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Pediatrics 2014;133:e39; originally published online December 30, 2013;
DOI: 10.1542/peds.2013-2418

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American Academy of Pediatrics

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Use of White Blood Cell Count and Negative Appendectomy Rate

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KEY WORDS

appendicitis, appendectomy, leukocyte count, diagnosis, differential, negative appendectomy

ABBREVIATIONS

AUC—area under the curve
CI—confidence interval
CT—computed tomography
NA—negative appendectomy
ROC—receiver operating characteristic
TA—true appendectomy
WBC—white blood cell

Dr Bates helped design the study, conducted the data collection and initial data analysis, and drafted the initial manuscript; Ms Khander conducted the data collection, helped with the data analysis, and contributed to the draft of the manuscript; Dr Steigman helped conceptualize and design the study, supervised data collection, supervised and finalized data analysis, and helped revise the manuscript; Dr Tracy conceptualized the study, supervised data analysis, and critically reviewed the manuscript; Dr Luks conceptualized the study, supervised the design of the study, supervised data collection, supervised and revised data analysis, and critically reviewed all edited versions of the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-2418

doi:10.1542/peds.2013-2418

Accepted for publication Oct 3, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest relevant to this article to disclose.



WHAT'S KNOWN ON THIS SUBJECT: Currently, the false-positive rate of appendicitis in children is $\leq 5\%$. Abdominal imaging and blood tests (particularly leukocytosis) help minimize the negative appendectomy rate, but appendicitis is not always associated with an elevated white blood cell count.



WHAT THIS STUDY ADDS: Reducing the threshold of leukocytosis as a criterion for appendicitis to 8000 to 9000 white blood cells per μL improves specificity (negative appendectomy: $<1\%$) while only marginally decreasing sensitivity.

abstract

BACKGROUND: Despite increased utilization of laboratory, radiologic imaging, and scoring systems, negative appendectomy (NA) rates in children remain above 3% nationwide. We reviewed the clinical data of patients undergoing appendectomy to further reduce our NA rate.

METHODS: A retrospective review was conducted of all appendectomies performed for suspected appendicitis at a tertiary children's hospital during a 42-month period. Preoperative clinical, laboratory, and radiographic data were collected. Variables absent or normal in more than half of NAs were further analyzed. Receiver operating characteristic curves were constructed for continuous variables by using appropriate cutoff points to determine sensitivity and false-positive rates. The results were validated by analyzing the 12 months immediately after the establishment of these rules.

RESULTS: Of 847 appendectomies performed, 22 (2.6%) had a pathologically normal appendix. The only variables found to be normal in more than half of NAs were white blood cell (WBC) count (89%) and neutrophil count (79%). A receiver operating characteristic curve indicates that using WBC cutoffs of 9000 and 8000 per μL yielded sensitivities of 92% and 95%, respectively, and reduction in NA rates by 77% and 36%, respectively. Results observed in the subsequent 12 months confirmed these expected sensitivities and specificities.

CONCLUSIONS: Absence of an elevated WBC count is a risk factor for NA. Withholding appendectomy for WBC counts <9000 and 8000 per μL reduces the NA rate to 0.6% and 1.2%, respectively. Missed true appendicitis in patients with normal WBC counts can be mitigated by a trial of observation in those presenting with early symptom onset. *Pediatrics* 2014;133:e39–e44

Appendicitis is one of the most common acute surgical emergencies in the pediatric population. The natural progression from acute inflammation to perforation and peritonitis typically occurs over a period of a few days.¹ Ideally, appendicitis should be diagnosed and treated before rupture occurs, while limiting the number of false-positive cases. Because no single test or clinical finding is 100% reliable, and because peritonitis has been traditionally associated with significant morbidity and mortality, the emphasis has always been on maximizing sensitivity. Classic teaching recommends a negative appendectomy (NA) rate of 5% to 15%,² given the relative safety of a negative exploration and the dire consequences of missing true appendicitis.^{3,4} This concept has endured for decades, even though modern surgical care (including the routine use of antibiotics) has dramatically reduced the morbidity of advanced appendicitis.

The most recent reports quote NA rates below 5%.^{5,6} Given the prevalence of this disease in children, this rate still represents a large number of unnecessary operations, pain, discomfort, disruption of families' lives, and increased health care costs. A negative exploration also exposes the patient to a small, but real, risk of postoperative complications. Herein, we analyze all NAs at our institution over the past 5 years, to detect common characteristics that, in the future, might further decrease our false-positive rate.

METHODS

We reviewed all children (<18 years of age) who underwent an open or laparoscopic appendectomy for suspected appendicitis at Hasbro Children's Hospital from 2009 to 2013. All patients had a clinical suspicion of appendicitis, and most (but not all) had undergone a confirmatory imaging test (ultrasonography,

computed tomography [CT], or MRI). Patients undergoing elective, incidental, or interval appendectomy were excluded. Preoperative clinical, laboratory, and imaging data were collected for each patient. Clinical data included demographic characteristics (age, gender), associated medical conditions, duration of symptoms, fever, presence of anorexia, nausea/vomiting, migration of pain to the right iliac fossa, tenderness, rebound tenderness, and other signs of peritonitis. Where possible, the preoperative variables were used to calculate the Alvarado score⁷ (migratory pain to, and tenderness in, the right iliac fossa; anorexia; nausea/vomiting; fever; leukocytosis; and neutrophilia). This score is typically used as a screening tool and determines whether appendicitis is unlikely, possible, or likely. Recorded details of the ultrasound examination, when performed, included visualization and size of the appendix, compressibility, hyperemia, presence of an appendicolith, periappendiceal inflammation, presence of peritoneal or pelvic fluid, lymphadenopathy, presence of "tip" appendicitis, and attending radiologist.

Discrepancies between clinical and radiographic impressions, or between 2 imaging tests, were recorded. Operative reports were reviewed for final clinical diagnosis and findings at operation. A definitive diagnosis of appendicitis was based on the pathology report.

Patients who underwent NAs between 2009 and 2012 were analyzed to determine possible correlations with preoperative clinical, laboratory, and radiographic data. Discrete variables (ie, true/false) that were absent or normal in >50% of NAs were further analyzed and compared against true appendectomies (TAs). For continuous variables (ie, leukocytosis), a receiver operating characteristic (ROC) curve was constructed. The area under the

curve (AUC) was calculated and appropriate cutoff points were identified to determine the sensitivity and false-positive (1-specificity) rates.

The records of patients undergoing an appendectomy in the 12 months after this analysis (January through December 2012) were then analyzed to validate the established rules. This study was approved by the Rhode Island Hospital Institutional Review Board.

RESULTS

Eight hundred forty-seven pediatric patients presented to our pediatric emergency department and underwent an appendectomy for presumed appendicitis between 2009 and 2012. Of those, 22 were found to have a pathologically normal appendix, an NA rate of 2.6%. Eight hundred and twenty-five appendectomies had pathologic findings consistent with acute (568, or 69%) or perforated (257, or 31%) appendicitis, a TA rate of 97.4%.

Age at time of presentation ranged from 1 to 16 years. The median age in the NA group was 12.6 years, which was not significantly different from the TA group. There was an even distribution of NA across both genders (11:11). Alvarado scores in the NA group ranged from 0 to 7 (likely appendicitis), with a median score of 3.5. Temperature at time of presentation ranged from 36.2°C to 38.9°C. Seventeen of 22 patients had a documented duration of symptoms at presentation; 10 of 17 (59%) had symptoms for <24 hours. In the TA group, 46% had symptoms for <24 hours. Nineteen of 22 NAs also had radiographic studies (either CT or ultrasonography or both). Findings are listed in Table 1.

A white blood cell (WBC) count was obtained in all patients who underwent appendectomies, either at our facility or at the referring hospital. Elevated WBC was defined as >11 500 per μ L. WBC count and percentage neutrophils

TABLE 1 Ultrasound and CT of Abdomen and Documented Findings in NAs

Findings	Number
Appendicolith only	2
Appendix not visualized	3
"Tip" enlarged/inflamed	5
Inconclusive	2
Enlarged appendix with focal inflammation	5
Normal visualized appendix	2

were the only variables found to be normal in more than half of NAs. A normal neutrophil count ($<75\%$) was present in 79% of NAs; WBC count was normal in 89% of the 22 patients with NAs. Of these, 17 of 22 (77%) had a WBC count of <9000 per μL and 8 (36%) had a WBC count of <8000 per μL . (In contrast, 68 of 825, or 8.2%, of TAs had a WBC count of <9000 per μL , and 43, or 5.2%, had a WBC count of <8000 per μL .) From these findings, 2 ROC curves were constructed (Fig 1). The axis in Fig 1 represents the false-positive rate (1-specificity), expressed in percentage of the originally observed rate of 2.6%. The ordinate represents the sensitivity of WBC count as a test, expressed as a percentage of all true appendicitis cases. Thus, a sensitivity $<100\%$ signifies that, based on the chosen WBC cutoff value, some

patients with appendicitis would have been missed had the decision not to operate been made on the WBC count alone. The first curve (solid line, Fig 1) represents all patients. The second one (dashed line) represents patients with a >24 -hour history of symptoms (46% of TAs with a normal WBC count had symptoms for <1 day).

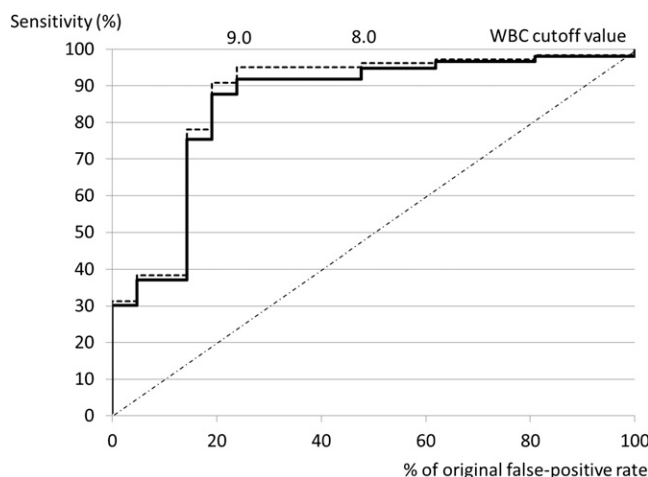
Using a WBC threshold of 9000 per μL (anything below 9000 per μL was considered not to be appendicitis) reduced the sensitivity to 92% (95% confidence interval [CI]: 90%–93%) and the NA rate by 77% (95% CI: 56%–90%). Using a WBC threshold of 8000 per μL would have yielded a sensitivity of 95% (95% CI: 93%–96%) while reducing the original NA rate by 36% (95% CI: 20%–57%). When cases of TA with symptoms for <24 hours were excluded, the sensitivities improved for each of the respective specificities. With a WBC threshold of 9000 per μL , the sensitivity increased from 92% to 95% (95% CI: 92%–97%) for the same false-positive rate. With a WBC threshold of 8000 per μL , the sensitivity increased to 96% (95% CI: 94%–98%) for the same false-positive rate. The AUCs were 0.86 and 0.87 for the entire group and the >24 -hour group, respectively.

In the 12-month period immediately after this analysis and the establishment of the ROC curves (expected values), 204 patients underwent an appendectomy (observed values). Two patients had an NA (0.98%). Their WBC counts on admission were 6400 and 8200 per μL respectively. During that same period, 18 patients with true appendicitis had a WBC count <9000 per μL . In 6 of those patients, the WBC was <8000 per μL . Four of those patients were found to have perforated appendicitis. In all 4, both the presentation and the diagnosis were delayed.

Thus, none of the 2 observed false-positive appendectomies had a WBC count >9000 per μL and only one had a WBC >8000 per μL , yielding false-positive rates of 0% and 0.5%, respectively, which was not statistically different from the expected values of 0.6% and 1.6%, respectively ($P = .56$ and 0.71 , respectively; χ^2 analysis for 2×2 tables). The observed sensitivities at WBC cutoffs of 9000 and 8000 were 91% (95% CI: 86%–94%) and 97% (95% CI: 94%–99%), respectively, which was not statistically different from expected values of 92% ($P = .74$) and 95% ($P = .27$), respectively.

DISCUSSION

The classic presentation of acute appendicitis has been well described for many years, and the diagnosis can often be made on clinical grounds alone. Appendicitis remains an acute surgical problem, but advances in surgical care and the availability of antibiotics have made it less of an emergency. Some patients, such as children under 3 years, the elderly, and those with significant comorbidities, are at a higher risk of complications. Furthermore, the morbidity and increased costs of perforated appendicitis are not insignificant. However, the mortality of appendicitis is virtually zero today.^{8,9} In addition, much progress has been

**FIGURE 1**

ROC curve for leukocytosis (WBC count) in the diagnosis of appendicitis. WBC cutoff values ($\times 1000$ per μL) indicate percentage of original sensitivity and false-positive rates. Solid line: all patients. Dashed line: restricted to patients with symptoms for >24 hours. See text for details.

made in medical imaging. Ultrasonography, CT, and MRI, although not infallible, have greatly enhanced our diagnostic accuracy in appendicitis.^{10–12} In recent years, there has therefore been an increased awareness that unnecessary appendectomies, and their inherent, pain, discomfort, and cost, should be avoided as much as possible. The current literature reveals NA rates at other institutions ranging from 3% to 11%,^{5,6,13,14} in keeping with our own NA rate of 2.6% (before implementation of the current recommendations).

The suspicion of appendicitis relies on constellation of signs, symptoms, and ancillary findings that have been combined into a variety of scoring systems. The most commonly used one is the Alvarado score,⁷ also known as MANTRELS,¹⁵ which weighs heavily toward the typical signs of localized peritonitis and an abnormal leukocytosis and differential. The higher the score, the higher the likelihood of appendicitis, which helps in decision-making regarding patient discharge, further investigations, observation, or surgical intervention. A recent systematic review of the Alvarado score confirmed that it is more appropriate as a triage tool than as a definitive diagnostic tool. A score <5 points was 94% to 99% sensitive in “ruling out” appendicitis. However, the data analysis did not support it as a “rule in” for surgery.¹⁶ The Pediatric appendicitis score, which is similar to the Alvarado score, revealed similar flaws: if applied to the decision to operate, it would have led to an NA rate of 12.9% in 1 study.¹⁷ Scoring systems that do not include laboratory variables and that are solely based on history and physical findings prove even worse, with NA rates as high as 17%.¹⁸

With the addition of imaging studies in diagnosing acute appendicitis, the NA rates in the literature have improved greatly over the past 2 decades.⁶ The

modalities that are currently used most are CT and ultrasonography. In addition, MRI is also available but is as yet mostly limited to a second- or third-line study.¹⁹ The current literature suggests that CT has better diagnostic accuracy, with sensitivities of ~94%.²⁰ The disadvantage of CT, especially in the pediatric population, is primarily related to ionizing radiation. Ultrasound has been shown to be slightly less accurate than CT overall, with sensitivities of 88%.²⁰ It is operator-dependent and may be more difficult to interpret by someone who did not personally perform the test. Ultrasonography has gained in popularity in the pediatric population, primarily because it involves no radiation exposure. In experienced centers, and in patients with a lean body habitus, accuracy mirrors or exceeds that of CT.^{10,11} At our hospital, ultrasonography is the primary imaging modality used to confirm the diagnosis of acute appendicitis, and >50% of patients undergo this examination. Anecdotal reports of a false-positive ultrasound still arise; however, a review of our NA cases over the past 4 years failed to identify a specific finding (or a particular operator) that would increase the suspicion of a false-positive result (Table 1).

After reviewing all NA cases at our institution in the past 4 years, we found clinical variables equally unhelpful in identifying false-positives. Details of the history and physical examination were comparable to those in patients with true appendicitis. The findings of a normal WBC count and a normal differential in the majority of patients who underwent NA was the only significant variable.

Leukocytosis is a supportive laboratory finding in the diagnosis of acute appendicitis, both in adults and children. A review of the literature reveals that the sensitivity and specificity of WBC counts range from 70% to 80% and 60% to 68%,

respectively.^{21–25} However, 1 study reported that as many as 20% of pediatric patients with pathologically proven appendicitis had a normal WBC count.²⁶ Our series revealed similar findings, with a small subset of patients with appendicitis without leukocytosis. Some of these patients had symptoms for <1 day, and it might be assumed that a number of those would have shown an increased WBC count upon repeat testing. Of patients without appendicitis in our series, the vast majority had a normal WBC count. An abnormal differential (“left shift”) is believed by some to be more sensitive than the absolute WBC count. In our experience, however, an elevated neutrophil count was present in 21% of NAs, compared with a leukocytosis finding of only 11%. Because the specificity of a WBC count was superior to that of the neutrophil count, we further evaluated the value of leukocytosis only.

Rather than using leukocytosis as a dichotomous value (present or absent, with a cutoff at 11 500 per μL), we chose to treat WBC count as a continuous variable to determine its performance as its discrimination threshold was changed. Our results indicate that WBC count performs well as a continuous variable, with an AUC of 0.86 and a clear change in the slope of the tangent (likelihood ratio) between 9000 and 10 000 per μL . Of course, the relative paucity of NA patients (22 of >800 appendectomies) resulted in a somewhat jagged ROC curve. Nevertheless, the validation portion of this study suggests that a cutoff of ~8000 to 9000 per μL significantly improves diagnostic accuracy. By using 9000 per μL as a cutoff in our series, the false-positive rate of appendicitis could have been further reduced from an already low 2.6% to 0.6%, but it would have decreased the sensitivity to 92% of its current value (ie, we would have failed

to operate on 8% of patients with appendicitis). Using 8000 per μL as a cut-off value would have yielded a slightly higher false-positive rate, 1.2%, but with a 95% sensitivity.

If we accept that early appendicitis poses only minimal risk of perforation, it is reasonable to observe some patients overnight. Doing so while using the same admission WBC cutoffs of 9000 and 8000 per μL , we would have obtained false-positive rates of 0.6% and 1.2% respectively, with respective sensitivities of 95% and 96%. It is important to note that this degree of accuracy was calculated after all other clinical and imaging variables had already suggested appendicitis. WBC count cannot reasonably be used as the sole determinant of acute appendicitis at the exclusion of all others, and it certainly does not replace clinical judgment. However, a WBC count <8000 to 9000 per μL in a child who has had symptoms for <24 hours merits a period of observation, provided there are no signs of advanced disease.

In the validation portion of our study, we applied the above principles and were able to further reduce our NA rate. By using a threshold of 9000 per μL we lowered our false-positive rate to 0.98% (2 NAs out of 204 appendectomies in 2012). By using WBC count alone, we would have decreased the sensitivity to 91% (18 of 204 patients had a WBC count <9000 per μL). However, other factors (clinical and imaging findings) helped make the correct diagnosis of appendicitis in all but 4 of these 18 patients, for a true

sensitivity of 98%. We were therefore able to lower our NA rate below 1% with minimal impact on the incidence of false-negative appendicitis: only 4 of 204 patients could be considered missed appendicitis, and all presented with considerable delay, making accurate diagnosis more difficult.

Once a common practice, hospital admission for serial examination and repeat testing may have become rarer as diagnostic accuracy has improved. The addition of near-routine imaging and a more cost-conscious approach are 2 factors that have shortened the decision-making time.¹¹ Nevertheless, observing patients with an equivocal diagnosis or contradictory findings has its place. It is important to note that, whereas judicious use of analgesics may be considered during the observation period, antibiotics should not, so as not to mask the evolution of possible appendicitis. In 1 retrospective study, active observation was practiced for patients presenting with doubtful clinical diagnosis based on clinical history, physical examination, and WBC and C-reactive protein results. Although the mean observation was long, at 2.5 days, the NA rate was only 2.6%.²⁷ A similar study incorporating active in-house observation for patients with questionable diagnosis of acute appendicitis showed a decrease in NA rate, decreased costs, and shortened hospitalization without an increase in morbidity.²⁸ We do not routinely obtain C-reactive protein levels, and despite promising results, this test is not yet used ubiquitously. Its addition to the diagnostic

panel could, in the future, prove helpful in further refining diagnostic accuracy.

Of course, clinical judgment should prevail, and certain patients are more at risk. Young children (<3–5 years), for example, are more likely to present with advanced appendicitis or frank peritonitis, and the disease may progress more rapidly in that age group. Therefore, any suspicion of advanced appendicitis should be treated as the true emergency it represents. Furthermore, it is unrealistic to expect zero NA rates, given the variability of the disease in onset, evolution, and body response. Nevertheless, several recent studies have confirmed that a false-positive rate <5% is safe and feasible, and a sophisticated use of adjunctive tests, such as leukocytosis, can help to achieve this goal.

CONCLUSIONS

Our diagnostic accuracy in acute appendicitis has greatly improved in recent decades, and its morbidity and certainly its mortality have dramatically decreased. It is therefore reasonable to try and further refine our surgical decision-making by reducing the NA rate. Using the WBC count as a continuous variable, rather than as a true/false measure of leukocytosis, may help us reduce our NA below 1% without significantly affecting the sensitivity of our diagnosis. Of course, these findings reflect the experience at a single institution and may need to be validated before generalized use can be recommended.

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DOI: 10.1542/peds.2013-2418

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