Predictive factors for failure of nonoperative management in perforated appendicitis

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BACKGROUND: Identifying patients on admission with perforated appendicitis who have phlegmon or abscess initially selected for but likely to fail nonoperative management may avoid delays in definitive treatment.

METHODS: Patients older than 15 years presenting to a university tertiary care hospital with perforated appendicitis and abscess or phlegmon and planned nonoperative management were reviewed. Comorbidities, clinical findings, laboratory markers, radiographic findings, and nonsurgical treatments associated with failure of nonoperative management were recorded.

RESULTS: Eighty-nine patients were identified, and 69 were managed successfully to discharge without operation. Length of stay was greater in the failure group (11 days vs. 5 days, $p = 0.001$), and intensive care unit care was more common (10% vs. 0%, $p = 0.049$). On univariate and multivariate analyses, smoking (odds ratio [OR], 13.20; 95% confidence interval [CI], 1.13–142; $p = 0.039$), tachycardia (OR, 4.93; 95% CI, 1.21–20.06; $p = 0.026$), and generalized abdominal tenderness (OR, 5.52; 95% CI, 1.40–21.73; $p = 0.015$) were associated with failure of nonoperative management. On computed tomographic scan, the failure group had higher rates of abscess (75% vs. 55%, $p = 0.110$), and their abscesses were more likely smaller than 50 mm (OR, 2.83; 95% CI, 1.01–7.92; $p = 0.043$).

CONCLUSION: Patients with perforated appendicitis and phlegmon or abscess who smoke or present with tachycardia, generalized abdominal tenderness, and abscesses smaller than 50 mm are more likely to fail nonoperative management and should be considered for early operation. These findings should be validated prospectively. (*J Trauma Acute Care Surg*. 2014;76: 976–981. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level III.
KEY WORDS: Appendicitis; abscess; phlegmon; perforation; nonoperative management.

Of the nearly 300,000 cases of acute appendicitis that occur in the United States every year, 15% to 20% are considered complicated appendicitis defined as the presence of phlegmon or abscess on computed tomography (CT) or ultrasound.[1] When a patient with complicated appendicitis undergoes urgent operative intervention, cecal resection may be required, and complications are more common. Despite this, some authors have advocated for the immediate surgery with ileocecal or right hemicolectomy performed as needed.[2,3] More recently, however, the use of imaging modalities provides for more accurate diagnosis of perforated appendicitis and facilitates image-guided drainage procedures. Therefore, nonoperative management of complicated appendicitis, consisting of intravenously administered antibiotics and percutaneous drainage, has been used more frequently.[4] Numerous groups have advocated nonoperative management for complicated appendicitis in patients without severe systemic illness. Appendectomy is performed if patients do not improve or if they clinically deteriorate.[5–8] Overall, however, no consensus exists among surgeons regarding the optimal treatment for patients who present with complicated appendicitis who do not exhibit systemic illness.[9]

Unfortunately, nonoperative management is not successful in all patients. We defined failure of nonoperative management as requiring unplanned appendectomy following a diagnosis of complicated appendicitis with planned nonoperative management. In a meta-analysis consisting of 61 studies, Andersson and Petzold[4] demonstrated an overall failure rate of 7.2% for patients treated nonoperatively for enclosed appendiceal inflammation. In the same study, however, when patients presenting with abscess or phlegmon were considered, the failure rate was 13% (range, 4.5–21.5%). Data were unavailable to determine which patients were likely to be managed nonoperatively and which patients will ultimately fail nonoperative management. Our objective for this study was to evaluate factors identified on presentation that will identify patients who ultimately fail nonoperative management and therefore should be considered for early operation.

PATIENTS AND METHODS

Study Design

This was a retrospective study approved by the Yale University Human Investigations Committee. Records were obtained from patients admitted to Yale-New Haven Hospital, between January 1, 2004, and January 1, 2011, with appendicitis as the primary diagnosis. Those undergoing appendectomy more than 48 hours after admission or admitted with a diagnosis of appendicitis and without evidence of appendectomy at our institution within 30 days of admission were reviewed in detail. This allowed us to identify those patients in whom there was an initial attempt to manage the patient nonoperatively. This initial attempt at nonoperative management was verified by record review. The following were additional inclusion criteria used: age greater than 15 years, admitted with diagnosis of appendicitis, and CT evidence of appendicitis with severe inflammation (phlegmon) and/or abscess. The failure group was defined as needing appendectomy after more than 48 hours of a planned trial of nonoperative management. Those patients successfully managed nonoperatively for at least 30 days after the acute episode were considered to be the "control" group. Exclusion criteria in both groups included outpatient management of appendicitis and insufficient data (e.g., CT scans performed at an outside hospital and unavailable for review).

Demographics, Physical Examination, and Laboratory Data

Age, sex, hospital length of stay, and hospital day of surgery (where applicable) were abstracted. The presence of the following comorbidities was recorded if present: coronary artery disease, chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus, tobacco use, and psychiatric disease. The duration of pain, physical examination findings, and laboratory values were abstracted from the record.

CT Findings

Most studies were performed on a 64-slice Lightspeed VCT scanner (GE Healthcare, Waukesha, WI). All patients in this study had complete CT scans of the abdomen and pelvis. CT scans were reevaluated by a blinded board-certified attending radiologist (J.B.), and the following data were recorded: presence of phlegmon (with size), presence of extensive (too large to measure) phlegmon, volume of phlegmon, presence of abscess, size of abscess, volume of abscess, diameter of appendix, presence of free fluid, presence of appendicolith, bowel wall thickening, loculated air, and free air.

Outcomes

The number of patients treated with CT-guided abscess drainage in each group was recorded. For the failure group, the following details were noted: time delay to operation, type of operation (laparoscopic appendectomy, open appendectomy, laparoscopic converted to open appendectomy, ileocecectomy), operative findings (presence of perforated appendix, abscess, or purulent fluid), as well as intensive care and hospital length of stay. Surgical site infections including intra-abdominal abscesses and other complications were noted in each group when present.

Statistical Analysis

Statistical analysis was performed using IBM SPSS (version 18, Chicago, IL). Descriptive statistical analysis was performed to compare characteristics of patients in the two treatment groups. Descriptive statistics are reported, and mean (SD) or median and interquartile range (IQR) where appropriate. Univariate analysis was performed using Student's *t* test for continuous variables with normal distribution, Wilcoxon rank-sum for nonnormally distributed variables, and χ^2 for dichotomous variables. Multivariable analysis with reverse stepwise logistic regression was also performed. Entry into the final model was defined by a p <0.2 on univariate analysis. A p < 0.05 was considered statistically significant.

RESULTS

Presentation

Between January 1, 2004, and January 1, 2011, approximately 2,860 patients were admitted to Yale-New Haven Hospital with a diagnosis of appendicitis. Of these, 98 patients were older than 15 years with evidence of abscess or phlegmon on CT scan and had an attempt at nonoperative management. Of the 98 patients, 20 failed nonoperative management (failure group), with appendectomy performed after 48 hours or more of planned nonoperative management. Sixty-nine patients (control group) were discharged home and managed for at least 30 days without operation. The remaining nine patients (one failure, eight controls) were excluded because of incomplete data.

The two groups (control vs. failure) were similar in terms of sex, age, and medical comorbidities. Tobacco use was 14 times more prevalent in the failure group than in the control group (20% vs. 1.4%, p = 0.002). The presence of COPD or diabetes mellitus was more common in the failure group, but this finding was not statistically significant (Table 1).

TABLE 1. Baseline Demographics, Medical Background, History of Illness, and Vital Signs at Presentation

	Controls (n = 69)	Failure (n = 20)	*p*
Male sex	44 (64%)	12 (60%)	0.759
Age, y	45	43	0.717
CAD	5 (7.2%)	2 (10%)	0.687
COPD	2 (2.9%)	2 (10%)	0.177
Hypertension	19 (28%)	5 (25%)	0.822
Diabetes mellitus	8 (12%)	5 (25%)	0.135
Tobacco use	1 (1.4%)	4 (20%)	**0.002**
Psychiatric disease	10 (15%)	3 (15%)	0.955
Days of symptoms, median (IQR)	5 (4)	5 (8)	0.793
Generalized abdominal pain	60 (87%)	16 (80%)	0.438
RLQ pain	47 (68%)	13 (65%)	0.793
Nausea	29 (42%)	12 (60%)	0.156
Vomiting	26 (38%)	8 (40%)	0.851
Anorexia	25 (36%)	8 (40%)	0.759
Diarrhea	12 (17%)	3 (15%)	0.801
Temperature	99.0	99.5	0.175
Febrile	7 (10%)	5 (25%)	0.087
Hypotension	1 (1.4%)	1 (5.0%)	0.345
Heart rate	89	98	0.010
Tachycardia	11 (16%)	10 (50%)	**0.002**

Continuous variable data are presented means unless specified.
CAD, coronary artery disease; RLQ, right lower quadrant.

Patients in the two groups presented with similar clinical histories. The most common symptoms were generalized abdominal pain and right lower quadrant pain, both of which were present in the majority of patients in each group. The median duration of symptoms was the same between groups, 5 days (IQR, 4 days) versus 5 days (IQR, 8 days) in failure and control groups, respectively (Table 1). When compared with their controls, patients who ultimately failed nonoperative management and required an appendectomy were more likely to be febrile (10% vs. 25%, p = 0.087), hypotensive (1.4% vs. 5%, p = 0.345), and tachycardic (16% vs. 50%, p = 0.002) (Table 1).

On physical examination, the vast majority of all patients in this study were found to have right lower quadrant tenderness (>80% in both groups). Localized peritonitis (26% vs. 45%, p = 0.105) and generalized peritonitis (0% vs. 5%, p = 0.062) were both found at higher rates in the failure group, but these findings did not reach statistical significance. Generalized abdominal tenderness was fivefold higher in the failure group than in the control group (9% vs. 45%, p = 0.001) (Table 2).

Laboratory Testing and Imaging

A similar degree of leukocytosis was present in both groups (control, 14,000; failure, 15,000; p = 0.452). Serum electrolytes, liver function tests, blood urea nitrogen, creatinine, as well as amylase and lipase were similar between the two groups (Table 2). All patients presented with CT evidence of phlegmon (74.0% vs. 85.0%, p = 0.304), abscess (55% vs. 75%, p = 0.110), or both (33% vs. 65% p = 0.259). The size of the average abscess in the failure group was smaller than that

TABLE 2. Comparison of Physical Examination Findings and Presenting Laboratory Values Between Control and Failure Groups

	Control	Failure	*p*
RLQ tenderness	88%	85%	0.684
Generalized tenderness	9%	45%	**0.001**
Localized peritonitis	26%	45%	0.105
Generalized peritonitis	0%	5%	0.062
Palpable mass	7.2%	10%	0.687
WBC	14,000	15,000	0.452
Hemoglobin	13.6	13.7	0.921
Sodium	136	135	0.528
Bicarbonate	23.6	23.3	0.619
BUN	14.6	12.7	0.374
Creatinine	1.14	0.98	0.400
AST	23	32	0.099
ALT	27	32	0.561
Total bilirubin	0.72	0.75	0.792
Amylase	33	29	0.583
Lipase	15	13	0.561

Continuous variable data are reported as means.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; RLQ, right lower quadrant; WBC, white blood cell count.

in the control group, although this finding did not reach statistical significance (45 mm vs. 101 mm, $p = 0.135$). Findings on CT of free air, loculated air, appendicolith, and free fluid were more common in the failure group than in the control group, but none of these trends were statistically significant (Table 3). A similar proportion of patients in the control and failure groups underwent CT-guided abscess drainage (41% vs. 35%, $p = 0.653$). Within both groups, there were 28 patients with abscesses less than 50 mm, of which 8 (28.6%) were drained. There were a total of 25 patients with abscesses greater than 50 mm, of which 19 (76%) were drained. In the control group, 5 of 18 small abscesses (<50 mm) were drained, whereas in the failure group, 3 of 10 similarly sized abscesses were drained (27.8% vs. 30%, $p = 0.901$).

On multivariate analysis, factors associated with failure of nonoperative management included smoking (odds ratio [OR], 13.20; 95% confidence interval [CI], 1.13–142.00; $p = 0.039$), tachycardia (OR, 4.93; 95% CI, (1.21–20.06; $p = 0.026$), and generalized abdominal tenderness (OR, 5.52; 95% CI, 1.40–21.73; $p = 0.015$). In addition, patients in the failure group had abscesses that were more likely to be less than 50 mm (OR, 2.83; 95% CI, 1.01–7.92; $p = 0.043$) (Table 4).

Outcomes

Patients who failed nonoperative management and required an appendectomy had hospital stays more than two times longer than those who were successfully treated nonoperatively. Those in the failure group also had high rates of respiratory failure (0.0% vs. 10.0%, $p = 0.008$) and were more likely to require intensive care unit admission (0% vs. 10%, $p = 0.049$; Table 5). The proportion of patients who experienced recurrent abscess formation was similar between groups (15% vs. 20%, $p = 0.551$).

Those patients who failed nonoperative management and ultimately required an appendectomy spent on average 4.8 days being treated with intravenously administered antibiotics and/or percutaneous drainage before surgery. Clinical deterioration was the most common indication for appendectomy. The type of operation performed for each appendectomy is outlined in Table 6. At operation, 70% of patients were noted to have perforated appendicitis. Of those patients who failed nonoperative management of complicated appendicitis, 15 (75%) of 20 were diagnosed with abscess by CT scan, whereas 17 (85%) of 20 were noted to have an abscess at operation. Of note, in the failure group, three patients developed an abscess during nonoperative management, and one patient had a regression of abscess.

The number of patients in each group who underwent a follow-up CT scan within 30 days of initial presentation was similar (control, 69% vs. failure, 65%; $p = 0.674$). Within the failure group, there was a shorter interval between initial and follow-up CT scan, but this finding was not statistically significant ($p = 0.167$). The median number of follow-up CT scans per patient performed within 30 days of presentation was similar between the two groups (control, 1.5 [IQR, 1] vs. failure, 2 [IQR, 2]; $p = 0.165$). Of those patients who underwent follow-up CT within 30 days, more abscesses were noted in the failure group than in the control group, and this finding was statistically significant (32% vs. 69%, $p = 0.016$). The volume of abscesses seen on follow-up CT scan increased in both failure and control group. This finding was statistically significant in the failure group, in which average abscess size increased from 60 mm to 92 mm ($p = 0.036$).

DISCUSSION

In 1945, McPherson and Kinmonth[10] published a study of 730 consecutive cases of appendicitis, of which 129 cases consisted of appendicitis with clinically palpable mass. Treating this subgroup of patients with nonoperative management and without the use of antibiotics, McPherson and Kinmonth reported a failure rate of 24%. Since then, despite advances in

TABLE 3. Evaluation of CT Findings in Control and Failure Groups

	Controls	Failure	*p*
Phlegmon	74%	85%	0.304
Extensive phlegmon	16%	12%	0.693
Size of phlegmon (longest axis), cm	6.1	6.8	0.171
Volume of phlegmon, mm	139	125	0.641
Presence of abscess	55%	75%	0.110
Size of abscess (longest axis), cm	4.9	4.4	0.346
Volume of abscess, mm	101	45	0.135
Free fluid	41%	60%	0.124
Diameter of appendix	1.25	1.41	0.114
Appendicolith	26%	40%	0.228
Bowel wall thickening	48%	55%	0.572
Loculated air	25%	45%	0.078
Free air	1.0%	10%	0.062

Continuous variable data are reported as means.

TABLE 4. Multivariate Analysis of Factors in Relation to Failure of Nonoperative Management in Complicated Appendicitis

			95% CI	
	p	OR	Lower	Upper
Diabetes mellitus	0.218	2.59	0.567	11.9
Smoker	**0.039**	**13.2**	**1.13**	**142**
Nausea	0.822	1.16	0.308	4.41
Febrile	0.893	1.12	0.203	6.21
Tachycardic	**0.026**	**4.93**	**1.21**	**20.1**
Generalized tenderness	**0.015**	**5.52**	**1.40**	**21.7**
Localized peritonitis	0.485	1.61	0.419	6.25
Abscess < 50 mm	**0.043**	**2.83**	**1.01**	**7.92**

antibiotics, imaging, surgical technique, and critical care, the management of complicated appendicitis remains a topic of debate among surgeons. Simillis et al.[9] helped clarify this debate in 2010 when they reported a systematic review of studies that compared acute appendectomy with nonoperative management for complicated appendicitis. This meta-analysis, which included 17 studies and more than 1,500 patients, demonstrated that nonoperative treatment of patients with complicated appendicitis led to fewer wound infections, abdominal or pelvic abscesses, episodes of ileus or bowel obstruction, and lower rates of reoperation. Despite these findings, the authors recognized that nonoperative management may not be successful in all patients and recommended examination of factors that might predict failure of nonoperative treatment to direct the optimal management strategy to the appropriate patients.

Few studies to date have investigated factors predicting failure of complicated appendicitis. Nadler et al.[11] published a study of 73 children who presented with perforated appendicitis and were treated nonoperatively. In that study, 26% of the patients failed nonoperative management and were more likely to have phlegmon present and to undergo CT-guided abscess drainage. In our study, both control and failure groups had similarly high rates of phlegmon (74% vs. 85%, respectively), and the majority had abscesses (55% vs. 75%). Our data also demonstrated that a similar proportion of patients in each group underwent CT-guided abscess drainage (41% for the control group and 35% for the failure group), a different observation from that reported in the study of Nadler et al. Importantly, the patients in the study of Nadler et al. were children, whereas our study population included adolescents and adults. Two other studies performed in pediatric patients with complicated appendicitis found that risk factors for failure included an initial band count more than 15%[12] and a presence of small bowel obstruction.[13] In our study, we did not assess white blood cell differential because of insufficient data. No patient in our cohort presented with bowel obstruction.

We found only one prospective randomized trial comparing nonoperative management of complicated appendicitis with or without interval appendectomy to immediate surgical appendectomy.[14] The number of patients in this study was small (n = 60), and few details were reported regarding failure of nonoperative management. More importantly, there are no published studies investigating factors on presentation of complicated appendicitis that could predict success or failure of nonoperative management.

This study focuses on radiologic factors on CT that have previously been associated with perforated appendicitis. CT has been increasingly used as an adjunct to physical examination and laboratory testing because it has been demonstrated to decrease the negative appendectomy rate from 26% without CT imaging to 6% to 10% with CT imaging.[15–17] The findings of this study are consistent with previous reports that demonstrated an association between presence of an appendicolith and severity of appendicitis.[18] Most importantly, there were no findings on CT scan that were predictive of failure of nonoperative management at a statistically significant level. Multiple findings were however slightly more common in patients who failed nonoperative management including free air, free fluid, and loculated air. In addition, despite the observation that smaller abscess were more common in the failure group, the rates at which small abscesses were percutaneously drained were similar between groups and not statistically significant. Most patients in both groups of this study underwent a follow-up CT scan, on average within 1 week of initial diagnosis. However, patients in the failure group were more likely to have an abscess present on follow-up CT scan. Moreover, patients in the failure group also had a statistically significant increase in the size of abscesses, which grew on average by nearly 50%. These findings suggest that follow-up CT scan is an important tool in evaluating the efficacy of nonoperative management of complicated appendicitis. If these studies were performed in a protocolized fashion early in the course of nonoperative management, failures might be identified earlier, thus decreasing hospital length of stay. To establish the need for follow-up CT scans and, if helpful, the best timing for these studies, further investigation will be required.

This retrospective study demonstrates that patients older than 15 years who present with complicated appendicitis and are tachycardic, have generalized abdominal tenderness, and have a history of tobacco use have a higher rate of failure when treated nonoperatively. Early operative intervention in those patients with signs of a systemic inflammatory response may be warranted; however, it should also be noted that more than half of patients in each category with a single sign of systemic illness were successfully managed nonoperatively. Moreover, patients who present with abscesses smaller than 50 mm also have a statistically significant increase in the rate of failure of nonoperative management. Given these findings, when presented with cases of complicated appendicitis and the

TABLE 5. Comparison of Management and Complications Between Each Group

	Controls	Failure	*p*
CT-guided abscess drainage	41%	35%	0.653
ICU admission	0%	10%	0.049
Length of stay, median (IQR), d	5 (5)	11 (6)	**0.001**
Recurrent abscess	15%	20%	0.551
Respiratory failure	0%	10%	**0.008**

ICU, intensive care unit.

TABLE 6. Surgical Details in Failure Group

Type of Operation	Within Group
Laparoscopic appendectomy	50%
Open appendectomy	15%
Laparoscopic converted to open appendectomy	0%
Ileocecectomy (laparoscopic or open)	30%
Other	5%

aforementioned signs and symptoms are present, immediate operative intervention should be strongly considered. These findings are particularly important in patients who have a small abscess, which may preclude percutaneous drainage. In these instances, a surgical drainage procedure with associated appendectomy may optimize outcomes and decrease lengths of stay.

The most significant limitation of this study is its retrospective nature. In addition, while the number of patients in this study is comparable with that performed in similar studies on pediatric patients, larger numbers of both failures and controls may have led to more clinical signs and symptoms and radiographic findings predictive of failure. However, because some factors did prove significant despite the small sample size, these should be heavily weighted in decisions regarding patient management.

Two questions remain unanswered by these data and the available literature, the first of which and perhaps most important, is whether there truly is an advantage to nonoperative management in patients with complicated appendicitis. Second, can patients who are likely to benefit from nonoperative management be definitively identified on presentation? Our study provides good evidence indicating that a subset of these patients should be strongly considered for early operative intervention. A prospective randomized study is needed to determine the true benefit of nonoperative management, and retrospective analysis of the prospectively collected data can likely add additional data regarding risk factors for nonoperative failure. Until these data become available, patients with appendiceal phlegmon or abscess and associated tachycardia, diffuse abdominal tenderness, and/or small abscesses should be considered for immediate operation.

AUTHORSHIP

K.M.S., M.W.M., and J.B. conceived of and designed this study. M.W.M., J.B., and E.A.M. acquired the data. M.W.M., K.M.S., J.B., and K.A.D. contributed to the analysis and interpretation of data. M.W.M., E.A.M., and J.B. drafted the manuscript, which M.W.M., K.M.S., and K.A.D. critically revised.

DISCLOSURE

The authors declare no conflicts of interest.

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