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Nonoperative management in children with early acute appendicitis: A systematic review☆,☆☆,★,★★

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ABSTRACT

Purpose: Appendectomy has remained the gold standard treatment of acute appendicitis for more than 100 years. Nonoperative management (NOM) has been shown to be a valid treatment alternative for acute uncomplicated appendicitis in adults. A systematic review of available evidence comparing operative management (OM) and NOM in children with acute uncomplicated appendicitis was performed.

Methods: Systematic searches of MedLine, Embase, and a clinical trial register (https://clinicaltrials.gov/) were performed in March 2016. Only articles that studied NOM for uncomplicated appendicitis in children were included. Data generation was performed independently by two authors, and quality was assessed using the rating schema by the Oxford Centre for Evidence-Based Medicine.

Results: 15 articles were selected: four retrospective analyses, four prospective cohort studies, four prospective nonrandomized comparative trials and one randomized controlled trial (RCT). Initial success of the NOM groups (a cure within two weeks of intervention) ranged from 58 to 100%, with 0.1–31.8% recurrence at one year.

Conclusion: Although present literature is scarce, publications support the feasibility of further studies investigating NOM of acute uncomplicated appendicitis in children. Higher quality prospective RCTs with larger sample sizes and robust randomization methods, studying the noninferiority of NOM with antibiotics compared with OM are required to establish its utility.

Level of evidence: This manuscript is a systematic review and thus assigned the lowest evidence used from the manuscripts analyzed which is a Level IV.

Acute appendicitis, the most common emergency operation in pediatric surgery, accounted for 8.2% of all operations at a major Australian tertiary children's hospital in 2009 [1].

This primary management modality has remained largely unchanged since it was described by McBurney in 1891, and reinforced by Swenson in 1958 when he said "A fundamental feature about acute appendicitis is that there is no medical treatment; only surgical excision is safe" [2,3]. However, operative management (OM) is not without its risks, including complications related to anesthesia, surgical complications such as bleeding, surgical site infections, ileus, and adhesive small bowel obstruction [4]. Two meta-analyses report complication rates of up to 2.6% for laparoscopic, and 2.7–5.7% for open operation [5,6]. Furthermore, despite advances in medical imaging, diagnostic accuracy remains a challenge, with reported negative appendectomy rates of 6.4–15.5% [7,8]. This may also be considered a 'complication', or undesired outcome.

While the management of uncomplicated appendicitis has remained operative, the management of other intraabdominal infections has evolved toward a nonoperative approach, including management of diverticulitis in adults [9], enterocolitis in neonates [10], and appendicitis complicated by contained perforation. Although the evidence varies, nonoperative management as initial treatment for complicated

Abbreviations: LOS, length of hospital stay; NOM, nonoperative management; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; OM, operative management; RCT, randomized controlled trial.

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appendicitis has been supported in a meta-analysis by Simillis et al. [11], and even interval appendectomy may be unnecessary [12,13]. A more recent systematic review of complicated appendicitis in children highlighted two randomized controlled trials (RCT) and suggested that, in the presence of an intraabdominal abscess, initial nonoperative management (NOM) was equivalent to OM in terms of adverse events, readmission, and costs [12,14,15].

Multiple prospective studies, systematic reviews and meta-analyses in adults over the last decade have supported the relative safety and effectiveness of antibiotic treatment alone for uncomplicated appendicitis [16–21], although this is not universal [20]. Kirby et al. [20] found a significantly lower rate of major complications following OM. A 2011 Cochrane Review, noting the poor quality of reviewed studies, supported OM as the definitive standard [22]. More recently, the multicenter Appendicitis Acuta noninferiority RCT (APPAC study) reported that, while 70 (27%) of the 257 patients who received initial NOM required appendectomy within one year, only seven of these had complicated appendicitis [23]. The others had uncomplicated appendicitis (58) or a normal appendix (5) [23]. McCutcheon et al. [24] reported that only a minority of NOM patients experienced treatment failure (5.9%) or recurrent appendicitis (4.4%) over a median follow-up of greater than seven years. The most recent meta-analysis of five RCTs involving 1430 adults, provided perhaps the strongest support yet, in favor of NOM—reporting a 39% risk reduction in overall complication rates compared to appendectomy [25].

With some support for NOM in the adult population, and absence of a comprehensive critical review of evidence in children, this paper aims to systematically review the available literature on NOM of acute uncomplicated appendicitis in the pediatric age group.

1. Methods

The review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guide [26]. A similar search strategy to the Cochrane review in adults [22] was used, seeking to translate the same methodology to the pediatric population (Supplemental Fig. 1).

1.1. Search strategy

A systematic search of the electronic databases MedLine (1946–2016) and Embase (1947–2016) was performed in March 2016, and updated in September 2016. The search strategy included the terms: appendicitis, antibacterial agents, antibiotic, conservative treatment, conservative management, nonoperative, and nonsurgical (Supplemental Fig. 1). It was limited to the English language for logistical reasons, human subjects, and children (0–18 years), with no year restriction, and supplemented with review of article references, 'related articles' links and the Clinical Trials Register (https://clinicaltrials.gov/).

1.2. Inclusion and exclusion criteria

All studies focusing on the NOM of acute uncomplicated appendicitis in children were included. In view of the small number of retrieved articles, all original research, including retrospective, prospective comparative, and prospective cohort studies along with RCTs, was included. Papers were excluded if they were nonprimary research, did not include the population of interest (for example, studies on adults or patients with other significant morbidity), or looked at antibacterial agents as surgical prophylaxis, or if NOM was not the primary intervention. Studies about complicated appendicitis (perforation, appendiceal mass or abscess) were also excluded.

1.3. Data extraction and management

One reviewer (J.X.) downloaded all relevant articles into EndNote (X7.5.3 http://endnote.com/), before removing duplicates. Preliminary screening of all titles and abstracts was performed independently by 2 reviewers (J.X. and Y.C.L.) to exclude irrelevant studies. Full texts of remaining articles were systematically assessed according to inclusion criteria with any disagreements in selection resolved by consensus through discussion (Supplemental Fig. 2).

Study designs of the final selected manuscripts were appraised using the rating schema of the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Table 1) [27].

2. Results

Fifteen articles met the inclusion criteria, covering thirteen studies: four retrospective analyses [28–31], four prospective cohort studies [32–35], four prospective nonrandomized comparative trials [36–41], and one pilot prospective RCT [42] (Table 2). Three articles were about one study at different time points [38–40].

Seven relevant ongoing trials were found in the clinical trials register at the time of writing: two prospective nonrandomized comparative trials; and five prospective RCTs—three of which are currently recruiting, one not yet open, and one in its final stages (Supplemental Table 1) [55–61]. To date, none are published, and are not further evaluated in this review.

2.1. Risk of bias

Assessment of the quality of included studies considered the study design, method of recruitment, and choice of NOM. There were three level 4 studies, nine level 3 and one level 2 (Table 2). Criteria for participant selection into study groups varied widely, partly because of the heterogeneity in diagnostic criteria between studies. All studies mentioned use of imaging with ultrasound and/or computed tomography. Eight incorporated laboratory findings of inflammation [28,30,31,35,36,40–42], and three used scoring systems—either Pediatric Appendix Score [30,36] or the Alvarado score [34].

Svensson et al. [42] performed the only RCT (level 2 evidence) where allocation of concealment was made via weighted minimization using a computer-based randomization program. As in any study comparing OM and NOM, mitigation of bias by blinding was not feasible.

Study designs of prospective nonrandomized comparative trials are intrinsically biased, as patient or physician selection of treatment choice may skew population characteristics, and enhance effects of confounding factors. Minneci et al. [40] recognized that patients who selected OM were more likely to be transferred from other institutions and may be influenced by travel concerns, and particular cultural preferences for NOM.

Two prospective cohort studies included children and adults, although a significant proportion were in the pediatric age group [34,35]. Gorter et al. [32] noted that patients under age seven had a higher incidence of complicated appendicitis, thus excluding them in their study.

The treatment choice of one prospective cohort study was skewed. While all children had a diagnosis of appendicitis, grading on ultrasound assessment was used to guide treatment, with low grades receiving antibiotics, and high grades operation [33]. Another study compared three outcomes: 'early' appendectomy in complicated appendicitis, 'successful' NOM in uncomplicated appendicitis, and 'late' appendectomy for patients who did not improve within 48 h of initial NOM. There was no direct comparison of NOM with OM for uncomplicated appendicitis [36].