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Controversies in Appendicitis*

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Abstract

Background: Appendectomy for appendicitis is a common operation that is performed by most general surgeons. Despite the large number of appendectomies, numerous management controversies continue.
Methods: Review of the pertinent English language literature.
Results: Controversy persists regarding the use of imaging studies for diagnosis, laparoscopic vs. open surgical methods, nonoperative management of uncomplicated appendicitis, delayed management of the patient with phlegmon from severe appendicitis, the necessity for interval appendectomy, and the merits of deferral of off-hour appendectomy until the following morning. This review identifies the published reports that support the pros and cons of each controversy.
Conclusions: Class I data generally are lacking to support the resolution of these controversies. Additional well-controlled clinical trials are necessary to obtain definitive answers.

Despite the fact that appendicitis is a common disease, with approximately 250,000 appendectomies performed annually in the United States [1], controversies continue regarding its optimal diagnosis and management, several of which are discussed with a review of the literature.

Diagnosis

Clinical scenario: A 16 year-old previously healthy male patient presents at 12:00 AM with < 24 h of abdominal pain, now localized to the right lower quadrant, associated with fever, nausea, and vomiting. Physical examination reveals tenderness at McBurney point. The white blood cell (WBC) count is 15,000 /mm^3. Should routine imaging be performed for suspected uncomplicated acute appendicitis?

Controversy exists regarding the optimal diagnostic strategy for uncomplicated acute appendicitis: (1) Clinical history and physical examination alone; (2) selective imaging in patients with intermediate clinical suspicion; and (3) routine imaging of all patients. The main proposed benefit of routine imaging is a decrease in the misdiagnosis of appendicitis, resulting in fewer negative appendectomies. Routine imaging may theoretically either increase or decrease perforations attributable to delay in diagnosis, depending on the effect on the time to the operating room. Furthermore, imaging is not without complications such as allergic reactions, contrast-induced nephrotoxicity, and radiation exposure associated with computed tomography (CT).

Multiple retrospective studies (n > 300 patients) suggest that use of CT in particular may decrease the negative appendectomy rate without an increase in the perforation rate [2-4]. However, a population-based analysis of 63,707 nonincidental appendectomies by Flum et al. demonstrated no improvement in these rates with preoperative imaging [5]. Despite a significant increase in the percentage of patients who received either CT or ultrasound scans, the authors identified no change in the rate of ruptured appendices or misdiagnosed appendicitis over a 10-year period from 1987 to 1997 [5, 6]. The authors speculated that the lack of benefit from preoperative imaging may have been attributable to the rate of false-positive tests (21.7% for CT and 20.8% for ultrasonography), which was higher in this analysis than in single-institution studies [6]. Furthermore, the authors noted that the advent of laparoscopy did not reduce the rate of negative appendectomy. In fact, laparoscopy was associated with a higher rate of misdiagnosis than open surgery among women of reproductive age [5].

Observational cohort studies and analyses of administrative databases are subject to multiple biases, namely confounding and selection bias. However, there is a paucity of randomized trials for diagnosing acute appendicitis that evaluate outcome according to imaging strategy. Hong et al. randomized 182 adults with intermediate probabilities of having appendicitis, defined as an Alvarado score of 2 to 8 [7] (Table 1), to either clinical assessment or mandatory CT scan [8]. The diagnostic accuracy was similar for the strategies—90% for clinical assessment and 92% for CT. Although the length of time from presentation to the operating room

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TABLE 1. ALVARADO SCORE FOR PREDICTING ACUTE APPENDICITIS

Sign/symptom	*Score*
Migration of pain	1
Anorexia	1
Nausea–vomiting	1
Tenderness in right iliac fossa	2
Rebound pain	1
Temperature ≥ 37.3°C	1
Leukocytosis > 10,000/mm^3	2
Neutrophils ≥ 75%	1
Total	10

From reference 7.

was significantly longer in the CT group, there was no difference in overall length of stay (LOS), hospital charges, or perforation rates in the two groups. The trial enrolled more patients than the predetermined sample size, but the power was determined using predicted accuracies of 95% for CT and 80% for clinical judgment. Thus, the trial was powered only to detect a 15% or greater difference in accuracy between the groups, and may have been underpowered to detect a difference in perforation rates. Additionally, the authors did not perform an intention-to-treat analysis, excluding 33 patients from analysis. Nonetheless, the strength of this trial was the standardization of criteria for obtaining a preoperative CT scan. Further modification of these criteria may be necessary given the crossover between the arms.

Lee et al. performed a randomized trial of selective vs. mandatory imaging in adults with suspected acute appendicitis [9]. The investigators did not standardize the criteria for selective imaging, but rather left the decision to the discretion of the examining physicians. The strategy of mandatory imaging resulted in more CT scans but decreased rates of negative appendectomies (3% vs. 14%; 95% confidence interval [CI] for the difference −3.5%, 26.3%) and perforation (10% vs. 18%; 95% CI −8%, 24%) compared with selective imaging. The observed differences were not statistically significant, but the trial was not powered to detect a difference smaller than 15% in negative appendectomy rates. There was no difference in the time to operative intervention in the two groups, although patients who did not receive a CT scan went to surgery faster. Despite the differences in negative appendectomy and perforation rates, the authors did not advocate mandatory imaging for all patients with suspected appendicitis but concluded that further, larger trials would be required to determine if there is a subset of patients who may benefit from routine imaging.

In the absence of definitive data from other randomized trials, a practical approach to determining the utility of preoperative imaging is to base the decision on the pre-test probability of acute appendicitis and the likelihood ratio (LR) of the imaging test. The LR describes how much the odds of having the disease increase if the test is positive (LR+) or negative (LR−), and is calculated from the sensitivity and specificity of the test. A positive LR test is defined as the ratio of the sensitivity: (1 − specificity), and LR− is defined as (1 − sensitivity): specificity. Table 2 illustrates the positive and negative LRs for CT and ultrasonography in adults and children calculated from a meta-analysis [10]. The post-test probability of having appendicitis can then either be calculated or determined using an LR nomogram (Figs. 1 and 2).

Take, for example, a patient with a high pre-test probability (e.g., 95%), according to the history and physical examination, of having acute appendicitis (Fig. 1). A positive CT scan, which has an LR+ of 16, increases the post-test probability to greater than 99%. A negative CT scan, which has an LR− of 0.06, reduces the post-test probability to 53%. A post-test probability of greater than 50% may still warrant operative intervention even with a negative CT scan. Thus, given that the original clinical suspicion was high, the surgeon is unlikely to change his/her management strategy on the basis of the findings of the scan.

On the other hand, if the pre-test probability of acute appendicitis is 50%, the results of a CT scan may change the management strategy (Fig. 2). A positive CT scan would increase the post-test probability to 94%, whereas a negative scan would decrease the probability to 6%. Thus, preoperative imaging determines the management strategy when the pre-test probability is in the intermediate range. Although systems are available for determining the likelihood of appendicitis, such as the Alvarado score [7], there are no widely accepted criteria for accurate determination of the pre-test probability of acute appendicitis.

In summary, the role of imaging in diagnosing acute uncomplicated appendicitis is yet to be determined. Despite the high sensitivity and specificity of CT and ultrasonography, particularly CT, an increase in the use of imaging has not

TABLE 2. SENSITIVITY AND SPECIFICITY OF CT AND ULTRASONOGRAPHY IN ADULTS AND CHILDREN

Imaging	*Sensitivity (%)*	*Specificity (%)*	*Positive likelihood ratio*[a]	*Negative likelihood ratio*
CT, adults	94	94	16	0.06
Ultrasonography, adults	83	93	12	0.2
CT, children	94	95	19	0.06
Ultrasonography, children	88	94	15	0.1

[a]Likelihood ratios for positive and negative test results are calculated using the following formulas:

$$LR+ = \frac{Sensitivity}{(1 - Specificity)}$$

$$LR- = \frac{(1 - Sensitivity)}{Specificity}$$

Data from reference 10.

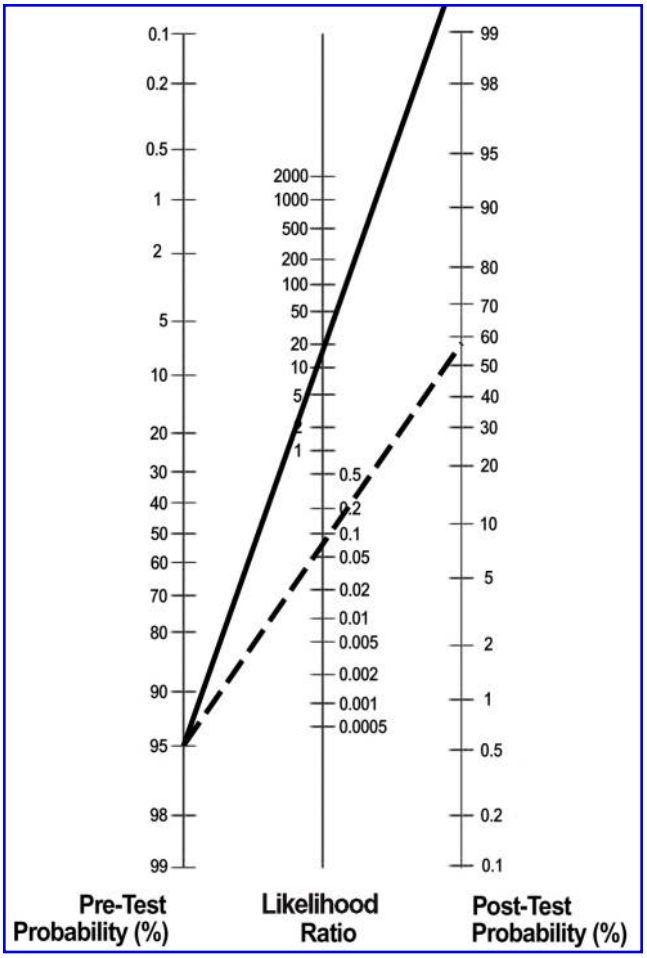

FIG. 1. Pre-test probability and likelihood ratio can be used to calculate post-test probability. First, pre-test probability must be converted to pre-test odds, which is equivalent to pre-test probability divided by (1 – pre-test probability). Multiplying the pre-test odds by the likelihood ratio (LR) results in the post-test odds, which can be converted to post-test probability. Post-test probability is equivalent to the post-test odds divided by (1 + post-test odds). In a patient with a pre-test probability of 95% of having acute appendicitis, positive CT scan (LR+ = 16) increases post-test probability to > 99% (solid line). A negative CT scan (LR− = 0.06) reduces post-test probability to 53% (broken line).

reduced the incidences of misdiagnosis or perforation in adults. Ultimately, the utility of preoperative imaging in guiding management strategy depends on the accurate assessment of the pre-test probability of having acute appendicitis. Further study is necessary to characterize those patients with an intermediate probability who may benefit most from scanning.

Management

Clinical scenario: A 16 year-old, previously healthy male patient presents with 36 h of abdominal pain associated with fever, nausea, and vomiting. Examination reveals tenderness at McBurney point and localized peritoneal signs. The white blood cell count is 25,000/mm^3. The decision is made to operate for acute appendicitis. Should patients with suspected acute appendicitis undergo laparoscopic or open appendectomy? Does the approach differ for uncomplicated vs. perforated acute appendicitis?

Once the decision has been made to operate on a patient with suspected appendicitis, the operative approach itself is controversial. The theoretical advantages of laparoscopic appendectomy (LA) over open appendectomy (OA) include smaller incisions with better cosmesis and fewer incisional complications, faster recovery with shorter hospital LOS and earlier return to work, and less pain. Suggested disadvantages of LA include longer operating room time and higher costs. Multiple randomized trials have been performed, but many contain methodological flaws such as inadequate allocation concealment, lack of reporting of randomization method, failure to blind the patient or healthcare provider, lack of analysis by intention-to-treat, and incomplete follow up data [11, 12].

A 2004 Cochrane review of 54 studies comparing LA with OA, of which 45 enrolled adults, demonstrated a significant reduction in surgical site infections (OR 0.45; 95% CI 0.35, 0.58) with LA. This estimate was derived from more than 5,000 patients; despite differences in laparoscopic technique, no significant heterogeneity of results was identified. Lapa-

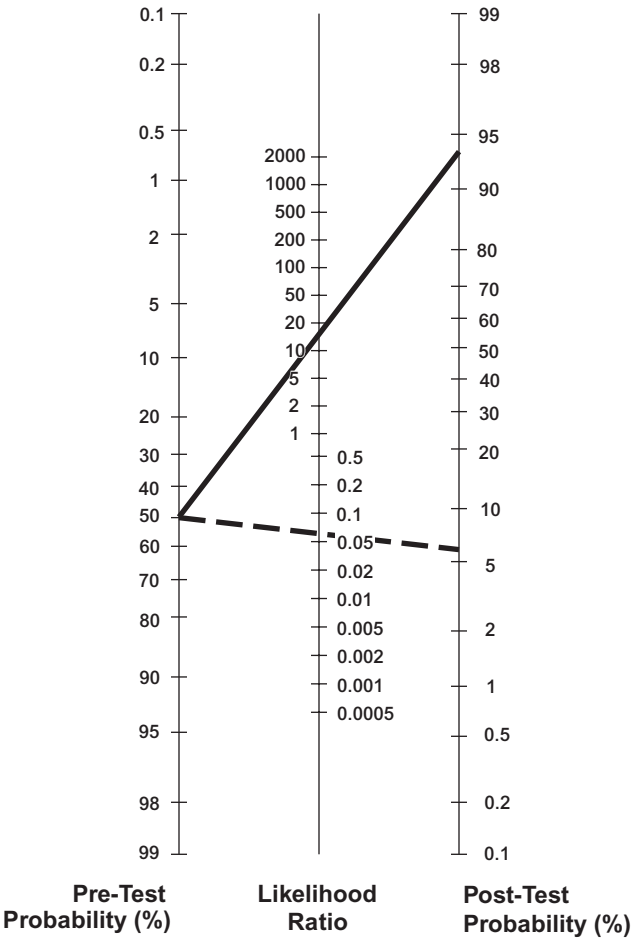

FIG. 2. In patient with intermediate pre-test probability (50%) of having acute appendicitis, positive CT scan increases post-test probability to 94% (solid line). Negative CT scan reduces post-test probability to 6% (broken line). Therefore, preoperative CT scan may change clinical management.

roscopic appendectomy was associated with a hospital stay shorter by 1.1 days (95% CI 0.6, 1.5 days), less pain on the first postoperative day of 9 points of 100 on a visual analog scale (95% CI 5, 13), and a faster return to normal activity by 6 days (95% CI 4, 8 days) [11]. However, LA was associated with longer operative time by 12 minutes (95% CI 7, 16 minutes) and higher operation and hospital costs (point estimate not calculated). There was significant heterogeneity in these analyses, and the authors noted decreasing differences in operative times between LA and OA in recent years. However, LA was associated with a higher risk of postoperative intra-abdominal abscess (OR 2.48; 95% CI 1.45, 4.21). The conclusions were that LA is preferred where the technical and surgical expertise is available.

A 2007 meta-analysis of 34 studies comparing LA with OA included a subgroup analysis of earlier vs. later studies [12]. The meta-analysis confirmed the findings of fewer surgical site infections (OR 0.52; 95% CI 0.39, 0.70) and shorter hospital LOS (0.62 days; 95% CI 0.18, 1.05 days) with LA. Comparison of pre- and post-2000 studies demonstrated a reduction in the difference in operative time from a mean of 20.3 min (95% CI 13.0, 27.4 minutes) to 4.9 min (95% CI 0.24, 9.55 minutes). Costs were not assessed. As reported in the Cochrane review, intra-abdominal abscesses were more common with LA; the risk actually increased in studies published after 2000. Whether greater experience with laparoscopy was accompanied by an increase in LA for perforated appendicitis, which is associated with intra-abdominal abscesses, is unknown. The authors concluded that LA was safe and effective, but that open surgery still conferred benefits, in particular, with regard to the likelihood of postoperative intra-abdominal abscess.

In summary, LA is associated with fewer incisional complications and shorter LOS than OA. With increased experience, operative times are becoming comparable. Whether in-hospital costs are tempered by savings as a result of a faster return to work and fewer incisional complications has not been evaluated formally by cost-effectiveness analysis. Further trials of LA for suspected perforated appendicitis are necessary, given the potential increase in intra-abdominal abscesses.

Does Suspected Uncomplicated Acute Appendicitis Mandate Appendectomy?

Clinical scenario: A 16 year-old previously healthy male patient presents with three days of abdominal pain associated with fever, nausea, and vomiting. Examination reveals tenderness at McBurney point. The WBC is 20,000/mm^3. A CT scan of the abdomen and pelvis reveals a right lower quadrant phlegmon and a dilated, non-filling appendix with an appendicolith. Should early or delayed appendectomy be performed for complicated acute appendicitis? Is interval appendectomy necessary after complicated acute appendicitis?

Until recently, appendectomy was accepted as the standard of care for uncomplicated acute appendicitis. In 1995, Eriksson and Granstrom published the results of the first randomized trial of antibiotics vs. surgery [13]. In this pilot trial in 40 patients, one patient treated with antibiotics required operation during the first admission for peritonitis, whereas seven patients were re-admitted within one year with recurrent appendicitis that necessitated surgery. Styrud et al. published the results of a subsequent multi-center randomized trial of 252 men between the ages of 18 and 50 with suspected non-perforated acute appendicitis [14]. Fifteen patients (12%) randomized to the antibiotic arm required operation within the first 24 h for local peritonitis and failure to improve, and 16 patients (15%) had recurrences within a year. The surgical group had a 14% complication rate (17 patients), largely SSIs, whereas the antibiotic group had a 3% rate (four patients) of complications from surgery after failing non-operative therapy. There was no difference in the initial hospital LOS. The authors concluded that acute non-perforated appendicitis could be treated non-operatively with antibiotics.

Critics of this trial cite several methodological flaws [15]. First, the authors did not define their primary outcome measure; they compared the 14% complication rate in the surgical group with the 15% recurrence rate in the antibiotic group and reported no statistical difference. They did not include the patients who required operative intervention within the first 24 h in the antibiotic group (12%) as a failure of non-operative therapy. Also, the authors did not report the basis for their sample size calculations; thus, the power of the trial to detect a difference in complication rates was questioned. Additionally, the results lack external validity, given that women and patients older than 50 years of age were excluded. Furthermore, only 6% of the patients underwent LA, which is associated with fewer SSIs, limiting generalization of the trial results to current practice, where laparoscopy is more common.

Farahnak et al. performed a randomized pilot comparison of a protocol for treating acute appendicitis on the basis of the Alvarado score with conventional therapy [16]. The protocol consisted of discharge from the hospital for an Alvarado score of 0–4 points, antibiotic treatment for 5–7 points, and appendectomy for 8–10 points. Twenty-one patients were randomized to each group. There was no difference in non-therapeutic appendectomies or perforation with the protocol, but there was a significant decrease in hospital LOS and time to surgery in patients undergo appendectomy. Most of the patients who underwent appendectomy had an Alvarado score of 8–10 points in both the case and control groups. Additionally, the majority of patients who received antibiotics for a score of 4–7 points may not have had appendicitis; only one of nine patients underwent an operation that confirmed the diagnosis. Thus, conclusions regarding the safety and efficacy of antibiotics for the treatment of appendicitis are not possible. Furthermore, as a pilot, the trial was underpowered to detect a difference in negative appendectomy or perforation rates, and recurrent appendicitis was not a measured endpoint. However, the trial was designed to be exploratory in order to obtain sample size estimates for a larger trial.

Despite their flaws, these are the only published randomized trials evaluating antibiotics without surgery for suspected uncomplicated acute appendicitis. Currently, one observational trial and two randomized trials in patients over 18 years of age with suspected appendicitis are recruiting subjects (www.clinicaltrials.gov). Thus, whereas non-operative therapy can be undertaken safely in patients with suspected non-perforated appendicitis, further study is necessary to clarify which patients are most likely to benefit from this strategy and to evaluate its cost effectiveness.

Another area of controversy is when to operate on perforated appendicitis with or without abscess. Data on the safety and efficacy of initial non-operative management of complicated appendicitis (perforated, with phlegmon causing a palpable mass, or with abscess) is derived from observational cohort studies, which are subject to selection bias and confounding [17, 18]. There are no published randomized trials evaluating timing of operation for complicated appendicitis, although there are three randomized trials in children that either are recruiting subjects or in the planning phases.

The potential advantages of initial non-operative therapy, if successful, are a decrease in hospital LOS, complications, and cost. The disadvantages include potential recurrence prior to interval appendectomy and a greater incidence of complications. Associated small bowel obstruction, abscess necessitating percutaneous drainage or re-operation, or bandemia of WBC on admission may be associated with delayed appendectomy [19, 20]. Selective initial non-operative management may be an alternative strategy, but predictors of failure of non-operative therapy must be identified to permit optimal patient selection. Data from the planned randomized trials may elucidate this controversial topic.

Interval appendectomy to prevent recurrence after successful initial non-operative management of complicated appendicitis is controversial as well. Data on the need for interval appendectomy are based on observational cohort studies and are limited. Proponents of an expectant management strategy argue that the recurrence rate is low and that routine interval appendectomy is associated with more complications and higher cost [21–23]. In a retrospective cohort study using discharge data, Kaminski et al. reported a 5% recurrence rate after initial non-operative management of acute appendicitis, with or without abscess, with a median four-year follow up [21]. On the other hand, opponents argue that expectant management may delay the diagnosis of an occult malignant tumor. In a retrospective study, Lai et al. estimated the incidence of carcinoma of the cecum associated with presumptive appendicitis to be 0.85% [24]. Patients undergoing expectant management therefore may benefit from colonoscopy or barium enema study to detect underlying diseases or neoplasm [22, 24].

Can Treatment of Acute Uncomplicated Appendicitis Be Delayed Until the Following Morning?

On the basis of data suggesting that antibiotic management of acute appendicitis is safe, as either initial or definitive therapy [14, 16, 21], the routine practice of operating immediately on acute appendicitis has come into question. The rationale for immediate operative intervention is to prevent perforation. Ditillo et al. performed a retrospective review of 1,081 adults with acute appendicitis [25] and found that longer time to the operating room was associated with progressively advanced pathology, with the spectrum ranging from acute to gangrenous to perforated appendicitis or phlegmon to periappendicular abscess. In particular, delay beyond 71 h compared with less than 12 h was associated with a 13-fold increase in the odds of advanced pathology. Delay in treatment also was associated with a higher complication rate and longer hospital LOS. Similarly, Bickell et al. demonstrated an increase in the risk of rupture for every 12 h beyond 36 h of symptoms [26]. Both groups of investigators concluded that delay in operation should be avoided to prevent perforations and a higher incidence of complications.

Conclusion

Despite the prevalence of acute appendicitis, questions remain regarding its optimal diagnosis and management. Large, multicenter randomized trials are required to answer these questions.

Author Disclosure Statement

No competing financial interests exist.

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