

CLINICAL PRACTICE

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Acute Appendicitis — Appendectomy or the “Antibiotics First” Strategy

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations.

A 56-year-old man presents with a 2-day history of abdominal pain. The pain began centrally but has moved to the right lower quadrant of his abdomen in the past 6 hours. He has a body-mass index (the weight in kilograms divided by the square of the height in meters) of 33, a body temperature of 100°F (37.8°C), and a white-cell count of 11,500 per cubic millimeter. The right side of his lower abdomen is tender to palpation. A computed tomographic (CT) scan was ordered by his primary care physician after he was examined in the clinic, and the results are consistent with appendicitis. He has had three prior surgical procedures: an open Nissen fundoplication complicated by a pulmonary embolism and two incisional hernia repairs with mesh. After receiving the results of his CT scan, he found information online about doctors in Europe who are using antibiotics alone to treat appendicitis, and he asks specifically about that option. How would you manage this case?

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THE CLINICAL PROBLEM

Approximately 300,000 people undergo appendectomy each year in the United States, with an estimated lifetime incidence of appendicitis that ranges from 7 to 14%, on the basis of sex, life expectancy, and the precision with which the diagnosis is confirmed.^{1,2} After accounting for the appendectomies in patients who do not have appendicitis (so-called negative appendectomies), many have used the rate of appendectomy as a surrogate for the rate of appendicitis. Although the incidence of appendectomy is similar in men and women, men have a higher incidence of appendicitis.³

The use of advanced imaging and laparoscopy may have increased the number of patients with the diagnosis,⁴ a certain proportion of whom may have a resolution of symptoms without appendectomy or may never have progression to clinical appendicitis.³ The “overdiagnosis” of what might otherwise be self-resolving appendicitis was suggested by a trial⁵ involving patients with nonspecific abdominal pain who were randomly assigned to either early laparoscopy or watchful waiting. Appendicitis was identified in approximately 30% of the patients in the laparoscopy group as compared with less than 6% of the patients in the observation group, findings that call into question the clinical importance of the additional cases identified by means of laparoscopy.

PATHOPHYSIOLOGY

A better understanding of the pathophysiology of appendicitis is important in evaluating the potential of an antibiotics-first treatment strategy. Appendicitis has



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KEY CLINICAL POINTS

ACUTE APPENDICITIS

- Appendicitis is the most common reason for emergency abdominal surgery, with a lifetime incidence of 7 to 14%.
- As compared with open appendectomy, laparoscopic appendectomy is associated with a reduced risk of surgical-site infection, a faster return to function, and a reduced risk of subsequent bowel obstruction.
- Several small, randomized trials comparing an antibiotics-first strategy (with appendectomy performed if patients do not have a response) with prompt appendectomy in patients with uncomplicated appendicitis showed no significant increase in complications with an antibiotics-first approach but also showed a substantial rate of crossover to surgery in the first 48 hours or appendectomy in the ensuing year.
- Appendectomy is still recommended for most people with uncomplicated appendicitis, but patients should be informed about options, and an antibiotics-first strategy may be considered in those who have strong preferences for avoiding an operation or who have contraindications to surgery.

historically been thought to result from luminal obstruction with a fecalith, distention, bacterial overgrowth, increased intraluminal pressure, and progressive tissue compromise with gangrene and perforation.⁶ However, a more recent study measuring the luminal pressure in patients with appendicitis has shown increased pressure in only a quarter of the patients.⁷ Similarly, in one study, fecaliths were identified in only 18% of the patients with appendicitis (and in 29% of those without appendicitis).⁸ Growing evidence also suggests that perforation is not necessarily the inevitable result of appendiceal obstruction. Perforated appendicitis and nonperforated appendicitis appear to be different entities,³ with perforation occurring more commonly in patients with altered inflammatory responses or alterations in the colonic microbiome.⁹

STRATEGIES AND EVIDENCE

DIAGNOSIS

The diagnosis of appendicitis is supported by a history of abdominal pain that begins in the central abdomen and migrates to the right lower quadrant, tenderness to palpation on physical examination of that area, nausea or vomiting, mild leukocytosis, and low-grade fever, but these features are inconsistently present, and fewer than 50% of patients may have all these features.¹⁰ In a study involving patients with abdominal pain in whom appendicitis was suspected (but ultrasonography was nondiagnostic), the strongest predictors of appendicitis were migration of pain to the right lower quadrant (odds ratio, 3.4; 95% confidence interval [CI], 1.5 to 7.8) and vomiting

(odds ratio, 5.4; 95% CI, 2.4 to 12.4).¹⁰ The use of diagnostic imaging, most often CT (Fig. 1) or ultrasonography, can minimize the risk that a diagnosis will be missed and can reduce the rate of unnecessary appendectomy.¹¹ Although the reported sensitivities and specificities of imaging tests for appendicitis vary widely across studies, both the sensitivity and specificity of CT, with or without oral contrast, are high (>90%)¹² and are superior to those of ultrasonography; in addition, the sensitivity and specificity of CT are more consistent among centers than are those of ultrasonography, for which the sensitivity ranges from 44 to 100% and the specificity from 47 to 99%.¹³ Magnetic resonance imaging has performance characteristics that are similar to those of CT,¹⁴ but because of the added cost, its use is best limited to patients who should not be exposed to radiation and in whom the performance of ultrasonography may be challenging, such as those who are pregnant.¹⁵

The use of the Alvarado scoring system,^{16,17} which includes clinical examination findings and laboratory values, is helpful in ruling out appendicitis (Table 1). Scores range from 1 to 10, with higher scores indicating a greater risk of appendicitis. When the score is less than 4, appendicitis is uncommon, and imaging and other interventions can be avoided.^{18,19} When imaging is used, high-quality ultrasonography should be considered a first approach, but only in practice settings where its accuracy is sufficiently high. If high-quality ultrasonography is not available or if ultrasonography fails to visualize the appendix, CT with lower-dose radiation protocols is often used. In practice settings in which high-quality diag-

nostic testing is not available or when radiation is a particular concern (e.g., during the first trimester of pregnancy), a strategy of watchful waiting may be appropriate. Among higher-risk patients (e.g., those with compromised immune function) with suspected appendicitis, in whom watchful waiting may be problematic, laparoscopy can also be performed to establish the diagnosis and remove the appendix, if needed.

SURGICAL TREATMENT

Urgent appendectomy has been the mainstay of treatment for appendicitis since the late 1800s, with a major advance made in the 1990s, when the use of the laparoscopic approach was suggested instead of the more conventional approach involving incision in the right lower quadrant (“open” procedure).²⁰ In the United States, appendectomy is performed laparoscopically in 60 to 80% of cases, with hospitalization lasting an average of 1 to 2 days and a rate of complications of 1 to 3%.^{21,22} The laparoscopic approach is contraindicated in patients for whom inflation of the abdominal cavity with gas is contraindicated, most commonly because of cardiopulmonary conditions. Most of the open procedures that are performed in the United States were initiated laparoscopically but were converted to the open approach because of technical limitations, body habitus, prior surgery, more advanced disease, or surgical inexperience.^{22,23}

A large, national cohort study showed a rate of skin infection of 3.3% after laparoscopic appendectomy versus 6.7% after open appendectomy, and a median length of hospitalization of 1 day after either procedure.²⁴ A systematic review of trials of laparoscopic and open appendectomy showed that the incidence of skin infection was more than 50% lower with the laparoscopic approach (odds ratio, 0.43; 95% CI, 0.34 to 0.54), and the hospital stay was 1.1 days shorter (95% CI, 0.7 to 1.5).²⁵ Unblinded assessments have shown that the laparoscopic approach is associated with less postoperative pain, but in a study in which patients were unaware of whether they had undergone a laparoscopic procedure or an open procedure, differences in pain between the groups were minimal.²⁶ The supplies used in the laparoscopic approach result in initially higher costs than those used in an open procedure, but formal cost-effectiveness assessments, which took into account these costs as well as the shorter hospi-

Table 1. Alvarado Score for Acute Appendicitis.*

Component	Possible Points
Symptoms	
Migration of pain to the right lower quadrant	1
Anorexia	1
Nausea or vomiting	1
Signs	
Tenderness in the right lower quadrant	2
Rebound pain	1
Elevated temperature	1
Laboratory findings	
Leukocytosis	2
Left shift†	1
Total score	10

* Points are ascribed to each symptom, sign, and laboratory finding; patients with a score of less than 4 are unlikely to have appendicitis.

† A left shift is an increase in levels of immature neutrophil forms circulating in the peripheral blood.

talization and quicker recovery associated with the laparoscopic approach, favored the laparoscopic approach.²⁷

Although it has been routine practice to perform appendectomy promptly after diagnosis, the value of early appendectomy has been called into question. In a statewide cohort of adult patients undergoing appendectomy, the time between evaluation in the emergency department and surgery was not a predictor of the risk of perforation.²⁸ These data raise questions about performing urgent appendectomy with the goal of preventing perforation. Another observational study similarly showed that a longer wait time to surgery was not associated with a higher risk of perforation but was associated with a higher risk of surgical-site infection.²⁹

AREAS OF UNCERTAINTY

A major uncertainty in the management of appendicitis is whether an appendectomy is needed or whether antibiotics alone, with an appendectomy performed only if the appendicitis does not resolve (an “antibiotics first” strategy), is a reasonable alternative. The treatment of appendicitis with an antibiotics-first strategy was historically reserved for patients who were many days into an inflammatory process, with phlegmon and perhaps an abscess. Currently, a course of intra-

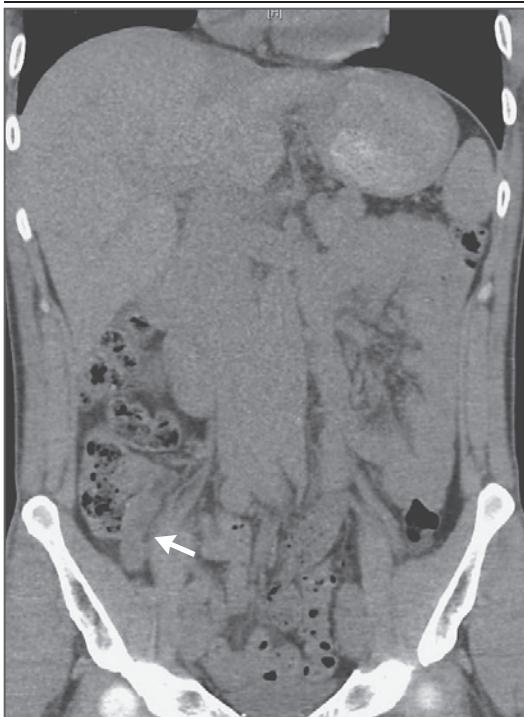


Figure 1. Computed Tomographic (CT) Image of Appendicitis.

A coronal CT reconstruction shows a blind-ending tubular structure in the right lower quadrant measuring 10 mm (arrow) with surrounding fat stranding, findings consistent with acute appendicitis.

venous antibiotics is administered in these patients, and drainage of the abscess is performed in an attempt to avoid a more extensive operation,³⁰ potentially involving an ileocecectomy or ileostomy. Success with an antibiotics-alone approach in Navy personnel in whom appendicitis developed while they were at sea (and did not have access to an operating room) supports this strategy in patients with uncomplicated appendicitis as well.³¹ Subsequently, several randomized trials³²⁻³⁷ compared appendectomy with an antibiotics-first strategy (with appendectomy as needed) for uncomplicated appendicitis and showed that most patients in the antibiotics-first group were able to avoid appendectomy. The rate of crossover to surgery within 48 hours after the initiation of antibiotics ranged among trials from 0 to 53%. Because the studies used different criteria to trigger a crossover, this variability suggests substantial heterogeneity of treatment effect across patients or variation in clinicians' willingness to adhere to the antibiotic approach.

Clinical outcomes among patients randomly assigned to the antibiotics-first strategy were generally favorable, but the metrics of success were inconsistent (including reduction in white-cell count,³³ avoidance of peritonitis,³⁷ and general symptom reduction),³⁴⁻³⁶ and several trials had very small samples (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). As compared with patients assigned to undergo prompt appendectomy, patients assigned to the antibiotics-first strategy had lower or similar pain scores,^{33,36,37} required fewer doses of narcotics,³³ and had a quicker return to work,^{33,36} but these outcomes were not assessed in all the studies. Perforation rates were not significantly higher among patients assigned to the antibiotics-first approach; unexpectedly, in two trials,^{35,36} the appendectomy-first group had a significantly higher rate of perforation than the antibiotics-first groups.

Eventual appendectomy after initial, successful treatment with antibiotics occurred in 10 to 37% of the patients randomly assigned to the antibiotics-first strategy (mean time to appendectomy, 4.2 to 7 months in the three studies in which this outcome was reported^{33,34,37}). Data from longer follow-up periods were unavailable, and therefore it is unclear whether the likelihood of appendectomy continued to increase or stabilized over time. In one report that included information on subsequent surgical pathological results,³⁷ 13% of the patients who underwent later appendectomy (after initially successful treatment with an antibiotics-first strategy) did not actually have appendicitis; thus, the true rate of recurrent appendicitis is unknown. A population-based study that used administrative data on hospitalizations in California showed that 5.9% of the patients who had a diagnostic code for appendicitis (but not appendectomy) at the index admission underwent an appendectomy within 30 days after discharge from the hospital, and only 4% had a repeat hospitalization for appendicitis in the subsequent years (median follow-up, 7.4 years; median time to repeat hospitalization, 1.9 years).³⁸

The randomized trials involved a range of interventions and durations of treatment. A typical protocol (Table 2) included 48 hours of intravenous antibiotics while the patient was in the hospital, followed by 7 days of oral antibiotics that are sensitive to the typical organisms found

Table 2. Common Features of Randomized Clinical Trials of “Antibiotics First” Regimens.

- Eligible patients are consenting adults who are not pregnant, do not have compromised immune function, and do not have certain implantable devices.
- Patients have no evidence of abscess or perforation on imaging.
- Patients have no evidence of sepsis or disseminated peritonitis on clinical examination.
- Patients are admitted to a hospital, and intravenous antibiotics are administered for 48 hours.
- Patients are assessed at intervals of 6–12 hours for progression of symptoms or development of sepsis.
- Patients begin oral intake of food; when pain is well controlled, patients are discharged home with 7 days of oral antibiotics.
- A patient proceeds to surgery if sepsis or shock, worsening fever, or disseminated peritonitis develops or if by 48 hours the patient’s pain or elevated white-cell count is not reduced or the patient is unable to eat.

in intraabdominal infection (e.g., ciprofloxacin and metronidazole), and did not include repeat imaging to confirm resolution of appendicitis. In some studies, patients were given oral antibiotics while in the hospital if they did not have unacceptable side effects. Given the low rates of adherence to antibiotic regimens for many health conditions, it remains to be determined whether the “real world” results of an antibiotics-first strategy will match those of the randomized, controlled trials. Moreover, all these studies were performed in Europe, and the fact that surgical patients more often underwent “open” appendectomy (34 to 82%), with an associated longer duration of hospital stay after surgery (mean, approximately 3 days) than is typical in the United States, limits extrapolation of the results to the United States. All the studies excluded patients with signs of perforation or sepsis and those who were pregnant or had compromised immune function, and one study excluded women,³⁴ further limiting generalizability.

Questions remain about whether complications related to delayed surgery; the number of days of antibiotic therapy; the amount of time spent in the hospital, doctors’ offices, and emergency departments (Table S1 in the Supplementary Appendix); anxiety about future episodes of abdominal pain; and total costs of care differ substantively between treatment options. Furthermore, factors associated with a higher risk of recurrence are unclear, and it is not currently possible to identify patients who should be directed to surgery or offered an antibiotics-first strategy. Large, multicenter trials in the United States are needed to address clinical and patient-reported outcomes of an antibiotics-first approach, as compared with prompt appendectomy. To determine whether the antibiotics-first approach is

“as good as” prompt appendectomy for uncomplicated appendicitis, the success in avoiding immediate appendectomy needs to be balanced against any increase in the length of hospitalization related to a delayed, rescue appendectomy, the fear and burden of recurrence, and any differences in the rate of complications and the quality-of-life effect of the two approaches.

The costs of the two strategies have not been directly compared except in small studies from Turkey (which compared all costs, including the cost of readmission for the patients who followed an antibiotics-first strategy)³⁵ and Sweden (which compared costs associated with the initial hospitalization only)³⁶; both studies showed higher total costs of care with prompt appendectomy. However, multiple rehospitalization events that result in an eventual appendectomy, potential differences in rates of complications related to the antibiotics-first approach, the cost of missed work, and the cost of caregiver support also require consideration in comparing the costs of these two approaches.

Another factor potentially relevant to the assessment of benefits and risks of appendectomy is the question of whether the appendix has an active physiological function or is simply a vestigial organ. The observation that the appendix appears to have evolved independently of the cecum across many species supports a possible functional role.³⁹ Bacteria sequestered in the appendix may act as a “safe house,” repopulating the gut with healthy bacteria after massive diarrheal disease. For example, recurrence of *Clostridium difficile* infection (although not primary *C. difficile* infection⁴⁰) is significantly more common among patients with a history of appendectomy than among those with an intact appendix.⁴¹

GUIDELINES

The American College of Surgeons,⁴² the Society for Surgery of the Alimentary Tract,⁴³ and the World Society of Emergency Surgery⁴⁴ all describe appendectomy (either laparoscopic or open) as the treatment of choice for appendicitis. Regarding an antibiotics-first strategy, the American College of Surgeons patient information guide indicates that it “may be effective, but there is a higher chance of reoccurrence”⁴²; the Society for Surgery of the Alimentary Tract patient care guidelines suggest that it is “not a widely accepted treatment”⁴³; and the World Society of Emergency Surgery states that “this conservative approach features high rates of recurrence and is therefore inferior to the traditional appendectomy. . . . Non-operative antibiotic treatment may be used as an alternative treatment for specific patients for whom surgery is contraindicated.”⁴⁴ The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has clinical symptoms and signs consistent with acute appendicitis, and the diagnosis was confirmed by diagnostic imaging. In the United States, the usual treatment recommendation for people with uncomplicated appendicitis is a prompt appendectomy. The laparoscopic approach is preferred to the open approach by most surgeons (owing to a lower incidence of surgical-site infection and a faster return for the patient to usual activities) in the absence of contraindications to laparoscopy. However, experience in Europe suggests that an antibiotics-first strategy is an alternative that warrants consideration, particularly in a patient who has had prior surgical complications and

has a strong preference for avoiding appendectomy. Patients should understand that European randomized trials comparing this approach with appendectomy have shown that it is not associated with an increased risk of perforation or a higher rate of complications; however, these trials have also shown that as many as half the patients so treated will have early treatment failures, and all have a risk of recurrent appendicitis that may ultimately require appendectomy.

It remains to be determined whether the benefits of potentially avoiding an operation with the antibiotics-first approach are outweighed by the burden to the patient related to future appendicitis episodes, more days of antibiotic therapy, lingering symptoms, and uncertainty that may affect quality of life. This is especially true given that appendectomy, as performed in the United States, has a very favorable safety profile and typically involves a short hospitalization. Although appendectomy remains the recommended treatment for appendicitis, clinicians should inform appropriate patients about the evidence related to an antibiotics-first strategy, as well as the uncertainties. I recommend that, pending more information regarding the effectiveness of an antibiotics-first approach and the longer-term outcomes of this strategy, patients interested in considering an antibiotics-first approach should be encouraged to participate in clinical trials. When an antibiotics-first strategy is used outside a clinical trial, I would encourage treating physicians to include their experience in a patient registry (see the Supplementary Appendix).

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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