COMMENTARY

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Appendicitis management: Is it time for a change?

Acute appendicitis is one of the most common general surgical emergencies, with an estimated lifetime risk of 7% to 9% in the United States.[1] More than 95% of US patients with appendicitis are managed by appendectomy,[2] representing a significant healthcare burden. Although antibiotic therapy has been successfully used as an alternative therapy for more than 60 years, it has not superseded surgical intervention as the primary treatment.[3]

SURGERY OR ANTIBIOTICS?

The management of acute appendicitis has been heavily researched and debated over the years. Randomized controlled trials have examined the management of appendicitis in adults, but many of these had small sample sizes and excluded patients with appendicolith, thus limiting the generalizability of study results.[4,5]

The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial[6] recently shed new light on the management of appendicitis with a larger study size and broader inclusion criteria than in previous trials. The study concluded that antibiotics were noninferior to appendectomy, based on a validated quality-of-life questionnaire.

But other aspects of management should be considered. Ultimately, the approach should be based on shared decision-making between the surgeon and the patient. Surgical appendectomy remains our general preference and our continued recommendation. However, in situations such as the COVID-19 pandemic, when hospital resources may be strained, management with antibiotics may be the best option for good stewardship of resources. Also, the effects of surgery and anesthesia in patients who may have COVID-19 are not completely understood, possibly favoring management with antibiotics at such times.

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THE CODA TRIAL: WHAT DID IT SHOW?

The CODA trial was a nonblinded, noninferiority, randomized trial that compared antibiotic therapy (10-day course) with appendectomy at 25 US centers.[6] Antibiotics were not standardized among centers, but the most common regimens were reported:

- Therapies for initial intravenous use of least 24 hours were ertapenem, cefoxitin, or metronidazole plus ceftriaxone, cefazolin, or levofloxacin
- Medications for oral use (remainder of 10 total days) were metronidazole plus ciprofloxacin or cefdinir.[6]

The primary outcome focused mostly on the 30-day health status of the patient, assessed using a validated health status survey, the European Quality of Life-5 Dimensions (EQ-5D) questionnaire.[7] Secondary outcomes recorded were the rate of eventual appendectomy in the antibiotics group and the rate of patient complications at up to 90 days.

CODA study participants included 1,552 adults randomized to antibiotic therapy or appendectomy, with 776 in each arm of the study.[6] The sample size in the CODA trial was larger than in previous studies and included patients with appendicolith.[6,8]

EVIDENCE FOR ANTIBIOTICS

Based on the 30-day EQ-5D scores, the CODA trial concluded that antibiotics were noninferior to appendectomy for adults with appendicitis, and this conclusion also applied to patients who had appendicolith. Resolution of symptoms such as pain, tenderness, and fever was similar for both groups at 7, 14, and 30 days. Nearly half of patients assigned to the antibiotics group were not hospitalized. Among patients who were admitted from the emergency department, the mean time from admission to discharge was comparable for both groups. However, subsequent

emergency department visits were more common in the antibiotics group. Overall, patients receiving antibiotics missed fewer work days than those undergoing appendectomy (5.26 days with antibiotics vs 8.73 days with appendectomy).[6] The largest previous randomized trial, Appendicitis Acuta,[9] also demonstrated fewer missed work days in patients treated with antibiotics.

Although the rate of serious adverse events was comparable for the 2 groups in the CODA trial, the rate of surgical complications as defined by the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) criteria was higher in those in the antibiotics group who eventually underwent surgery.[6] The difference was attributable to patients with appendicolith, which has been linked to higher rates of complications in other studies.[6,9] A recent meta-analysis of 5 randomized controlled trials also showed lower complication rates and shorter disability with antibiotic treatment than with appendectomy.[10]

THE CASE FOR APPENDECTOMY

Although the patients in the CODA antibiotics arm had comparable initial hospital visit times, they subsequently required 3 times more emergency department visits and had twice as many NSQIP-defined complications than those who underwent appendectomy.[6] Percutaneous drainage procedures were also more common in the antibiotics group.[6]

About one-third of the patients assigned to receive antibiotics ultimately underwent appendectomy within 90 days. About 11% of patients in the antibiotics group required a redosing of antibiotics, and 10% were noncompliant with their medications. A few patients had adverse reactions to antibiotic therapy, including one that was life-threatening.[6] Longer-term outcomes were reported subsequently by the CODA Collaborative for patients as far as 4 years out from treatment.[8] In the antibiotics groups, the percentage of patients who underwent subsequent appendectomy was 40% at 1 year, 46% at 2 years, and 49% at 3 and 4 years.[8]

Appendectomy permits pathologic examination of the specimen. Neoplasms were identified on subsequent pathologic examinations in 9 patients (7 in the appendectomy group and 2 in the antibiotics group who eventually underwent appendectomy), all of whom were excluded from the study. These might have been missed with antibiotics-only management.[6]

CONCLUSIONS FOR ADULT PATIENTS

In the CODA trial, 3 in 10 patients in the antibiotic therapy group ultimately required surgery. But from the other perspective, 7 in 10 avoided surgery and missed less work time.[6] The EQ-5D outcome established noninferiority of treatment with antibiotics alone compared with surgery in terms of resolution of symptoms and incidence of serious adverse events. Because quality-of-life measures were comparable between study groups, the secondary outcomes (eg, need for eventual appendectomy, percutaneous drainage, and repeat courses of antibiotics) become arguably more important when deciding between therapies.

Selection bias may have been introduced into the process because of 3,987 patients excluded due to language barriers, clinical reasons, or refusal to participate (2,629 did not agree to undergo randomization). Still, the overall trial population is likely representative of most patients being treated for appendicitis. Patients with appendicolith were associated with an increased risk of need for appendectomy and NSQIP-defined complications. These patients may be better treated with surgery initially. Although inpatient hospitalization rate is important, presentation to the emergency department is equally significant, especially in the COVID-19 era.

The optimal timing for follow-up to evaluate patients treated with antibiotics alone is undetermined. Until lifetime data are available for nonsurgical treatment of appendicitis, each patient's case should be considered carefully. Decisions regarding therapy should be based on thorough discussion between the patient and physician.

Recommendation

We believe that compared with antibiotic therapy, appendectomy is the more definitive solution, as it limits the risk of further emergency department visits, hospitalizations, or interventions. Additionally, during times such as the COVID-19 pandemic or other public health emergency that can strain healthcare resources, it may be valuable and often necessary to reconsider treatment paradigms, as with appendectomy vs antibiotic therapy, to optimize patient care and maximize resources.

APPENDICITIS IN CHILDREN

Appendicitis affects approximately 250,000 people in the United States annually, with the highest incidence in children and young adults age 10 to 19.[1] It accounts for approximately one-third of pediatric

hospital admissions for abdominal pain and for nearly one-third of the total cost of all pediatric general surgical conditions.[11,12] A body of research is emerging to investigate antibiotic therapy as a safe and effective alternative to surgery for treatment of appendicitis in pediatric patients.

Most studies of antibiotic treatment of appendicitis in children and young adults are retrospective and involve relatively small numbers of patients.[13–17] Other trials have been prospective but nonrandomized, patient-preference cohort trials comparing nonoperative management with surgical control.[10,18–21] Most patients had nonperforated appendicitis.

Less disability and cost, but risk of recurrence

Antibiotic regimens vary in studies of children, but typically involve broad-spectrum intravenous agents during the initial hospitalization, with a course of oral amoxicillin-clavulanate or ciprofloxacin and metronidazole after discharge. Follow-up intervals of at least 1 year are common. From 20% to 36% of patients initially treated with antibiotics undergo subsequent appendectomy for persistent or recurrent symptoms. The presence of appendicolith in the appendix is associated with increased risk of failed nonoperative management.[10,13,19,20] Compared with appendectomy, the nonoperative groups have significantly fewer disability days[18] and lower hospital costs.[22]

In a meta-analysis that included many of these studies, complication-free success was higher with operative than with nonoperative management.[23] Among the authors' conclusions were the following:

- Nonoperative management for uncomplicated appendicitis does not increase the perforation rate significantly in those receiving antibiotics
- Nonoperative management may fail during the initial hospitalization in 8% of cases
- An additional 20% of patients may need a second hospitalization for recurrent appendicitis.

A meta-analysis by Maita et al[24] looked at 21 studies of nonoperative management in children with appendicitis. They concluded that 92% of patients had initial resolution of symptoms, and 16% of patients underwent appendectomy after discharge from the initial hospital stay. Complications and length of hospital stay did not differ significantly between those patients treated with antibiotics alone and those treated with surgery.

A randomized controlled pilot trial studied 50 patients age 5 to 15 who had imaging-confirmed nonperforated appendicitis.[25] Of these, 24 patients received antibiotic therapy alone with meropenem and metronidazole intravenously followed by ciprofloxacin and metronidazole orally. Treatment was initially successful in 22 patients (92%). At 1 year, however, the success rate had decreased to 62%, with appendectomy classified as failed management. A subsequent follow-up study showed that 46% of the patients treated with antibiotics for acute nonperforated appendicitis underwent appendectomy within a 5-year period, although only 17% of pathology specimens confirmed appendicitis histologically.[26]

The Midwest Pediatric Surgery Consortium studies

The Midwest Pediatric Surgery Consortium[27] designed and executed one of the most comprehensive studies for the nonoperative management of acute appendicitis in children, using a prospective controlled intervention design. Eligibility criteria included children between ages 7 and 17 diagnosed with uncomplicated appendicitis confirmed by imaging with the following specifications[27]:

- Ultrasonography showing hyperemia, appendix less than or equal to 1.1 cm in diameter, compressible or noncompressible, no abscess, no appendicolith, no phlegmon
- Computed tomography or magnetic resonance imaging showing hyperemia, fat-stranding, size less than or equal to 1.1 cm in diameter, no abscess, no appendicolith, no phlegmon
- White blood cell count greater than 5.0×10^9/L and less than or equal to 18.0×10^9/L
- Abdominal pain starting 48 hours or less prior to the start of antibiotics.[27]

Patients were excluded from the study if they had any of the following:

- History of chronic intermittent abdominal pain
- Diffuse peritonitis on physical examination by the surgical team
- Positive urine pregnancy test at time of diagnosis
- Appendicolith on imaging
- Evidence on imaging of evolving perforated appendicitis including abscess or phlegmon
- Difficulty communicating (eg, due to severe developmental delay).

Nonoperative management included hospital observation with a minimum of 24 hours of intravenous antibiotics—piperacillin-tazobactam or, in the presence of penicillin allergy, ciprofloxacin and metronidazole. Patients who tolerated a regular diet were switched to oral amoxicillin and clavulanate or, in the event of penicillin allergy, ciprofloxacin and metronidazole. Patients who tolerated a regular diet and oral therapy with minimal pain were discharged

home with a 7-day prescription for oral antibiotics.

Nonoperative management was determined to be a failure in patients who had persistent or worsening clinical or symptomatic status after receiving 24 hours of intravenous antibiotics or who returned after discharge with abdominal pain and a clinical evaluation consistent with appendicitis.

Of the 1,068 patients who participated, 370 (35%) chose nonoperative management.[28] The success rate for nonoperative management at 1 year was 67%. There was a statistically significant decrease in patient disability days at 1 year for patients who underwent nonoperative management compared with patients who underwent surgery (6.6 vs 10.9 days). The authors noted a 19% loss to follow-up at 1 year as a limitation, along with the nonrandomized study design.[28]

APPENDICITIS IN THE COVID-19 ERA

COVID-19 has raised new questions about the treatment of appendicitis. Numerous reports have identified multisystem inflammatory syndrome in children as a condition that mimics appendicitis and occurs with appendicitis.[29,30] Early in the pandemic, lockdown restrictions were associated with changes in the incidence of appendicitis. One study found a dramatic decrease in the number of patients presenting with appendicitis in 2020,[31] with the authors considering whether the decrease could be attributed to altered social factors or environmental influences.

COVID-19 outbreaks can affect appendicitis treatment decisions

Limited inpatient resources during COVID-19 outbreaks resulted in some centers shifting to nonoperative management of appendicitis. In a multicenter study, pediatric patients presenting with appendicitis in a major metropolitan area from March through May 2020, corresponding with a peak COVID-19 outbreak in that region, were compared with historical control patients.[32] Control variables were collected from the same institutions for the preceding 5 years. In 55 children presenting with acute appendicitis over the 10 weeks in 2020, the perforation rate was 45% compared with a rate of 27% in the controls. There were no differences in perforation rates or length of stay between COVID-positive and COVID-negative children. Investigators postulated that disruption of local healthcare delivery systems by the pandemic may continue to impact conditions for which outcomes reflect the timeliness of care.[32]

A separate retrospective study evaluated nonoperative management of acute appendicitis during the same spring 2020 COVID-19 peak.[33] The investigators used the protocol established by the Midwest Pediatric Surgery Consortium,[27] but they expanded inclusion criteria to include all patients with acute appendicitis. Patients who demonstrated improvement were discharged home promptly on oral antibiotics. The authors found that 78.2% of patients treated were outside the Midwest Pediatric Surgery Consortium guidelines for inclusion, but 45.5% (25/55) were treated successfully with antibiotics within a short-term follow-up interval.[33]

CONCLUSIONS AND RECOMMENDATIONS FOR PEDIATRIC PATIENTS

Recent studies of appendicitis management in pediatric patients show that pediatric patients with appendicitis can be treated safely with antibiotics alone, but that nonoperative management will fail within 1 year in up to one-third of patients. The presence of appendicolith is associated with increased risk of failure of nonoperative management.

In our view, appendectomy should remain the routine choice of therapy for appendicitis in pediatric patients. At the time of diagnosis, pediatric patients have a longer life expectancy than adult patients and therefore an increased likelihood of developing recurrent appendicitis if treated nonoperatively at the initial presentation.

Questions that need to be addressed in clinical studies include the risks associated with repeated radiologic studies in patients whose nonoperative management was unsuccessful and whose symptoms recur, and the possibility that a neuroendocrine tumor within the appendix is causing acute appendicitis.

Surgeons and patients together will continue to decide whether the risk for recurrent appendicitis with nonoperative management outweighs the risks of surgery, and whether the benefit of fewer disability days and decreased hospital costs seen in nonoperative management is great enough to influence how appendicitis is managed in the future.

DISCLOSURES

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