

Is It Safe to Delay Appendectomy in Adults With Acute Appendicitis?

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Objective: To examine whether delayed surgical intervention in adult patients with acute appendicitis is safe by correlating the interval from onset of symptoms to operation (total interval) with the degree of pathology and incidence of postoperative complications.

Summary Background Data: Prompt appendectomy has long been the standard of care for acute appendicitis because of the risk of progression to advanced pathology. This time-honored practice has been recently challenged by studies in pediatric patients, which suggested that acute appendicitis can be managed in an elective manner once antibiotic therapy is initiated. No such data are available in adult patients with acute appendicitis.

Methods: A retrospective review of 1081 patients who underwent an appendectomy for acute appendicitis between 1998 and 2004 was conducted. The following parameters were monitored and correlated: demographics, time from onset of symptoms to arrival at the emergency room (patient interval) and from arrival to the emergency room to the operating room (hospital interval), physical, computed tomography (CT scan) and pathologic findings, complications, length of stay, and length of antibiotic treatment. Pathologic state was graded 1 (G1) for acute appendicitis, 2 (G2) for gangrenous acute appendicitis, 3 (G3) for perforation or phlegmon, and 4 (G4) for a periappendicular abscess.

Results: The risk of advanced pathology, defined as a higher pathology grade, increased with the total interval. When this interval was <12 hours, the risk of developing G1, G2, G3, and G4, was 94%, 0%, 3%, and 3%, respectively. These values changed to 60%, 7%, 27%, and 6%, respectively, when the total interval was 48 to 71 hours and to 54%, 7%, 26%, and 13% for longer than 71 hours. The odds for progressive pathology was 13 times higher for the total interval >71 hours group compared with total interval <12 hours (95% confidence interval = 4.7–37.1). Although both prolonged patient and hospital intervals were associated with advanced pathology, prehospital delays were more profoundly related to worsening pathology compared with in-hospital delays ($P < 0.001$). Advanced pathology was associated with tenderness to palpation beyond the right lower quadrant ($P < 0.001$), guarding ($P < 0.001$), rebound ($P < 0.001$), and CT scan findings of peritoneal fluid ($P = 0.01$), fecalith ($P = 0.01$), dilation of the appendix ($P < 0.001$), and perforation ($P < 0.001$). Increased length of hospital stay

($P < 0.001$) and antibiotic treatment ($P < 0.001$) as well as postoperative complications ($P < 0.001$) also correlated with progressive pathology.

Conclusion: In adult patients with acute appendicitis, the risk of developing advanced pathology and postoperative complications increases with time; therefore, delayed appendectomy is unsafe. As delays in seeking medical help are difficult to control, prompt appendectomy is mandatory. Because these conclusions are derived from retrospective data, a prospective study is required to confirm their validity.

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Acute appendicitis is the most common surgical emergency in the United States.¹ Although the exact mechanisms leading to this condition are still obscure, it is likely that luminal obstruction by external (lymphoid hyperplasia) or internal (m-spissated fecal material, appendicoliths) compression plays a key pathogenic role. The luminal obstruction leads to increased mucus production, bacterial overgrowth, and stasis, which increase appendiceal wall tension. Consequently, blood and lymph flow is diminished, and necrosis and perforation follow. As these events occur over time, it is conceivable that early surgical intervention prevents progression of disease. Indeed, this notion provided the basis for the historical concept of immediate operation for patients with acute appendicitis. Nevertheless, a review of the literature indicates that the common practice of early appendectomy is supported by limited data. Furthermore, recent reports in pediatric patients suggest that postponing surgery with fluid and antibiotic treatment can be safely pursued.^{2–5}

The present study was designed to evaluate whether acute appendicitis in adult patients is indeed a surgical emergency requiring immediate intervention or a disease that can be approached in a semi-elective manner. To that end, the relationships between duration of symptoms, timing of surgery, degree of pathology, and complications were determined in all adult patients who underwent an appendectomy for acute appendicitis during a 6-year period in a tertiary care urban hospital.

PATIENTS AND METHODS

Patients

A retrospective analysis was performed on 1287 adult patients (≥ 16 years of age) who underwent an appendectomy for acute appendicitis at Yale New Haven Hospital between

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February 1998 and December 2004. Patients found to have a normal appendix (96, 7.5%), whose pathologic analysis differed from the intraoperative assessment (14, 1.9%), or without a documented time of onset of symptoms (96, 7.5%) were excluded. Preoperative data extracted from the patients' charts included: gender, age, physical and computed tomography (CT scan) findings, time from onset of symptoms to the emergency room (patient interval), and time from emergency department admission to the operating suite (hospital interval). Interval from onset of symptoms to surgery (total interval) was calculated by adding the patient and hospital intervals. Operative and pathologic findings were graded G1 for acute appendicitis, G2 for gangrenous appendicitis, G3 for perforated appendicitis or a phlegmon, and G4 for a periappendicular abscess. Postoperative data retrieved included length of hospital stay and of antibiotic treatment, complications, and mortality.

Statistical Analysis

Data were maintained on an Excel (Microsoft) spreadsheet and analyzed using the Mantel-Haenszel χ^2 test for trend, ordinal logistic regression, and linear regression where appropriate, as specified below.

The ordinal logistic regression is a proportional odds model that determines the cumulative odds of a less favorable response compared with a more favorable response.⁵ In this model, 3 log odds ratios (G4 vs. others; G4 or G3 vs. others; and grade G4, 3, 2 vs. 1) were defined and assumed to be parallel (ie, the effects of the risk factors were the same for the different log odds, but the intercepts are different). The resulting odds ratios may be interpreted as the relative likelihood for worsening pathology in the presence compared with the absence of a given risk factor. Separate multivariable models were evaluated for physical examination (PE) and CT findings using an automated backward selection procedure with a 0.05 significance level to stay in the model.

RESULTS

Demographics

Most patients were males in their 30s (Table 1). Advanced pathology was associated with the female gender ($P = 0.006$) and increase in age ($P < 0.001$).

Relationship Between Timing of Surgery and Degree of Pathology

The prevalence of advanced pathology, defined as a higher pathology grade, positively correlated with prolonged

total interval (P for trend, <0.001 , Fig. 1A). Odds ratios comparing the likelihood of advancing pathology between increasing total intervals were estimated using an ordinal logistic regression (Fig. 1B). The reference category for these odds ratios is a total interval <12 hours. The odds of advancing pathology were greater in prolonged total intervals compared with the reference category (P for trend, <0.001). For example, the risk for progressive pathology increased 13-fold when the total interval was greater than 71 hours. Patient (Fig. 2A) and hospital (Fig. 2B) intervals, the components of total interval, also increased with advanced pathology (P for trend, <0.01). However, there was a positive relationship of increasing patient to hospital interval ratio with pathology grade (P for trend, >0.001 , Fig. 2C).

Relationship Between Severity of Pathology and Physical Findings

The incidence of tenderness to palpation outside of the right lower quadrant (RLQ), RLQ rebound and guarding, and acute abdomen were associated with advanced pathology ($P \leq 0.001$) (Table 2). Similarly, as shown by the odds ratios, the risk of advanced pathology was increased for each of these findings (Table 2). For example, when tenderness outside of the RLQ was present, the likelihood of progressive pathology was increased by 2-fold. The association between these findings and advanced pathology remained significant in the multivariable model (Table 2).

Relationship Between Severity of Pathology and CT Scan Findings

The presence of peritoneal fluid and perforation increased with advanced pathology ($P < 0.001$) while visualized appendix was inversely related to severity of disease ($P < 0.001$) (Table 3). The odd ratios for advanced pathology correlated with these CT scan findings and remained significant in the multivariable analysis. In unadjusted analysis, dilatation, wall thickening, and nonfilling of the appendix were inversely related with worsening pathology (Table 3). However, in the multivariable model, these CT scan findings were not significantly associated with pathology grade (Table 3). Furthermore, the presence of a fecalith was not related to advanced pathology (Table 3), although after adjustment for the other CT scan findings, a positive correlation emerged between the presence of fecalith and advancing pathology (Table 3).

TABLE 1. Demographics of 1081 Studied Patients

	Pathology Grade				Total
	G1	G2	G3	G4	
n	802	64	172	43	1081
M:F ratio	1.42	1.78	1.05	0.59 [†]	1.32
Age (yr, mean \pm SD)	31.8 \pm 13.1	39.4 \pm 18.9	44.2 \pm 17.1	43.5 \pm 18.9 [†]	34.6 \pm 15.3

[†] P for trend = 0.006 by Mantel-Haenszel χ^2 .

[†] P for trend = 0.001 by linear regression. Please note that advanced pathology was associated with greater age and with female predominance. G1-G4 indicates pathology grades as defined in Patients and Methods.

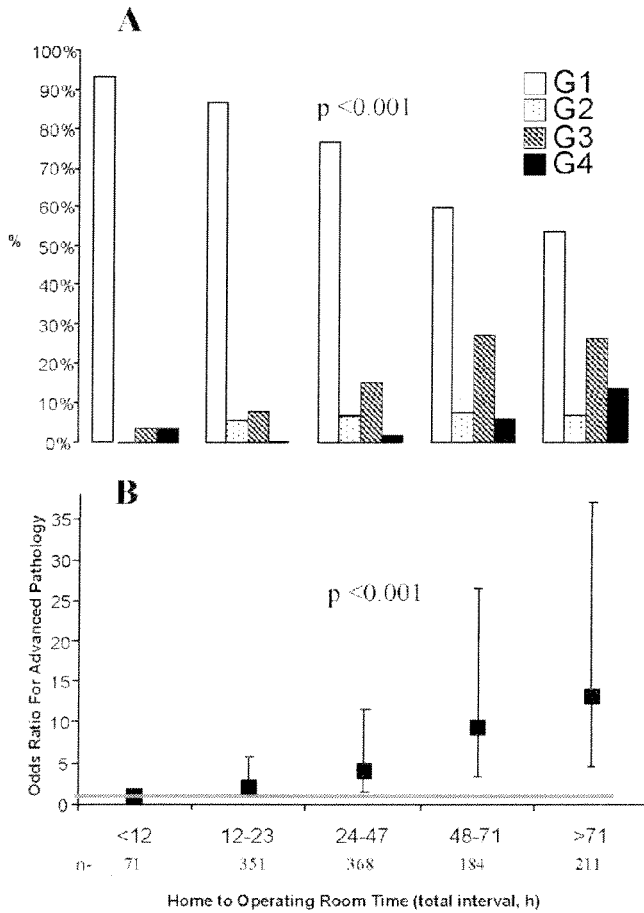


FIGURE 1. Relationship between advanced pathology and interval from onset of symptoms to surgery (total interval). A, Distribution of pathology grades per total intervals. B, Total interval and pathology grade proportions were compared using Mantel-Haenszel χ^2 test for trend. Odds ratios (OR) compare the likelihood of advanced pathology for a given total interval to those with a total interval less than 12 hours. Bars represent 95% confidence intervals (CI) and the dashed line indicates OR = 1 (ie, if 1 is contained within the 95% CI, then the odds for advanced pathology for this total interval are not significantly different than the odds for the <12 hours group). G1–G4, pathology grades as defined in Patients and Methods.

Relationship Between Severity of Pathology and Clinical Course

Length of hospital stay and antibiotic treatment (Table 4) as well as postoperative complications (Table 5) increased with advanced pathology. No mortality was recorded (Table 5).

DISCUSSION

The present study demonstrates that the severity of pathology and complication rate in adult patients with acute appendicitis are time dependent, and therefore suggests that delaying appendectomy is unsafe. This observation contrasts with reports in pediatric patients whose appendectomy was postponed overnight without an increase in perforation rate, morbidity,

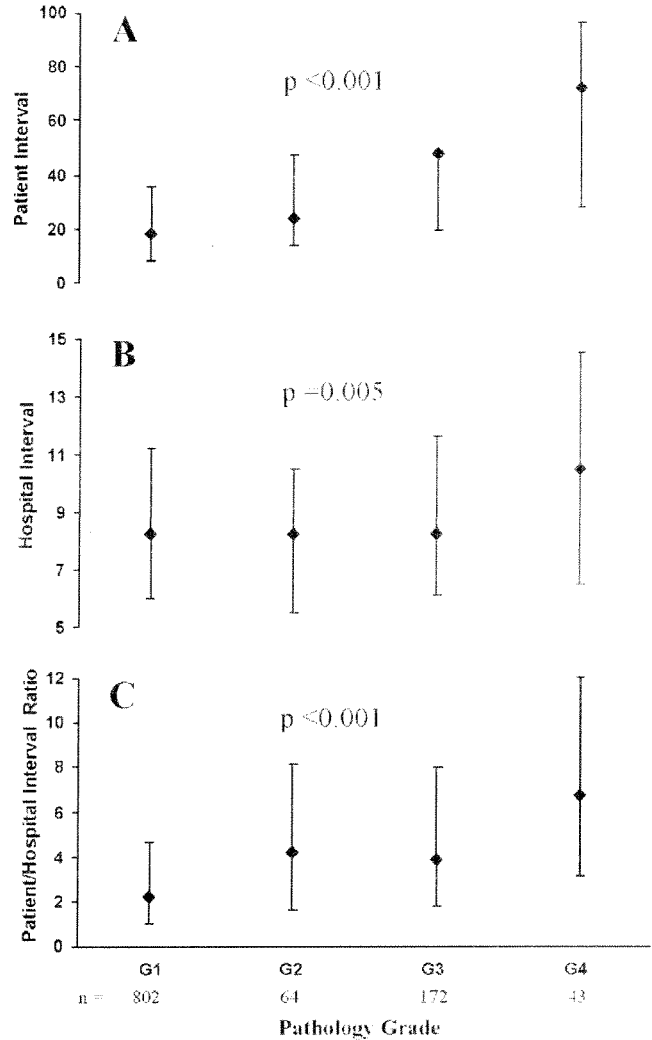


FIGURE 2. Relationship between patient to hospital interval ratio and degree of pathology. A, Relationship between patient interval and pathology grade. B, Relationship between hospital interval and pathology grade. C, Relationship between patient and hospital interval ratio and degree of pathology. Please note that increased patient and hospital intervals as well as patient and hospital interval ratio were associated with advanced pathology (P for trend from linear regression <0.01). This indicates that patient delay more significantly contributes to progressive pathology. Data are expressed as medians with bars representing 25th and 75th percentile. G1–G4, pathology grades as defined in Patients and Methods.

and duration of hospitalization.²⁻⁴ The reasons for these diverse observations remain speculative. Potential explanations include differences in the immune status and etiologies of acute appendicitis in adult compared with pediatric patients.

The core finding in support of the observation that pathology grade and symptom duration correlate positively is the quantification of the relationship between these 2 parameters. The use of a new pathology grading system, which unlike

TABLE 2. Relationship Between Advanced Pathology and Physical Findings

PE Findings (n = 1081)	Pathology Grade				P*
	G1	G2	G3	G4	
Tender to palpation: RLQ (n = 1040)	96.5	92.2	96.5	95.4	0.64
Tender to palpation: Other (n = 292)	22.9	29.7	39.5	48.8	<0.001
Guarding RLQ (n = 442)	37.7	51.6	51.2	44.2	0.001
Rebound RLQ (n = 344)	28.6	42.2	40.7	41.9	<0.001
Nontender (n = 8)	0.8	0	0	4.7	0.42
Acute abdomen (n = 17)	0.4	0	5.8	9.3	<0.001

PE Findings (n = 1081)	OR	95% CI	Adjusted OR [†]	95% CI
Tender to palpation-RLQ	0.79	0.41, 1.55	NS	—
Tender to palpation-other	2.19	1.65, 2.92	2.17	1.62, 2.92
Guarding RLQ	1.62	1.24, 2.13	1.34	1.05, 1.85
Rebound RLQ	1.72	1.30, 2.28	1.60	1.19, 2.15
Non tender	1.33	0.31, 5.78	NS	—
Acute abdomen	11.92	4.85, 29.33	6.20	2.46, 15.61

Estimated using Mantel-Haenszel χ^2 test for trend.

[†]Adjusted odds ratios obtained from multivariable ordinal logistic regression.

G1-G4 indicates pathology grades as defined in Patients and Methods; CI, confidence interval; PE, physical examination; NS, not selected for inclusion in multivariable model

TABLE 3. Relationship Between Advanced Pathology and CT Scan Findings

CT Findings (n = 689)	Pathology Grade				P*
	G1	G2	G3	G4	
Visualized appendix (n = 564)	86.0	81.4	73.0	58.3	<0.001
Fluid (n = 212)	26.7	20.9	43.7	52.8	<0.001
Fat stranding (n = 532)	77.5	81.4	79.4	61.1	0.34
Dilatation [‡] (n = 364)	57.2	53.5	46.0	16.7	<0.001
Wall thickening [‡] (n = 246)	37.6	34.9	33.3	19.4	0.05
Fecalith (n = 131)	16.7	32.6	27.0	5.6	0.25
Perforation (n = 54)	1.7	0	27.0	33.3	<0.001
Nonfilling Appendix (n = 114)	19.6	16.3	7.1	8.3	<0.001

CT Scan Findings (n = 689)	OR	95% CI	Adjusted OR [§]	95% CI
Visualized appendix	0.40	0.27, 0.58	0.36	0.24, 0.55
Fluid	2.03	1.45, 2.84	1.59	1.10, 2.29
Fat stranding	0.89	0.61, 1.29	NS	—
Dilatation [‡]	0.83	0.62, 1.11	NS	—
Wall thickening [‡]	0.73	0.52, 1.03	NS	—
Fecalith	1.41	0.95, 2.09	1.76	1.16, 2.68
Perforation	13.82	7.87, 24.28	11.70	6.55, 20.89
Nonfilling appendix	0.41	0.24, 0.69	NS	—

Estimated using the Mantel-Haenszel χ^2 for trend.

[‡]Defined as more than 6 mm.¹³

[‡]Defined as more than 3 mm.¹¹

[§]Adjusted odds ratios obtained from multivariable logistic regression.

G1-G4 indicates pathology grades as defined in patients and methods.

TABLE 4. Length of Hospital Stay and Antibiotic Treatment per Pathology Grade

	Pathology Grade				Total
	G1	G2	G3	G4	
n	802	64	172	41	1081
Length of hospital stay [days, median 25, 75th percentiles]	2 (1,2)	3 (2,4)	5 (3,7)	5 (4,6)	2 (1,3)
Length of antibiotic use [days, median (25, 75th percentiles)]	1 (1,1)	3 (2,4.5)	5 (3,6)	5 (3,6)	1 (1,3)

Please note that advanced pathology was associated with increased length of stay and antibiotic use.

*P for trend <0.001 by linear regression.

G1-G4 indicates pathology grades as defined in patients and methods.

previous studies includes the entire spectrum of acute appendicitis, and the exact time recording of events, allowed the calculation of the additional risk for advanced pathology per time interval. For example, when the total interval was less than 12 hours, the risk of developing G1, G2, G3, and G4, was 94%, 0%, 3%, and 3%, respectively. These values changed to 60%, 7%, 27%, and 6% when the total interval was 48 to 71 hours and to 54%, 7%, 26%, and 13% for longer than 71 hours. The odds for progressive pathology was 13 times higher when the total interval exceeded 71 hours compared with a total interval below 12 hours.

The data presented herein suggest that both patient and hospital factors affect the severity of acute appendicitis at the time of operation. However, the positive relationship of increasing patient to hospital interval ratio with pathology grade (Fig. 2C) indicates that patient delay in presenting to the emergency room was more profoundly related to worsening pathology compared with in-hospital delays. A similar observation was previously reported in 2 series,^{6,7} which included a much smaller number of patients (114 and 95, respectively). As the ability to minimize patient delay is limited, it is imperative that every effort is made by the hospital and physicians to expedite the evaluation and operation of patients with acute appendicitis. It should be noted that a previous study in 486 patients aged 5 to 85 years with acute appendicitis demonstrated that only patient but not hospital delay adversely affects the severity of disease.⁸ The lack of correlation between hospital factors and pathology grade in the latter study can be related to the inclusion of pediatric patients, who can be safely managed in a delayed fashion.²⁻⁴

Although the physical findings of acute appendicitis are well established,¹⁰ it is still unknown which ones predict advanced pathology. Analysis of the present data indicates that tenderness to palpation outside the right lower quadrant, right lower quadrant rebound and guarding, and acute abdomen correlate with advanced pathology as well as an increased risk for advanced pathology. Although intuitive, this observation has not been established previously in the literature.

Abdominal CT scan has become the main diagnostic tool for patients with acute appendicitis with a high sensitivity and specificity.¹⁰ Scanning of patients with suspected acute appendicitis has been shown to shorten the admission to operating

TABLE 5. Postoperative Complications per Pathology Grade and Number of Infectious and Noninfectious Complications

	Pathology Grade				Total
	G1	G2	G3	G4	
Infectious complications (n)	11	4	22	5	42
Noninfectious complications (n)	3	3	9	4	19
Total (n)	14	7	31	9	61
Mortality (n)	0	0	0	0	0
Infectious Complications					n
Intraabdominal infection					20
Wound infection					13
Pneumonia					3
Urinary tract infection					3
<i>C-difficile</i> colitis					1
Infected V-P shunt					1
Systemic infection					1
Total					42
Noninfectious Complications					n
Small bowel obstruction					4
Myocardial infarction					3
ARDS					1
Ischemic bowel					1
Duodenal ulcer					1
Pancreatitis					1
Aspiration					1
Lower GI bleed					1
Enterocutaneous fistula					1
Upper extremity neuritis					1
Wound hematoma					1
Stroke					1
Atrial fibrillation					1
Pulmonary embolus					1
Total					19

P for trend < 0.001 by Mantel-Haenszel χ^2 analysis.
G1-G4 indicates pathology grades as defined in Patients and Methods.

theater interval, reduce overall admission cost, and reduce the number of nontherapeutic appendectomies.¹⁰ The present study demonstrates that the presence of peritoneal fluid, perforation, and fecalith were associated with advancing pathology in the multivariate analysis. This supports an earlier report, which demonstrated correlation between the appendix diameter, dependent fluid, appendolithiasis, and extraluminal air with histologic diagnosis.¹¹ In contrast, another previous study failed to associate CT scan finding including visualization of the appendix, free

fluid, blurred pericecal fat, mesenteric fat stranding, and free air with final pathology results.¹²

CONCLUSION

The present study confirms the time dependency of pathology grade and complication rate on symptom duration in adult patients with acute appendicitis. Furthermore, it quantifies the relationships between these endpoints and identifies physical and CT scan findings, which can predict progressive pathology. Taken together, these findings suggest that appendectomy should be performed as expeditiously as possible once the diagnosis of acute appendicitis is established in adult patients. This information could impact hospital resource utilization and quality of life of the entire operating room team. It should be noted that the retrospective nature of the study does not allow definitive conclusions, which can be obtained in a prospective fashion only.

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