

Antibiotics versus appendectomy in the management of acute appendicitis: a review of the current evidence

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Background: Acute appendicitis remains the most common cause of the acute abdomen in young adults, and the mainstay of treatment in most centres is an appendectomy. However, treatment for other intra-abdominal inflammatory processes, such as diverticulitis, consists initially of conservative management with antibiotics. The aim of this study was to determine the role of antibiotics in the management of acute appendicitis and to assess if appendectomy remains the gold standard of care.

Methods: A literature search using MEDLINE and the Cochrane Library identified studies published between 1999 and 2009, and we reviewed all relevant articles. The articles were critiqued using the Public Health Resource Unit (2006) appraisal tools.

Results: Our search yielded 41 papers, and we identified a total of 13 papers within the criteria specified. All of these papers, while posing pertinent questions and demonstrating the role of antibiotics as a bridge to surgery, failed to adequately justify their findings that antibiotics could be used as a definitive treatment of acute appendicitis.

Conclusion: Appendectomy remains the gold standard of treatment for acute appendicitis based on the current evidence.

Contexte : L'appendicite aiguë demeure la plus fréquente cause de l'abdomen aigu chez les jeunes adultes et dans la plupart des centres, la base du traitement repose sur l'appendicectomie. Toutefois, le traitement des autres processus inflammatoires intra-abdominaux, comme la diverticulite, consiste initialement en une prise en charge conservatrice par antibiothérapie. Cette étude avait pour but de déterminer le rôle des antibiotiques dans la prise en charge de l'appendicite aiguë et de vérifier si l'appendicectomie reste la norme thérapeutique.

Méthodes : Une interrogation des publications dans MEDLINE et la Collaboration Cochrane a permis de recenser des études publiées entre 1999 et 2009 et nous avons passé en revue tous les articles pertinents. Nous avons soumis les articles à un examen critique en appliquant les outils d'évaluation de la Public Health Resource Unit (2006).

Résultats : Notre recherche a retrouvé 41 articles, et nous avons retenu 13 articles à partir des critères spécifiés. Tous, même s'ils posaient des questions pertinentes et établissaient le rôle de l'antibiothérapie comme étape de transition avant la chirurgie, ont échoué à démontrer de façon adéquate leurs conclusions selon lesquelles les antibiotiques pourraient être utilisés en traitement définitif de l'appendicite aiguë.

Conclusion : Si l'on se fie aux preuves actuelles, l'appendicectomie reste la norme thérapeutique privilégiée pour le traitement de l'appendice aiguë.

Acute appendicitis is inflammation of the vermiform appendix and remains the most common cause of the acute abdomen in young adults. The mainstay of treatment in most centres is an appendectomy, and, consequently, this is one of the most common operations performed on the acute abdomen.¹ However, appendicitis can be notoriously difficult to diagnose, and there exists a negative appendectomy rate of 10%–20% despite the use of preoperative computed tomography (CT).^{2–6} In addition, as with all operations, postoperative complications exist, including wound infections, intra-abdominal abscesses, ileus and, in the longer term, adhesions. With this in mind, it is worth considering that the mainstay of treatment for

other intra-abdominal inflammatory processes, such as diverticulitis, consists initially of conservative management with antibiotics.⁷

Traditionally, appendectomy has been the treatment of choice for acute appendicitis.¹ However, in view of the potential morbidity associated with an open appendectomy, is there a role for conservative management with antibiotics? A number of reports exist regarding possible conservative management of appendicitis, with or without interval appendectomy, and many pediatric centres practise this approach in patients with advanced appendicitis.⁸⁻¹⁰

Consequently, the aim of this review was to evaluate the current literature on the role of antibiotics versus appendectomy in the management of acute appendicitis and to assess if appendectomy remains the gold standard of care.

METHODS

We performed a literature search on MEDLINE and the Cochrane Library databases, using the medical subject headings “appendectomy,” “appendicitis” and “anti-bacterial agents.” The search was limited to papers published in English in the previous 10 years (1999–2009) to ensure the evidence was contemporaneous. The populations of studies we considered included male and female patients of all ages, including children. All systematic reviews, randomized controlled trials (RCTs), prospective and retrospective studies were included. We excluded letters to the editor, case reports and articles not related to the use of antibiotics in the management of appendicitis. One of us (G.J.F.) reviewed the full text of all articles to maintain consistency.

The articles were critiqued using the Public Health Resource Unit (2006) appraisal tools, a standard critiquing tool used to assess articles based on their methodology.¹¹ The tool focuses on 3 key areas: the validity of the trial, its results and whether the results will assist in patient care locally. It consists of a 10-question assessment of the methodology for each particular study, providing a standardized technique to evaluate each paper. For example, in the evaluation of a systematic review, the questions include “Is there a clearly focused question?”, “Did the review include the correct type of study?”, “Were all relevant studies likely to have been included, and was the quality of those studies assessed?”, “If results were combined, was that appropriate?”, “What were the findings, and how accurate are they?”, “Are the results applicable to the local population?”, “Are there any confounding factors?” and “Should policy change as a result of this study?”¹¹ The hierarchy of evidence was standardized as outlined by Guyatt and colleagues,¹² ranking a study based on its methodology. The strongest evidence is provided by systematic reviews and meta-analyses, with an evidence level of 1, whereas the weakest level of evidence is provided by case reports and expert opinion, with an evidence level of 7. Randomized controlled trials with definitive results provide an evidence

level of 2, RCTs with nondefinitive results provide an evidence level of 3, cohort studies provide an evidence level of 4, case-control studies provide an evidence level of 5 and cross-sectional studies provide an evidence level of 6.¹²

RESULTS

Our search yielded 41 articles. Of these, we excluded 28 papers for the following reasons. Three papers were response letters, 1 was a critique based on papers that were among those to be reviewed, 4 dealt with laparoscopic versus open appendectomy in the treatment of confirmed appendicitis, 2 related to postoperative complications following appendectomy, 5 related to the management of appendiceal perforations, 1 related to predictors of failure of nonoperative management of a perforated appendix, 4 related to prophylactic antibiotic use in the prevention of postoperative infections following appendectomy, 1 discussed oral prophylactic antibiotic use following intravenous antibiotic treatment for acute appendicitis, 1 explored peritoneal taurolidine lavage in children with appendicitis, 2 related to various techniques to reduce postoperative wound infections following appendectomy, 1 dealt with the mortality following appendectomy, 1 related to recurrent appendicitis, 1 dealt with CT to assess outcomes of appendicitis and 1 was a case report.^{3,13-39} After all exclusions, 13 papers remained for analysis.

Systematic reviews

Mason⁷ performed what he described as a systematic review of the published literature to assess whether it was necessary to perform surgery for appendicitis. He did not detail the search methods or the databases used, nor the period of time covered by the study. However, he did assess the quality of the studies used, which examined the nonoperative management of uncomplicated appendicitis. There were important limitations in all of these studies, ranging from no design or a poor design to anonymous authors. Mason presented the results individually, and a number of the studies quoted did not provide outcome data. Despite this, he concluded that appendectomy may not be necessary for up to 70% of patients who could be appropriately treated with antibiotics. Mason did accept that the availability of evidence examining the question of nonoperative management of appendicitis was “scant and of poor quality.” Whereas Mason’s study does serve to question the traditional approach to the management of acute appendicitis, it should in no way alter local management of the condition and may be classified as level-7 evidence.¹²

Randomized controlled trials

Hansson and colleagues⁴⁰ performed an RCT to assess the use of antibiotic therapy versus appendectomy as the

primary treatment of acute appendicitis (Fig. 1). The study was completed in Sweden at 3 separate hospitals in Gothenberg between May 2006 and September 2007. All 369 patients over 18 years of age admitted during this time period were included; there were no exclusions. The primary outcome measures were treatment efficacy and the occurrence of major complications. The authors defined efficacy with antibiotic treatment as “definite improvement without the need for surgery within a median follow-up of 1 year,” and they defined surgical efficacy as “confirmed appendicitis at operation or another appropriate surgical indication for operation.” Patients were randomly assigned to a treatment group based on date of birth; 202 patients with an uneven date of birth were assigned to antibiotic treatment and 167 patients with an even date of birth were assigned to surgical treatment. However, there was no blinding, and the surgeon

was allowed to change a patient’s treatment assignment from antibiotics to surgery at any point, which accounted for 96 of 202 patients in the antibiotic group actually receiving surgery. This compared with 13 of 167 patients in the surgical group who received antibiotic treatment only. Consequently, there was a clear bias toward surgical intervention, and the patients with more severe conditions potentially received surgery. This was highlighted by the fact that patients who underwent surgery had a higher white cell count, pyrexia and peritonism compared with patients who were treated with antibiotics.

The authors point out that 15 of the 106 patients initially treated with antibiotics returned for further treatment and that 12 of them required surgery. They also highlighted that 2 of the patients who proceeded to surgery were found to have malignancies and underwent hemicolectomies. The authors determined a treatment

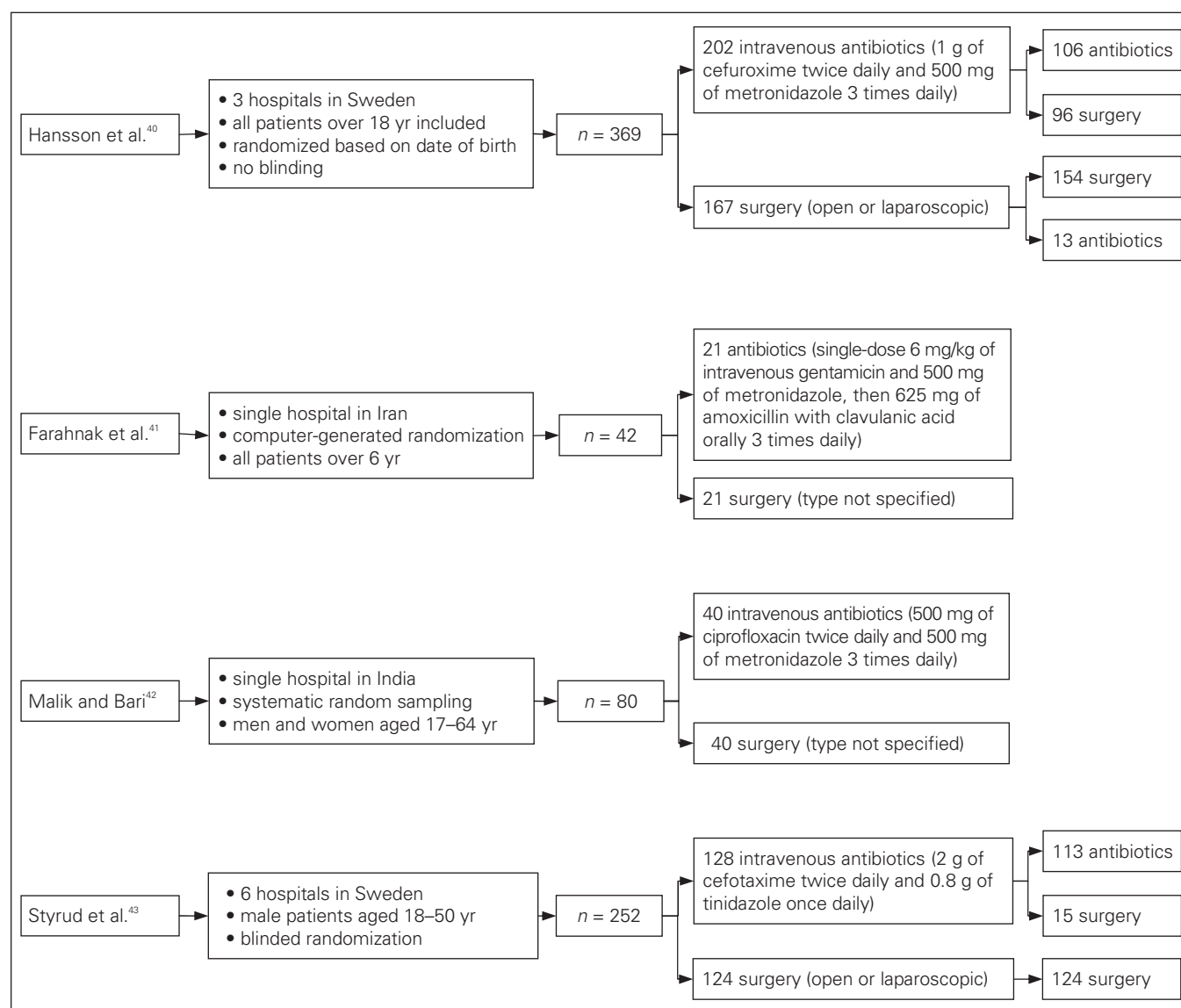


Fig. 1. Summary of randomized controlled trials comparing antibiotics and surgery in the treatment of appendicitis.

efficacy of 90.8% for antibiotic therapy and 89.2% for surgical treatment; however, they also demonstrated that the overall incidence of major complications was 3 times higher in patients who underwent surgery compared with those treated with antibiotics ($p < 0.05$). Whereas this was an interesting initial study that explored the possible use of antibiotics in the treatment of appendicitis, the conclusion that antibiotics appeared to be a safe first-line therapy in the treatment of patients presenting with acute appendicitis was not justified. The authors demonstrated that patients presenting with symptoms and signs suggestive of appendicitis can be initially managed with antibiotics; however, once the diagnosis of appendicitis becomes clear, then the patient should undergo an appendectomy. This study may be classified as level-3 evidence.¹²

Farahnak and colleagues⁴¹ completed an RCT to assess the use of the Alvarado score with antibiotic therapy versus conventional therapy in the management of acute appendicitis. The Alvarado score is a numerical scoring system ranging from 1 to 10 that assesses symptoms, signs, temperature and blood results to provide an indication of the likelihood of acute appendicitis.⁴⁴ The study took place in Iran from September to December 2005 and included 42 patients. The study excluded patients who were peritonitic and those who had undergone radiologic imaging. These criteria substantially affected the study findings because they excluded those patients who were most likely to actually have appendicitis. The primary outcome measures were time to surgery and duration of hospital admission. The authors found that the median time to surgery (2.05 v. 8.35 h, $p = 0.030$) and the median duration of hospital admission (37.00 v. 60.40 h, $p = 0.034$) were shorter in the intervention group than the control group. However, the small participant numbers meant that no statistical level could be achieved, and the conclusion that institution of the protocol improved patient care was difficult to accept. This study may be classified as level-3 evidence.¹²

Malik and Bari⁴² performed an RCT to assess the role of antibiotics as the sole treatment for appendicitis. The study was conducted in India between August 2003 and July 2005 and included 80 patients, which was a small number for even 1 centre over such a long period. The method by which the patients were randomly assigned to treatment groups was not clearly explained, and it was unclear whether the assignment was made before or after the completion of investigations, which included radiologic imaging. There was also no clear indication of whether there was blinding. Further, whereas the inclusion criteria were clearly stated, there was no mention of the exclusion criteria, which must have had an impact owing to the low participant numbers over such a long study period. No specific criteria for assessing a primary outcome were described; however, the authors detailed a significantly lower analgesic consumption and less pain at 12 hours in the antibiotic group ($p < 0.001$). Four patients (10%) who

were treated initially with antibiotics had recurrent appendicitis and proceeded to surgery. Whereas the authors concluded that within their locality antibiotic treatment appeared to be a viable alternative to surgery, they accepted the limitations of this study, and it may be classified as level-3 evidence.¹²

Styrud and colleagues⁴³ performed a prospective multi-centre RCT to assess antibiotic treatment versus surgery in the treatment of acute appendicitis. The study was conducted in 6 hospitals in Sweden. It excluded women as a condition for ethical approval and included 252 men aged 18–50 years who presented between March 1996 and June 1999. There was no explanation given for the choice of age range, and it would have made the study more robust to have a wider range or at least justify the limits. However, the authors clearly detailed the method of random assignment, which appeared to be blinded. The primary outcome measures were not specifically reported but appeared to include complications, level of pain and number of sick days over the preceding 1 year of follow-up. All of the participants were accounted for at the conclusion of the study. The authors concluded that antibiotic treatment for acute appendicitis was sufficient in most patients; however, the numbers quoted in the discussion differed from those quoted in the results. The authors detailed 15 patients in the antibiotic treatment group who underwent surgery in the first 24 hours in the results section; however, this number increased to 17 patients in the discussion section, and was 18 patients in the abstract. The authors declared that they would present p values for any statistically significant results, but none were provided. Whereas this article certainly raised a number of relevant questions regarding the management of acute appendicitis, the level of evidence provided was not sufficient to affect management locally. The study may be classified as level-3 evidence.¹²

A number of other studies assessed the role of antibiotics in the management of acute appendicitis, and they may be considered as a group (Table 1). Liu and colleagues⁴⁵ concluded that patients with acute appendicitis could be managed with antibiotics alone. However, this was based on a retrospective review of patients at 1 centre where 151 patients underwent surgery and only 19 were treated with antibiotics. Although not specifying primary outcome measures, the authors assessed overall complications and length of hospital admission. They reported an overall complication rate of 8.6% for surgical patients and 10% for patients treated with antibiotics ($p = 0.22$); however, all complications in the antibiotic group developed after a subsequent appendectomy. Abes and colleagues⁴⁶ performed a retrospective analysis of patient records to assess the impact of nonoperative treatment of acute appendicitis in children and concluded that antibiotics have a role in the management of localized abdominal tenderness. However, the article only analyzed the autumn and winter period, and all patients underwent radiologic imaging before a decision on

treatment. No specific outcome measures were detailed. The authors found a statistically significant decrease in appendix size in the antibiotic treatment group ($p < 0.001$), and they found that 93.7% (15 of the 16 patients) who received antibiotic treatment were managed successfully, with the only complication being recurrence in 2 patients who subsequently underwent appendectomies. The level of evidence provided in both articles could not support the authors' conclusions, and both may be classified as level-7 evidence.¹²

A number of studies assessed the feasibility of delaying appendectomy and using antibiotics as a bridge to surgery. Stahlfeld and colleagues⁴⁷ performed a retrospective analysis of patients who had undergone appendectomy to determine if conservative management of acute appendicitis outside of normal working hours had a negative effect on patient morbidity and mortality. A more specific primary outcome measure was not detailed. The article was a retrospective study performed at a single institution and involved only 2 surgeons. Additionally, the total number of participants changed from 81 to 71 between the methods and the results section. This combination of factors inhibited the reliability of this study. The authors found that

there was no statistically significant difference between patients who underwent appendectomy within 10 hours of diagnosis and those who underwent appendectomy more than 10 hours after diagnosis (length of operation, $p = 0.84$; length of stay in hospital, $p = 0.21$; wound infections, $p = 0.32$). The authors' conclusion that delaying surgical intervention may benefit the patient could not be accepted based on the evidence provided. The study may be classified as level-7 evidence.¹²

Friedell and Perez-Izquierdo⁴⁸ detailed a similar study that assessed the role of interval appendectomy in the management of acute appendicitis. The article was a retrospective analysis of the authors' appendectomy patients, which demonstrated a study with bias and poor design. There was no specific primary outcome measure reported. The article described the management of 5 of the 73 patients who underwent appendectomy at this centre and, as such, must be classified as a case report. The conclusion that the authors' treatment algorithm for appendicitis makes management "simple and straightforward with minimal morbidity" based on 5 cases could not be supported sufficiently from the available evidence. The study may be classified as level-7 evidence.¹²

Table 1. Summary of findings for studies assessing the role of antibiotics in the management of acute appendicitis, using various methodologies, included in the review and meta-analysis

Study	Aim	Methodology	Results	Outcomes
Balzarotti et al. ⁵⁰	In complicated appendicitis: urgent appendectomy v. antibiotic therapy followed by elective appendectomy	Retrospective review, all admissions at single centre, with acute appendicitis included, 1998–2007	40 patients had urgent appendectomy v. 16 who had antibiotic treatment, of whom 15 had elective surgery	Fewer postoperative complications but longer duration of hospital stay/antibiotic use in elective group
Gillick et al. ⁹	Assess safety of interval laparoscopic appendectomy after initial antibiotic treatment	Retrospective review, all children at single centre between 1999 and 2006	103 patients total: 93 had antibiotics followed by interval laparoscopic appendectomy, 10 patients had abscesses requiring earlier intervention	3 postoperative complications in interval group; 10 patients required early intervention: 7 open drainage, 3 laparoscopic drainage
Mason ⁷	Assess if surgery for appendicitis is necessary	Systematic review of published literature and expert opinion	Evidence regarding nonoperative management "scant and poor quality"	Surgery may not be needed for uncomplicated appendicitis
Abes et al. ⁴⁶	Assess nonoperative management of acute appendicitis	Retrospective review, all children at single centre between 2003 and 2006	95 children with acute appendicitis: 16 had nonoperative treatment	Nonoperative treatment successful in 15 of 16 patients
Liu et al. ⁴⁵	Assess if uncomplicated appendicitis may be treated with antibiotics only	Retrospective review, all patients at single centre between 2002 and 2003	170 patients: 151 had surgery, 19 received antibiotics	No complications in antibiotic group
Stahlfeld et al. ⁴⁷	Assess if delaying appendectomy negatively affected outcome	Retrospective review, appendectomy patients at a single centre between 2000 and 2002	81 patients: 53 had surgery < 10 h and 18 had surgery > 10 h from diagnosis (10 patients unaccounted for)	No difference in outcome among groups
Owen et al. ⁸	Report of their experience of interval appendectomy in complicated appendicitis	Retrospective review, all children at single centre between 2000 and 2004 offered interval surgery	36 patients: median 10 d antibiotics, 35 had interval surgery, 5 had percutaneous drainage	No complications following surgery
Yardeni et al. ⁴⁹	Assess morbidity associated with delayed v. immediate surgery for acute uncomplicated appendicitis	Retrospective review, single centre, all patients with acute appendicitis between 1998 and 2001 included	126 patients: 38 had surgery within 6 h and 88 within 24 h of emergency department triage	No significant difference in outcomes
Friedell et al. ⁴⁸	Assess role of interval appendectomy in management of acute appendicitis	Retrospective review, single centre, all patients who underwent surgery by the senior author between 1990 and 1998 included	73 patients: 5 underwent interval appendectomy (35–66 d later) after antibiotic treatment	No complications

Yardeni and colleagues⁴⁹ performed a retrospective analysis of patients treated for acute appendicitis between 1998 and 2001 at 1 centre to determine if a delay in surgical intervention of up to 24 hours affected patient morbidity. All of the participants were children, but the age range was not given. The outcome measures included time to operation, presence of perforation, length of hospital admission and total hospital cost. The authors concluded that delaying surgery for up to 24 hours did not significantly affect complication rates; however, it did afford clinicians a better lifestyle ($p > 0.05$). Whereas the article did make some contribution to this debate, the evidence was lacking and would not affect local management. The study may be classified as level-7 evidence.¹²

Balzarotti and colleagues⁵⁰ detailed a retrospective study that included only 56 patients and concluded that antibiotic therapy may have a role to play in the initial management of acute appendicitis. The outcome measures assessed were response to treatment, failure of medical therapy, length of hospital admission and rate of recurrence. They found a longer duration of surgery among the urgent appendectomy group compared with the elective appendectomy group (98 v. 74 min, $p = 0.06$), a higher rate of complications among the urgent group (25% v. 0%, $p = 0.027$), but a longer length of stay in hospital (12.2 v. 7.7 d, $p = 0.027$) and a longer duration of antibiotic use (27.9 v. 11.3 d, $p < 0.001$) among the elective group. Owen and colleagues⁸ detailed a similar study but with a smaller number of participants. They found a median length of stay in hospital for conservative treatment of 6 (3–23) days, time to interval appendectomy was 93 (34–156) days, and there were no complications following laparoscopic appendectomy. No statistical analysis was provided. Gillick and colleagues⁹ also performed a retrospective study with a population of only 93 patients. They found that 90.2% responded to initial conservative management with antibiotics, 94.2% successfully underwent an interval laparoscopic appendectomy, and 3 patients (3.1%) experienced postoperative complications. No statistical analysis was provided. Both of these studies reported local experience without specific primary outcome measures. Whereas all of these studies certainly contributed to the debate regarding the use of antibiotics in the management of acute appendicitis, they were inherently flawed and could not support the conclusions made. They may be classified as level-7 evidence.¹²

DISCUSSION

Acute appendicitis remains enigmatic, and of late many surgeons avail of imaging studies to complement clinical findings before undertaking surgical intervention.⁴⁷ However, there are important implications of imaging, particularly the radiation exposure associated with CT scanning in younger patients. There is also significant morbidity and mortality associated with an appendectomy.¹ As such,

it is important to determine whether appendectomy remains the gold standard for treating acute appendicitis.

A number of authors have recently proposed that acute appendicitis may be managed conservatively with antibiotics.^{7,10,40–43} Some authors advocate interval appendectomy owing to the potential for recurrent appendicitis and the possibility of a missed carcinoma; however, there appeared to be a growing trend toward the sole use of antibiotics and avoidance of surgery altogether.^{8,9,48} The patient may then undergo future radiologic or endoscopic examination to exclude a missed neoplastic lesion. In view of this evolving debate, it is worth considering that other intra-abdominal inflammatory processes are managed conservatively and that the current management of acute appendicitis is based mainly on tradition rather than evidence.⁷

However, antibiotic use in the treatment of appendicitis is actually complex and depends on many factors (e.g., children v. adults, uncomplicated v. complicated appendicitis, interval to appendectomy v. definitive treatment, other treatment options such as percutaneous drainage). St. Peter and colleagues,⁵¹ in a recent paper, examined complicated appendicitis in children and found that interval appendectomy with initial percutaneous drainage of an abscess where possible had similar outcomes to initial appendectomy. Marin and colleagues⁵² have also demonstrated that the use of percutaneous drainage in the management of complicated appendicitis with abscess formation is both safe and effective, which adds further potential treatment strategies in this evolving debate. And with the potential long-term complications, such as bowel obstruction, inherent with appendectomy, the potential use of antibiotics as a treatment strategy appears reasonable.⁵³

Consequently, this review was undertaken to assess the role of antibiotics versus appendectomy in the management of acute appendicitis. Following a review of the literature, we raised a number of issues. First, it has been demonstrated that acute appendicitis may be managed conservatively with antibiotics as a bridge to definitive surgery. However, the current evidence does not support the sole use of antibiotics as an alternative treatment modality to appendectomy in the management of acute appendicitis. Despite this, the evidence is minimal and poorly constructed for varying reasons. Consequently, to accurately determine the optimal management course for acute appendicitis, further studies, such as an appropriately constructed and adequately powered RCT would need to be undertaken. In such studies, standard inclusion criteria representative of general surgical practice for acute appendicitis and suitable diagnostic methods, such as ultrasonography, would need to be determined. Statistical analysis on an intention-to-treat basis would be preferred to determine the actual benefit of each treatment course and account for the effect of crossover. As a consequence of the poor data available and pending the outcome of further studies, the gold standard of treatment remains an appendectomy.

Authors do acknowledge that whereas antibiotics appear to have a potential role in the management of acute appendicitis, there is simply insufficient evidence currently to lead to an alteration in practice.

CONCLUSION

Acute appendicitis is the most common cause of the acute abdomen in young adults, and whereas conservative management may have a role as a bridge to surgery, the mainstay of treatment is currently operative. As clinicians, the practice of evidence-based medicine has become the cornerstone of patient care and consequently the management of such a common intra-abdominal pathology should ideally be examined more comprehensively. The evidence suggests that further studies should be undertaken to accurately determine best practice in the management of acute appendicitis.

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Contributors: All authors participated in study design, data analysis and article review and approved the article's publication. Dr. Fitzmaurice acquired the data and wrote the article.

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