Nonoperative Management of Appendicitis in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Appendicitis remains the most common intra-abdominal surgical emergency, with an annual incidence of 250,000 patients in the US, 50,000 patients in the UK, and a lifetime risk of 8%.[1,2] The vast majority of these cases are managed by appendectomy, underpinned by the dogma that uncomplicated appendicitis inevitably progresses to abscess formation, gangrene, and perforation. However, more routine use of imaging has improved diagnostic accuracy and identification of the majority of patients with uncomplicated appendicitis at admission.[3]

In parallel, there is increasing recognition that the pathogenesis and natural history of appendicitis is variable. Logically, some patients will have an episode that will not progress or perhaps may even be self-limiting,[4] and antibiotics alone will sometimes suffice. Indeed, this approach is necessary in remote environments[5] and historically antibiotics have been considered the treatment of choice for delayed presentations with an appendix mass.[6]

Consequently, a number of randomized controlled trials (RCTs) and attendant meta-analyses have explored the role of routine nonoperative management with antibiotics. Some have concluded that it represents an equally valid alternative to surgery for uncomplicated appendicitis, with an equivalent safety profile and possibly, fewer complications,[7,8] although this view was not supported by the most recent Cochrane review of 5 RCTs.[9] At present, appendectomy remains the treatment of choice recommended in the US and Europe.[10-12] However, these guidelines, reviews, and meta-analyses were published before a recent relevant RCT in 2015.[13] Although this did not demonstrate noninferiority of antibiotics, the significant reduction in complications seen with antibiotics has frequently been interpreted as additional evidence that antibiotics represent a valid alternative to surgery.[14,15] The aim of this study was to perform an up-to-date systematic review and meta-analysis of primary antibiotic therapy vs surgery for the management of acute appendicitis.

METHODS

Literature search

A literature search was performed of the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials in May 2016 by 2 authors (JEK and CH), independently using standardized data collection software, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[16,17] The following search terms were used: ([antibiotics OR appendectomy OR appendicectomy OR surgery] AND [trial OR randomized] AND [appendicitis OR appendix]). Bibliographies of retrieved articles were searched. Any disagreement was resolved by a third author (JMF). Data were extracted and studies similarly assessed by 2 authors (JMF and JEK). We contacted the corresponding authors of 3 studies with questions regarding methodology and requests for data,[18-20] although none could be provided.

Inclusion criteria

We included randomized and quasi-randomized prospective controlled trials, randomizing patients aged 16 and older to either primary antibiotic therapy or appendectomy for acute appendicitis.

Endpoints

Successful treatment was defined pragmatically as resolution of the presenting acute episode of appendicular inflammation without recurrence: ie removal of the appendix without subsequent inflammation of the stump or ileum/

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Abbreviations and Acronyms

GRADE = Grading of Recommendations Assessment, Development, and Evaluation
ITT = intention to treat
PP = per protocol
RCT = randomized controlled trial
RR = risk ratio

cecum, or significant improvement in clinical/biochemical evidence of inflammation, not requiring further antibiotics or appendectomy. This was either during the initial episode or admission, or at 1 year. Recurrent appendicitis was defined as a clinical or radiologic diagnosis. Complicated appendicitis was defined as intra-abdominal pus, enteric contamination, or necrotic/gangrenous appendicitis. For 2 studies not stipulating the presence of pus (all categorized as phlegmonous, gangrenous, or perforated[18,19]), gangrene or perforation were used.

Complications were as defined in studies. Variable presentation precluded meaningful synthesis of complications reported by all studies, so we performed pragmatic analyses for all, minor, and major complications. Minor complications included wound infections, presumed adhesional/wound pain, urinary catheterization at discharge, minor anesthetic complications (eg tooth injury), and fungal infections. Major complications constituted death, intra-abdominal abscess/post-intervention peritonitis, enterocutaneous fistula, major medical complications (eg pneumonia, acute coronary syndrome, pulmonary embolism, *Clostridium difficile* colitis), incisional hernia, wound dehiscence, or surgery for bowel obstruction.

Meta-analysis

Two analyses were performed for all comparisons: intention-to-treat (ITT) and per protocol (PP). For the index admission, it was possible to perform a PP analysis that included patients crossing over after randomization in 1 study.[18] However, this could not be performed at 1 year. For ITT, all patients were included, irrespective of protocol violations and follow-up. For PP, only patients completing treatment per protocol and follow-up at the relevant time point were included. For 1 study,[13] although a few patients were formally lost to follow-up, the authors were confident they had identified subsequent appendectomies. These patients were therefore included in primary but not secondary analyses.

Statistical analysis

Heterogeneity was assessed using chi-square ($p < 0.05$), and quantified using I^2. We used random effects models due to methodologic and comparison heterogeneity, although we performed sensitivity analyses using fixed effects, and individual studies. For binary variables Mantel-Haenszel risk ratio (RR) was used. For the 2 studies[18,20] presenting standard error (SEM) rather than standard deviation (SD), we converted the former to the latter. One study presented length of stay as median and range, rather than mean and SD[13]; the latter were estimated.[21] Funnel plots were inspected visually for evidence of asymmetry. All analysis was performed using Review Manager v5.2[22] and R v3.0.2.[23]

RESULTS

Literature search

There were 1,146 studies identified, 69 of which were retrieved for full text evaluation (Fig. 1). Seven RCTs were identified. One was excluded due to subsequent retraction.[24]

Study characteristics and quality

Six RCTs conducted between 1992 and 2012 were included (Table 1),[13,18-20,25,26] 2 with noninferiority designs.[13,25] A total of 1,724 patients were randomized to antibiotics (n = 837) or surgery (n = 887). Studies varied considerably in their interventions, inclusion, exclusion, and diagnostic criteria. All reported a maximum 1-year follow-up. None were blinded. Randomization was by sealed envelope,[13,19] computer generation,[25] date of birth,[18] or an unclear method.[20,26] One study[18] allowed crossover after randomization, whereby clinicians or surgeons could alter treatment. All except 1 study[19] described dropouts and withdrawals.

Overall, there were many generic areas of potential bias. These included major differences in inclusion, exclusion, and diagnostic criteria; differences in antibiotics and therapy duration; major variability in surgical approach (open procedures being used selectively); follow-up methods; and definition and reporting of complications.

Inclusion, diagnostic, and exclusion criteria

Five studies included patients aged 18 and older; 1 study included patients 16 and older.[20] Two had upper age limits of 60 years[13] and 50 years.[19] One included only male patients.[19] Two studies mandated CT diagnosis,[13,25] and 3 had clinical diagnosis with or without ultrasound/CT[18] or ultrasound alone alone.[26]

Overall, exclusion criteria effectively amounted to radiologic or clinical evidence of perforation or abscess formation. Four studies excluded radiologic[13,25] or clinical suspicion of perforation or abscess.[19,26] One study[18] did not formally exclude such patients, but clinicians could