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A Clinical Review of Antibiotic Therapy Versus Appendectomy for Treatment of Acute Uncomplicated Appendicitis

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ANTIBIOTICS VERSUS APPENDECTOMY FOR ACUTE APPENDICITIS

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INTRODUCTION

Acute appendicitis (AA), defined as the inflammation of the vermiform appendix due to luminal obstruction from various etiologies, is the most common cause of acute abdomen in all ages.[1] Over 300,000 appendectomies are performed each year in the United States, and the likelihood of developing AA over the course of one's life is approximately 7%.[1,2] Historically, intervention for AA has required surgical removal of the appendix, with laparoscopic appendectomy being the favored option over open laparotomy due to being less invasive, fewer postoperative complications, shorter length of stay, and decreased likelihood of infection.[2] Emerging evidence in recent literature challenges that antibiotic therapy can be considered a first-line and potentially sole therapy in patients with acute uncomplicated appendicitis (AUA) as opposed to standard laparoscopic appendectomy.[2-9]

A diagnosis of AA is usually made in an emergency room setting after a thorough history, physical exam, labs, and imaging. By interpreting these results, a reliable diagnosis of AA occurs in more than 90% of patients.[3] Accurately diagnosing AA reduces morbidity and mortality from complications that can occur without intervention. Imaging with computerized tomography (CT) or ultrasound aids in differentiating complicated versus uncomplicated cases. The most concerning complication is perforation, which occurs in 17% to 32% of patients and has a mortality rate of around 5%.[2] Other complications of AA include abscess, necrosis, peritonitis, and sepsis; urgent surgical intervention is nearly always required in these cases to prevent poor outcomes. These findings indicate acute complicated appendicitis, which is beyond the scope of this review.

MATERIAL AND METHODS

PubMed was searched for literature comparing antibiotic therapy alone versus appendectomy. The initial PubMed search using the keywords "acute appendicitis and antibiotics" yielded exactly 2,800 results but was reduced to 690 results when the five-year publication date filter was selected. The search was further narrowed to 496 results by selecting the "full text" filter option and adding "and appendectomy" to the other keywords. Sample size <100 people, patient population <5 years of age, and articles examining only acute complicated appendicitis were excluded.

SIGNIFICANCE

This review aims to present the literature results comparing non-operative management of AUA to standard operative interventions. Treating AUA with antibiotics alone is a relatively new notion. There are evidence gaps in the medical literature regarding the feasibility of antibiotic-alone therapy to treat a medical condition that has historically relied on surgical intervention as the mainstay of treatment. These areas include additional studies examining the effectiveness of conservative treatment, optimizing antibiotic-specific guidelines, long-term outcomes, and which patients would benefit most from avoiding surgery. There is no consensus that conservative treatment should routinely replace appendectomy due to these knowledge gaps. This review presents conclusions from studies comparing the effectiveness of antibiotics versus surgical intervention with the hope that future clinical guidelines may be adjusted to adapt to the updated research. Avoiding surgical intervention in eligible patients with AUA will reduce healthcare costs and morbidity of surgical complications.[4]

RESULTS

Evidence promotes the notion that patients suffering from AUA should be offered a choice between non-operative management and surgery; however, there are still significant barriers to implementing this into routine practice. These barriers exist due to a lack of clinician and patient familiarity with the most up-to-date evidence-based medicine regarding treatment for AUA. Other barriers preventing implementation are the concern for repeated treatment requirements during the first year, the need for more robust studies examining long-term outcomes, and a lack of antibiotic regimen guidelines. Studies concluded that the clinician and patient should heavily consider the benefits and risks of both treatment options in a shared decision-making process. Specific recommendations for non-operative management versus antibiotics should consider individual patient preferences, past medical history, and radiographic findings.[3]

DISCUSSION

Diagnosis

Beginning with the history and physical exam, an astute clinician will consider AA in any patient complaining of right lower quadrant abdominal pain. Classic signs and symptoms include periumbilical abdominal pain that settles in the right lower quadrant with tenderness at McBurney's point, anorexia (80-85%), nausea (40-60%), fever, Rovsing's sign (pain in the right lower quadrant with palpation of left lower quadrant), positive psoas sign (right lower quadrant

pain with passive right hip extension), obturator sign (right lower quadrant pain with flexion and internal rotation of the right hip), and leukocytosis on complete blood count (67-90%).[3]

The American College of Radiology designates CT as the study of choice to diagnose AA in nonpregnant adults because of its superior sensitivity, specificity, and diagnostic accuracy compared to ultrasound.[3] There is ionizing radiation exposure with CT scans which increases the risk of future cancer development; therefore, pregnant patients and children undergo ultrasound for diagnosis. The utilization of CT allows for the categorization of AA into either complicated or uncomplicated appendicitis. This is a crucial distinction to make as it guides the clinician in forming the most appropriate treatment intervention. Findings of AUA on CT include dilated appendix (>7 mm), thickening of cecal apex, appendiceal wall thickening or hyperenhancement, and inflammatory stranding of the surrounding fat tissue.[3]

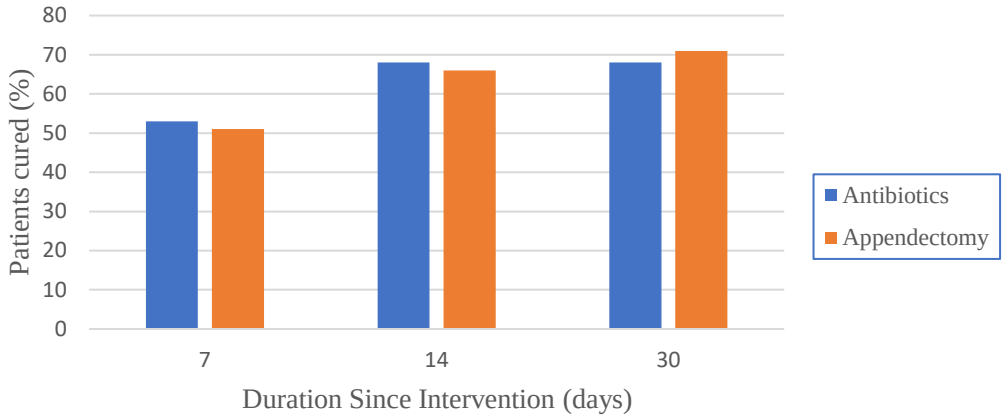
Current Literature

For more than 200 years, AA has been considered a progressive disease that requires rapid surgical intervention. The first reported open appendectomy was performed in 1735.[3,4] Advancements in surgery over the last four decades, especially the development of laparoscopy, revolutionized medicine and this became the standard surgical repair for AA.[3] Conservative treatment for AUA with antibiotics alone has gained extensive popularity in recent years. Most notably, a study comparing the two treatment modalities was recently published in *The New England Journal of Medicine* as recently as 2020. The Comparison of the Outcomes of Antibiotic Drugs and Appendectomy Trial, or CODA, is the largest study to date comparing appendectomy versus the use of antibiotics for AUA. This trial included 1,552 participants enrolled from 25 sites across 14 states.[5] This nonblinded, randomized, comparative effectiveness study from *The New England Journal of Medicine* demonstrated that antibiotics were non-inferior to appendectomy based on the results of a standardized 30-day overall health status questionnaire.

Eligible participants with similar sociodemographic and clinical characteristics were randomly assigned to two groups; 776 received antibiotics (intravenous route for at least 24 hours, followed by oral medication for a 10-day total course based on Surgical Infection Society antibiotic guidelines), and 776 underwent an appendectomy.[5] At 90 days after randomization, the risk of appendectomy in patients without an appendicolith was 25%, and the time spent in the hospital was similar between the appendectomy and antibiotic groups.[5] When an appendicolith

was not present, the rate of total complications was 3.7 per 100 in the antibiotics group, and the appendectomy group had a rate of 3.5 per 100 participants.[5] The percentages were very similar when comparing the number of participants with complete resolution of symptoms from both the appendectomy and antibiotic groups on days 7, 14, and 30 (Figure 1).[5] This pivotal trial supports the hypothesis that antibiotics are as good as surgical intervention in the treatment of AUA.[5]

Figure 1. Complete Resolution of Symptoms: The CODA Trial



a. Data derived from the CODA Trial comparing duration required to achieve complete resolution of symptoms in each group.[5]

Historically, clinicians have been concerned that delayed surgical intervention to trial antibiotic treatment for AUA would increase perforation and complication rates. A systemic review and meta-analysis conducted by Podda et al. evaluated twenty studies (n=3,618) comparing antibiotics and appendectomy in pediatric and adult populations.[4] This review supports that conservative management is a safe option for most patients eager to avoid surgery, and the study concluded it is successful in more than 70% of AUA cases.[4] However, there is an 8% risk of treatment failure within 48 hours, and an additional 20% of cases require hospitalization for recurrent AA in the first year.[4] The meta-analysis concluded that the rate of postintervention complications in the antibiotic group was significantly lower compared to surgical intervention, but the duration of primary hospital stay was equivalent between the two groups.[4] This study concluded that antibiotic-alone therapy in AUA does not statistically increase the risk of perforation in patients, and postponing an appendectomy to trial antibiotics does not result in more postoperative complications.[4]

The paucity of evidence regarding the long-term clinical efficacy of sole antibiotic therapy was one of the most compelling limitations preventing the widespread approval of antibiotic therapy for AUA.[4] The published studies to date that include follow-up usually examine outcomes to a maximum of one year after treatment. More high-quality studies evaluating the long-term clinical efficacy are required before treatment guidelines can be changed. An unprecedented study by Salminen et al. reported the 5-year outcomes for patients enrolled in the Appendicitis Acuta (APPAC) trial. This study enrolled 530 patients who received either antibiotics or surgery and followed them for more years than in previous studies. The authors deduced that of the 257 patients treated with antibiotics for AUA, the cumulative incidence of recurrent appendicitis requiring subsequent surgical treatment was 27.3% at one year, 34.0% at two, 35.2% at three, 37.1% at four, and 39% at five years.[6] In addition, the 24.4% complication rate in the appendectomy group was significantly more than the 6.5% complication rate in the conservative group at five years.[6] This extended observational follow-up supports the feasibility of antibiotics as an alternative to surgery for AUA and confirms the claim that almost all recurrences of AA after antibiotics happen within the first two years.[6,7]

In a meta-analysis examining 11 studies published in 2019 by Yang et al., 1,463 patients with AA were treated conservatively with antibiotics. This management of AUA was associated with significantly fewer complications compared to surgery and had an overall effective rate of 95.2%.[8] The advantages of surgical intervention include slightly higher overall effective treatment rates and lower re-operation rates; however, these advantages must be weighed against the drawback of higher complication rates and extended hospital stays.[8]

Advantages of antibiotic therapy over appendectomy include reduced healthcare costs and a lower morbidity rate from surgical complications.[4] Podda et al. asserted in their meta-analysis that successful antibiotic-alone therapy reduced overall cost by half ($2,509 for antibiotics vs. $4,898 for appendectomy) when compared to surgical intervention. When analyzing the cost of all appendicitis-related care (e.g., including antibiotic treatment failure requiring surgery and surgical complications), antibiotic-alone therapy is still the most cost-effective option ($4,074 vs. $5,117).[4] Many trials demonstrated that the incidence of significant complications was 2-4-fold higher in the surgical group.[3] These complications include postoperative infections, re-operation risk, hernias, and small bowel obstruction.

Medical Decision Making

More trials are required to study which patients could benefit from attempting non-operative management first and who should undergo surgery. Additionally, scientific efforts should focus on developing clinical, laboratory, and radiological scores to enable surgeons to quickly identify patients with the highest chance of responding to antibiotics.[4] According to some experts, complicated appendicitis and AUA are considered different disease entities. This distinction must be made prior to intervention because complicated findings on imaging are negative predictive factors of primary antibiotic treatment failure.[9] CT findings of acute complicated appendicitis include the presence of an appendicolith, appendix diameter >13mm, abscess, extraluminal gas, ileus, free air or fluid, periappendiceal phlegmon, and these patients nearly always require surgical intervention.[3] In addition, conservative treatment has higher failure rates and morbidity in those with a BMI > 30kg/m^2, patients over 65, immunocompromised patients, and pregnant women.[1]

Trials examining antibiotic treatment vary in their route of administration, antibiotic selection, and duration of treatment.[10] Antibiotics known to target *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococci*, *Pseudomonas aeruginosa*, and *Enterococci* are preferable as these are the most common microorganisms isolated in AA.[10] Total intravenous and oral therapy durations ranged from 4-15 days, with the most common duration being 7-10 days. There is no established optimal antibiotic regimen; the treatment is selected based on expected isolated microorganisms, disease severity, the risk for antibiotic resistance, major medical comorbidities, and history of recent travel or allergic reactions (Table 1).[3]

Table 1. Suggested Antibiotic Regimens for Treatment of Acute Uncomplicated Appendicitis

Intravenous Options During Hospital Stay (Usually first 24-48 hours)	**Oral Medication Options Upon Discharge** (Recommended duration of 7-10 days)
-2nd or 3rd generation cephalosporin PLUS metronidazole* -Piperacillin-tazobactam 3.375 g or 4.5 q.i.d.* -Ertapenem 1g (or other carbapenem) -Ampicillin-sulbactam 3 g q.i.d.	-Levofloxacin 500 mg daily plus metronidazole 500 mg t.i.d.* -Amoxicillin-clavulanate 875-125 b.i.d. -Moxifloxacin 400 mg once daily -Cephalosporin PLUS metronidazole 500 mg t.i.d.
*Most common regimens	

a. Table 1 outlines acceptable antibiotic regimens for the treatment of acute uncomplicated appendicitis during hospital admission, followed by oral step-down treatment options upon discharge from the hospital.

CONCLUSION

Acute appendicitis is the most common reason for emergency abdominal surgery worldwide, and the role of sole antibiotic therapy for managing AUA is a controversial topic.[7] Research in the past decade has challenged the dominance of the surgical approach, and accumulating evidence has shown the shift in medicine towards conservative management of AUA. However, laparoscopic appendectomy remains the standard treatment of AUA.[1,3] This revolutionary new concept of antibiotic-alone therapy can potentially reduce healthcare costs and complications from unnecessary surgical intervention and allows AUA to be managed in resource-limited settings.[4,6] Using the evidence-based medicine approach, informed shared decision-making with the patient should be standard when considering which treatment modality would be best for an individual with AUA.

KEYWORDS: Uncomplicated appendicitis, Antibiotic therapy, Appendectomy, Non-operative treatment, Conservative management

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