Management of complicated acute appendicitis

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Appendicitis, denoting the appendix inflammation, is the most common emergent condition in children (1). The global incidence of acute appendicitis (AA) ranges between 76 and 227 cases per 100,000 population annually (2). The acute appendicitis lifetime risk varies from 7-8% in the USA (3) to 16% in South Korea (4). All age groups could be affected, but there is a peak incidence in children of 10 to 20 years of age (5).

Pathophysiology

Acute appendicitis results from obstruction of the appendiceal lumen, usually by lymphoid hyperplasia but in some circumstances by a foreign body or a fecalith, foreign body (5). The obstruction cause distention and often also bacterial overgrowth and severe inflammation, which may lead to ischemia. If a prompt surgical evaluation and treatment are not possible, complications may occur, including necrosis, gangrene, and occasionally perforation. Recently, some genetic factors have been identified as potentially causative of severe acute appendicitis (6). The genetic factors may also contribute and interact with additional environmental causes, including metabolic and immunomediated causes (7). This intricated pathophysiology reflects how complex molecular mechanisms underlie different pediatric emergency conditions (8-16). In fact, in recent years, next-generation sequencing technologies, including exome and mRNA sequencing studies, have been essential in dissecting the pathophysiology of a wide array of childhood disorders (17-19), this led to a better understanding of the sub-cellular alterations underlying diseases, including several regulatory networks and genetic together with non-genetic factors (20-24).

Diagnosis

Based on the appendix's histological evaluation or macroscopic appearance, AA may be defined as uncomplicated appendicitis (UA) or complicated appendicitis (CA), the latter defined by a gangrenous, necrotizing or perforated appendix on pathology examination or the presence of purulent peritonitis. The incidence of CA varies between 15% and 50% of all patients with AA. (25) Despite all the excellent papers and research in literature, clear and definitive guidelines about the AA diagnosis are not well established.

Classic symptoms of AA, such as pain in the right iliac fossa, vomiting, fever, occur in less than half of the patients; in the other half of children, many further symptoms overlapping with other pathologies could appear, leading to a more challenging diagnosis. (25) It is evident that a good clinical examination, with physical signs investigation, is fundamental to orientate

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the diagnosis. Laboratory tests could help AA diagnosis and management, even if there is not a specific blood marker for AA. White Blood Cells (WBC) combined with C-Reactive Protein (CRP) do not predict AA directly, but they increase the odds. (26) Furthermore, WBC and CRP together with Procalcitonin (PCT) are usually used to differentiate UA from CA; moreover, CRP level greater than 10 mg/L and leucocytosis greater than 16,000/mL are solid predictive factors for appendicitis in pediatric patients. (27). HMGB1 serum level may be altered (28-29).

Imaging is often required to support symptoms, clinical examinations, and laboratory tests in the diagnosis. Ultrasound (US) is the first-line imaging because of its wide availability, low cost, and absence of ionizing radiation. It usually allows to diagnose AA, sometimes even differentiating UA from CA. The US diagnosis relies on direct signals for AA, such as a diameter greater than 6 mm, a wall thickness greater than 3 mm, non-compressibility of the appendix, appendicolith, or US Color Doppler hypervascularity in early stages, along with indirect signs for local inflammation, such as free fluid surrounding the appendix, abscess formation, increased echogenicity of local mesenteric fat or enlarged local mesenteric lymph nodes. (30) In all the situations where the diagnosis is still unclear, a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) could be used.

Complicated appendicitis management

CA could be managed differently with operative management, including early appendectomy at presentation and initial antibiotic treatment followed by delayed appendectomy, or conservative management, using antibiotic treatment alone without any appendectomy. Predicting values for CA are age < 5 years, symptoms duration more than 24h, WBC greater than 12,000/ml, CRP greater than 10mg/l (30).

Loss of submucosal layer, hyperechoic periappendiceal fat greater than 1 cm, maximum outside diameter more than 6 mm, presence of an appendicolith are significantly associated with CA (31, 32).

Operative management

Early appendectomy at presentation is adopted as treatment of choice in many centres because it reduces adverse events and unplanned readmissions. Appendectomy, the surgical removal of the appendix, is performed primarily as an emergency procedure, usually within the first 24 h of hospitalization, to treat acute appendicitis (33). Appendectomy could be performed using an open or laparoscopic approach. However, lower postoperative pain, fewer postoperative complication, and better quality of life seem to be associated with minimally invasive surgery (MIS), therefore for both UA and CA, laparoscopic should be preferred over open appendectomy where MIS equipment and expertise are available (27).

Early appendectomy is reported as the treatment of choice for CA in many studies, but few studies with substantial scientific evidence are available at this time. However, even if the timing for surgical management in CA is still debated, a recent metanalysis underlined that early appendectomy reduces the unplanned readmissions, complications, and hospitalization costs (34).

An appendectomy performed 6 to 8 weeks from the initial diagnosis is called “interval”. Operating when peritoneal contamination has resolved seems advantageous for the patient because it potentially results in fewer intraoperative and/or postoperative complications (35).

Analyzing the type of CA, Fugazzola et al. found that immediate operative management is the favoured option if perforated appendicitis without abscess is suspected. At the same time, delayed appendectomy should be performed in CA with abscess or phlegmon; when the imaging-based greater risk of operative complications is suspected (36, 37).

Non-operative management

However, the usual indications that an urgent surgical intervention is required for CA has changed in the last decade. Antibiotic therapy could be used to manage CA without significantly compromising complications, return to the emergency department, readmission, failure of non-operative treatment requiring surgery. Pennell et al. conducted a prospective study to implement the non-operative CA management, founding that a standardized protocol for a conservative approach reduces resource

utilization without affecting the outcomes (38).

A European survey revealed that 96% of surgeons administrate a preoperative antibiotic therapy for CA, and most of them choose a triple therapy (aminoglycoside, b-lactam and an anaerobe covering) (39). However, broad-spectrum single (piperacillin/tazobactam) or double (ceftriaxone and metronidazole) therapy seems to be similarly effective and less costly than triple therapy, and they are recommended from the guidelines of the American Pediatric Surgical Association (40). The antibiotic therapy duration should be based on clinical (pain, fever, bowel function) and laboratory criteria (white blood cell count); 5 days intravenous antibiotics and 2 days oral antibiotics (7 days in total) should be the administration (40).

When a conservative approach with antibiotic therapy is chosen, it should also be considered a treatment option for intra-abdominal or pelvis abscess, which seems to be associated with CA in 3.8% of patients (41). Beneficial results for complications and patient recovery have been found with percutaneous abscess drainage (42). In contrast, significant complications, such as intestinal and bladder perforations, have been reported for patients undergoing the drainage procedure compared with the interval appendectomy group, where a phlegmon treated with antibiotic therapy was the only concern. (43, 44). In order to reduce the occurrence of complication rate, Gasior et al. proposed to drain only abscesses greater than 20 cm^2 (45). Therefore, although disagreements for percutaneous abscess drainage, there is evidence that, in selected patients, it may have positive results; in fact, non-operative management with antibiotics and percutaneous drainage, when available, for CA with a periappendicular abscess, is suggested in settings where laparoscopic expertise with a very low conversion rate is not available (27). Melatonin administration may be a beneficial (46-50).

CONCLUSION

In conclusion, the type of antibiotics and its length for CA conservative treatment needs further investigation with RCTs. Early operative management is favoured for CA without abscess, while delayed non-operative management is preferred for CA with abscess or phlegmon. Nevertheless, because of the lack of high-quality studies, there is a need for more RCTs to delineate the specific management strategy for CA.

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