric patients needed the intensive care unit, and around 9.5% died. Again, a concomitant sepsis resulted 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, the supportive therapy (analgesia, rehydration) is mandatory. Moreover, oral feeding is usually suspended until the amelioration, in order to avoid the stimulation of the bile production, and the evacuation of gastric contents *via* nasogastric tube could be appropriate in some cases. Consequently, the intravenous fluid replacement and, if needed, parenteral nutrition is paramount[5,6].Importantly, children must receive an effective pain relief through nonsteroidal anti-inflammatory drugs, whereas opiates should be avoided. Finally, considering the frequent implication of infections in the development of AAC, the antibiotic therapy resulted to be almost always recommended and should include antibiotics against both gram-negative and anaerobic microorganisms, unless there is different indication from the clinical situation and/or microbiological results. The antibiotic therapy is often prescribed even in AAC cases with a high suspicion of viral infection, in order to prevent further complications, as it emerges from Table 3. Most used antibiotics resulted to be 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 needed in order 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 it 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 managed conservatively, whereas 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 resulted to be more prone to develop complications (*e.g.*, empyema, perforation), which represent the main indication to surgery in children. Actually, most pediatric AAC cases were associated with viral infections (in particular, HAV and EBV), which showed lower rates of complications. In these cases, a supportive management (including appropriate rehydration, temporary suspension of oral feeding and analgesic therapy) resulted to be sufficient. However, in almost all cases, the wide-spectrum antibiotic therapy has been implemented, despite the viral etiology; frequently, it is not possible to achieve a conclusive etiologic diagnosis immediately and that was probably the reason why antibiotics were often or initially used. Therefore, in the management of pediatric AAC, the pediatricians should be aware that many cases of AAC in children 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 recommendable to start an appropriate antibiotic therapy. Moreover, children with AAC should be always admitted to the hospital, in order to provide a tight clinical and sonographic follow-up, which can allow evidence timely the occurrence of complications, requiring a surgical approach.

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

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

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

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Authors (yr)** | **Age** | **Sex** | **Comorbidity** | **Clinical manifestations** | **Ref.** |
| Ashley *et al*[28], 2000 | 4 | M | *B. abortus* | RUQ pain, fever, constipation, anorexia | [28] |
| Ciftci *et al*[29], 2001 | 7 | M | HAV | Abdominal pain, fever, jaundice | [29] |
| Lo *et al*[30], 2002 | 5 | M | *Salmonella* group D | Abdominal pain, fever, vomiting, diarrhoea | [30] |
| Batra *et al*[31], 2003 | 12 | M | *S. aureus* | RUQ pain, fever, jaundice, maculopapular rash | [31] |
| Garel *et al*[32], 2003 | 4 | M | NA | Abdominal pain, fever, vomiting, diarrhoea | [32] |
| Saha *et al*[33], 2005 | 7 | F | *P. falciparum* | RUQ pain, fever | [33] |
| Axelrod *et al*[44], 2007 | 3 | F | *S. typhi* | Abdominal pain, fever, vomiting | [34] |
| Kuttiat *et al*[35], 2007 | 8 and 9 | M | *P. falciparum and P. vivax* | RUQ pain, fever, vomiting (*P. vivax*) | [35] |
| Lagona *et al*[36], 2007 | 4 | F | EBV | RUQ pain, fever, jaundice, vomiting, anorexia | [36] |
| Anthoine-Milhomme *et al*[37], 2007 | 7 | F | *Plasmodium spp.* | Abdominal pain, fever, diarrhoea, jaundice | [37] |
| Prassouli[38], 2007 | 13 | F | EBV | Abdominal pain, fever, vomiting, jaundice | [38] |
| Gora-Gebka *et al*[39], 2008 | 9 and 4 | F | EBV + CMV and EBV | RUQ pain, fever, jaundice, enlargment of liver and spleen | [39] |
| Kumar *et al*[40], 2008 | 3 | F | *P. falciparum* | Abdominal pain, fever, vomiting | [40] |
| Bouyahia[41] 2008 | 14 | M | HAV | Abdominal pain, vomiting, fever | [41] |
| Attilakos *et al*[42], 2009 | 5 | M | EBV | Fever, jaundice, enlargment of liver and spleen | [42] |
| Suresh *et al*[43], 2009 | 2 | F | HAV | Abdominal pain, fever, vomiting | [43] |
| Souza *et al*[44], 2009 | 16 | M | HAV | Abdominal pain, fever, vomiting | [44] |
| Arroud *et al*[45], 2011 | 11 | M | HAV | Abdominal pain, fever, vomiting, jaundice | [45] |
| Herek *et al*[46], 2011 | 9 | M | HAV | Abdominal pain, fever, vomiting, jaundice | [46] |
| Prashanth *et al*[47], 2012 | 12 | F | HAV | Abdominal pain, vomiting | [47] |
| Newcombe *et al*[48], 2013 | 9 | M | *C. burnetii* | NA | [48] |
| Gnassingbe *et al*[49], 2013 | 5-13 | 4 M, 2 F | *S. typhi* | Mainly abdominal pain, fever and vomiting | [49] |
| Poddighe *et al*[50], 2014 | 7 | F | EBV | RUQ, fever, vomiting, jaundice, liver enlargment. | [50] |
| Kim *et al*[51], 2014 | 10 | F | EBV | RUQ pain, fever, cervical lymphadenopathy | [51] |
| Fretzajas *et al*[52], 2014 | 11 and 12 | F | EBV | Abdominal pain, fever, jaundice, hepatosplenomegaly | [52] |
| Strehle *et al*[53], 2014 | 14 | F | EBV | Fever, RUQ pain, vomiting, anorexia, eyelid swelling | [53] |
| Suga K *et al*[54], 2014 | 6-F | - | - | Abdominal pain, epigastralgia | [54] |
| Alkoury *et al*[55], 2015 | 15 | F | EBV | Abdominal pain, fever, vomiting | [55] |
| Pawlowska-Kamieniak *et al*[56], 2015 | 17 | F | EBV | RUQ pain, fever, anorexia | [56] |
| Majdalani *et al*[56], 2016 | 16 | F | EBV | Abdominal pain, fever, vomiting | [57] |
| Gomes *et al*[58], 2016 | 3 | M | HHV-6 | Abdominal pain, vomiting, generalized maculo-papular skin rash | [58] |
| Ismaili-Jaha[59] 2018 | 1, 2, 4, 10 | F, F, F, M | *Ascaris lumbricoides* | Mainly fever, diarrhea, vomiting | [59] |
| Aguilera-Alonso[60] (2018) | 5 | F | *P. falciparum* | Abdominal pain, fever, jaundice | [60] |

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

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Authors (ethiology, year, country)** | **Age/sex** | **Surgery** | **Antibiotic** | **Observations** | **Ref.** |
| 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) | [28] |
| Croteau *et al*[75] (N/A, 2001, United States) | 2-M | Laparoscopic cholecystectomy | Second-generation cephalosporin | Removal of gallbladder after AAC recurrence | [75] |
| Lo *et al*[30] (*Salmonella group D*, 2002, Taiwan) | 5-M | Laparotomic cholecystectomy | Ceftriaxone | Removal of gallbladder for AAC complicated by empyema | [30] |
| Batra *et al*[31] (*S. Aureus*, 2003, United States) | 12-M | Laparotomic cholecystectomy | Ampicillin/sulbactam Ceftriaxone, metronidazole | AAC developed for bacteriemia during osteomyelitis. | [31] |
| Saha *et al*[33] (*P. Falciparum*, 2005, India) | 7-F | - | Ceftriaxone | Intravenous quinine as soon as the definitive diagnosis was achieved | [33] |
| 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) | [13] |
| Kuttiat *et al*[35] (*P. falciparum* and *P. Vivax*, 2007, India) | 8-M  9-M | - | Ceftriaxone | Intravenous quinine as soon as the definitive diagnosis was achieved | [35] |
| Lagona *et al*[36] (*EBV*, 2007, Greece) | 4-F | - | - | Only supportive therapy and close follow-up | [36] |
| Anthoine-Milhomme *et al*[37] (*Plasmodium spp.*, 2007, France/Ivory Coast) | 7-F | - | Amoxicillin triamphenicol | Halofantrin was started as soon the diagnosis was achieved | [37] |
| Prassouli *et al*[38] (EBV, 2007, Greece) | 13-F | - | Cefotaxime, tobramicin, metronidazole |  | [38] |
| Shin *et al*[14] (Nephrotic syndrome, 2007, South Korea) | 5-M | - | Ampicillin, cefotaxime | Deflazacort 60 mg/m2 | [14] |
| Gora-Gebka *et al*[39] (EBV + CMV and EBV, 2008, Poland) | 9-F, 4-F | - | Cefotaxime |  | [39] |
| Bouyahia *et al*[41] (HAV, 2008, Tunisia) | 14-M | - | Cefotaxime, gentamicin |  | [41] |
| Suresh *et al*[43] (HAV, 2009, India) | 2-F | - | - |  | [43] |
| Souza *et al*[44] (HAV, 2009, Brazil) | 16-M | - | - |  | [44] |
| Medonca[15], (SLE, 2009, Brazil) | 12-F | - | - | Concomitant SNC vasculitis findings: treated with high-dose prednisolone for 3 d. | [15] |
| McNaughton *et al*[76] (N/A, 2010, United Staes) | 14-M | Laparoscopic cholecystectomy | Antibiotics (not specified) |  | [76] |
| Karkera *et al*[77] (N/A, 2010, India) | 11-M  11-M | Laparotomic cholecystectomy | Antibiotics (not specified) | Both patients developed complicated (perforated) AAC | [77] |
| Arroud *et al*[45] (HAV, 2011, Morocco) | 11-M | - | Amoxicillin-clavulanic acid, gentamicin |  | [45] |
| Herek *et al*[46] (HAV, 2011, Turkey) | 9-M | - | - |  | [46] |
| Pal K[24], (type I Diabetes mellitus, 2011, Saudi Arabia) | 11-M | Laparoscopic cholecystectomy | Antibiotics (not specified) | Emphysematous AAC associated to secondary appendicitis. Bile bacteriology revealed *E. Coli* and *Ebterococcus spp* | [24] |
| Prashanth *et al*[47] (HAV, 2012, India) | 12-F | - | - |  | [47] |
| Newcombe *et al*[48] (*C. Burnetii*, 2013, Australia) | 9-M | - | Ampicillin, gentamicin, metronidazole | AAC as probable complication of infection-associated anti-phospholipids syndrome | [48] |
| Shihabuddin *et al*[22] (*Cystic fibrosis*, 2013, United States) | 10-F | - | Antibiotics (not specified) |  | [22] |
| Poddighe *et al*[50] (EBV, 2014, Italy) | 7-F | - | Cefotaxime | Patient coming from South-East Asia | [50] |
| Kim *et al*[51] (EBV, 2014, South Korea) | 10-F | - | Antibiotics (not specified) |  | [51] |
| Strehle *et al*[53] (EBV, 2014, United Kingdom) | 14-F | - | Antibiotics (not specified) |  | [53] |
| Sanches *et al*[17] (JDM, 2014, Portugal) | 11-F | - | - | high-dose prednisolone for 3 d | [17] |
| Suga *et al*[54] (EBV, 2014, Japan) | 6-F | - | - | Only supportive therapy | [54] |
| Alkoury *et al*[55] (EBV, 2015, United States) | 15-F | - | N/A |  | [55] |
| Pawlowska-Kamieniak *et al*[56] (EBV, 2015, Poland) | 17-F | - | Antibiotics (not specified) | UDCA, analgesics, and relaxants | [56] |
| Muta *et al*[78] (N/A, 2015, Japan) | 6-M | Laparoscopic cholecystectomy | N/A | Case of eosinophilic cholecysitis without evidence of other eosinohilic disease | [78] |
| Majdalani *et al*[57] (EBV, 2016, Lebanon) | 16-F | - | Ciprofloxacin, metronidazole |  | [57] |
| Rodà*et al*[79] (EBV, 2016, Spain) | 2-M | - | Ceftriaxone, gancyclovir | Concomitant nephrotic syndrome and EBV infection | [79] |
| Özkaya *et al*[18] (Henoch-Schonlein purpura, 2016, Turkey) | M | Laparotomic cholecystectomy | Antibiotics (not specified) |  | [18] |
| Gomes *et al*[58] - (HHV-6, 2016, Portugal) | 3-M | - | - |  | [58] |
| Naselli *et al*[23] (ALL-T, 2017, United Kingdom) | 12-M | - | Piperacillin-tazobactam, metronidazole | Neutropenia during chemotherapy (dexamethasone, daunorubicin, vincristine, PEG-asparaginase) | [23] |
| Aguilera-Alonso *et al*[60] (*Plasmodium Falciparum*, 2018, Spain/Equatorial Guinea) | 5-F | - | Clindamycin, cefotaxime, metronidazole | intravenous quinine as soon as the definitive diagnosis was achieved | [60] |
| Ismaili-Jaha *et al*[59] (*Ascaris lumbricoides*, Albania, 2018) | 1-F, 2-F, 4-F, 10-M | - | Antibiotics (not specified) | Mebendazole | [59] |
| Ng *et al*[80] (N/A, *concomitant pneumonia*, 2018, Australia) | 7-M | - | Ceftriaxone, metronidazole |  | [80] |

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