

Risk of Perforation in the Era of Nonemergent Management for Acute Appendicitis

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Prompt appendectomy has long been the standard of care for acute appendicitis because of the risk of progression to perforation. Recently, studies have suggested nonemergent management of acute appendicitis. Our study aimed to determine changes in risk of rupture and complications in patients with appendicitis, with increasing time from symptom onset to treatment. Retrospective study of patients aged ≥ 18 years presenting to the University of North Carolina Hospitals with signs and symptoms of acute appendicitis who subsequently underwent appendectomy from 2011 to 2015 was performed. Demographic, clinical, laboratory, and pathologic data were reviewed. Bivariate analysis was performed to assess variables associated with increased risk of perforation. Poisson regression modeling was completed to evaluate the risk of perforation and postoperative abscess based on time from symptoms to treatment. Within our database of 1007 patients, the mean time from onset of symptoms to operative intervention was 3.24 ± 2.2 days. Modified Poisson regression modeling demonstrated the relative risk for perforation increases by 9% (RR 1.09, $P < 0.001$) for each day delay. Age (RR 1.03), male gender (RR 1.50), temperature on admission (RR 1.32), and the presence of fecalith (RR 1.89) statistically significantly increased the risk of perforation. Furthermore, for each day delay, there is an 8% increased risk of postoperative abscess (RR 1.08, $P = 0.027$). The relative risk for appendiceal perforation is 9 per cent per day delay with a resultant 8 per cent increased risk of postoperative abscess. Thus, appendectomy for acute appendicitis should remain an emergent procedure, given that delays in operative management lead to complications and increases in cost of care.

ACU TE APPENDICITIS IS a common cause of abdominal pain in both pediatric and adult patient populations, with a lifetime risk of 7 to 8 per cent.¹ The peak incidence of the disease occurs in the second or third decade of life.² Most studies demonstrate a slightly higher incidence in male patients. The pathophysiology of appendicitis disease is thought to be luminal obstruction *via* a fecalith, tumor, lymphoid hyperplasia, or other causes.² Prompt appendectomy, either laparoscopic or open, has been the standard of care for acute appendicitis because of the risk of progression to perforation. Based on data from 2006 to 2008, more than 280,000 appendectomies are completed in the United States every year.^{3, 4} Approximately 16 per cent of these are for perforated appendicitis, but some estimates are as high as 24 per cent.^{4, 5}

Although appendicitis has long been treated as a surgical disease, recent studies have suggested non-emergent, or urgent, operative management of acute appendicitis. Following the recent publication of the

Finnish APPAC (appendectomy *versus* antibiotics in the treatment of acute uncomplicated appendicitis) randomized clinical trial, the use of antibiotics alone as the initial management of uncomplicated appendicitis has also emerged.⁶ A meta-analysis of randomized controlled trials comparing the safety and efficacy of nonoperative management (NOM), or treatment with antibiotics, *versus* appendectomy for the treatment of uncomplicated acute appendicitis demonstrated a 63 per cent initial success rate.⁷ NOM has especially been recommended for patients with acute uncomplicated, or nonperforated, appendicitis and in pediatric populations. However, NOM has a 25 to 30 per cent failure rate at one-year of treatment. Although antibiotic treatment may be initially successful in some patient populations, appendectomy continues to have higher one-year efficacy than NOM (98.3% *vs* 75.9%, respectively).⁸

Delays in surgical management, due to either initial treatment with antibiotics or nonemergent appendectomy, allow for the potential progression of acute appendicitis to appendiceal perforation. This puts patients at risk for serious sequelae including peritonitis, sepsis, and death. Increasing time between symptom onset and treatment may be a risk factor for a ruptured appendix,

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but little is known about how the risk changes with passing time. Furthermore, it is unclear whether the risk of appendiceal perforation is mainly related to the duration of inflammation or is secondary to patient-related factors. A recent multicenter retrospective cohort study demonstrated that delays in appendectomy are associated with an increase in the odds of perforation within a pediatric population.⁹ Understanding the progression of appendicitis to appendiceal perforation, and given the recent movement toward nonemergent management and NOM of acute appendicitis, we sought to evaluate the risk of perforation with increasing time from symptom onset to appendectomy.

Methods

A retrospective case-control study was completed by reviewing all patients at the University of North Carolina (UNC) Memorial Hospital who underwent appendectomy from January 1, 2011, to December 31, 2015. The UNC Institutional Review Board approved this study. The electronic medical record was reviewed to confirm whether appendectomy was performed after clinical suspicion of appendicitis. Only patients who were aged ≥ 18 years at the time of appendectomy were included in the study. Variables collected included basic demographics, clinical and laboratory findings on admission, abdominal imaging modalities, operative procedure and characteristics, postoperative complications, and the histopathology report. Time to appendectomy was defined as the length of time from onset of symptoms to appendectomy in days.

Bivariate analysis was performed to assess variables associated with increased risk of perforation, including time to appendectomy, age, gender, WBC count and temperature on initial presentation to the emergency department, and presence of a fecalith. Chi-square

analysis was completed for categorical variables, and for continuous variables, either an independent sample *t* test or Wilcoxon rank-sum test was used based on a normal or nonnormal distribution, respectively. Modified Poisson regression modeling was used to evaluate the association of these variables with risk of appendiceal perforation with increasing time to appendectomy. Binomial regression was used to determine the risk for postoperative abscess based on time to appendectomy. All calculations and statistical analysis were performed in Stata version 15 (2017, StataCorp LLC, College Station, TX).

Results

From 2011 to 2015 at the UNC Memorial Hospital, 1647 patients underwent appendectomy. After the exclusion criteria, 1007 patients who underwent appendectomy for acute appendicitis were analyzed. Within our database of 1007 patients, the mean time from onset of symptoms to operative intervention was 3.2 ± 2.2 days (Table 1). Bivariate analysis revealed that gender, race, age, temperature at admission, time to appendectomy, and presence of a fecalith were all significantly correlated with risk of perforation.

Modified Poisson regression modeling demonstrated that the relative risk for perforation increases by 8.8 per cent (RR 1.09 [95% confidence interval (CI): 1.05, 1.13], $P < 0.001$) for each day delay from symptom onset to appendectomy (Table 2). Other factors that increased the relative risk of appendiceal perforation were increasing age, male gender, temperature at admission, and the presence of a fecalith (Table 2). With each one-year increase in age, there was a 3 per cent increased relative risk of appendiceal perforation (RR 1.03 [95% CI: 1.02, 1.03], $P < 0.001$). When considering a patient's temperature on admission, for every

TABLE 1. Baseline Characteristics and Bivariate Analysis

	Overall (n = 1007)	No Perforation (n = 832)	Perforation (n = 175)	P Value
Gender				0.004
Female	503 (50%)	433 (52%)	70 (40%)	
Male	504 (50%)	399 (48%)	105 (60%)	
Race				0.017
White	622 (62.2%)	505 (60.7%)	117 (66.9%)	
Hispanic	220 (22%)	193 (23.2%)	27 (15.4%)	
Black	94 (9.4%)	79 (9.5%)	15 (8.6%)	
Asian	34 (3.4%)	22 (2.6%)	12 (6.9%)	
American-Indian	1 (0.1%)	1 (0.1%)	0 (0%)	
Other	29 (2.9%)	26 (3.1%)	3 (1.7%)	
Age (years)*	38.4 \pm 16.7	36.4 \pm 15.8	47.6 \pm 17.6	<0.001
WBC (1,000)*	13.5 \pm 4.3	13.5 \pm 4.3	13.9 \pm 4.8	0.177
Temperature ($^{\circ}$ C)*	36.8 \pm 1.29	36.7 \pm 1.4	37 \pm 0.9	0.006
Time to appendectomy (days)*	3.2 \pm 2.2	3.1 \pm 2.1	3.9 \pm 2.7	<0.001
Fecalith	112 (11.1%)	74 (8.9%)	38 (21.7%)	<0.001

* Includes SD.

TABLE 2. *Modified Poisson Regression Model for Appendiceal Perforation*

	RR	P Value	95 per cent CI
Time to appendectomy (days)	1.09	<0.001	(1.05, 1.13)
Age (years)	1.03	<0.001	(1.02, 1.03)
Male gender	1.50	0.003	(1.15, 1.95)
Temperature (°C)	1.32	0.001	(1.12, 1.56)
Fecalith	1.89	<0.001	(1.38, 2.59)

TABLE 3. *Logistic Binomial Regression Model for Postoperative Abscess*

	RR	P Value	95 per cent CI
Time to appendectomy (days)	1.08	0.027	(1.01, 1.16)
Age (years)	1.02	0.001	(1.01, 1.04)
Male gender	1.14	0.618	(0.68, 1.91)
Temperature (°C)	1.38	0.045	(1.01, 1.89)
Fecalith	1.38	0.364	(0.69, 2.76)

TABLE 4. *Association of Perforation with Postoperative Complications*

	Overall (n = 1007)	No Perforation (n = 832)	Perforation (n = 175)	P Value
Postoperative abscess	55 (5.5%)	21 (2.5%)	34 (19.4%)	<0.001
Postoperative wound infection	17 (1.7%)	9 (1%)	8 (4.6%)	0.001

1°C increase, there was a 32 per cent increased relative risk of developing appendiceal perforation (RR 1.32 [95% CI: 1.12, 1.56], $P = 0.001$). Male gender was associated with a 50 per cent increased relative risk of having perforation (RR 1.50 [95% CI: 1.15, 1.95], $P = 0.003$). Finally, the presence of a fecalith on pathology was associated with an 89 per cent increased relative risk of appendiceal perforation (RR 1.89 [95% CI: 1.38, 2.59], $P < 0.001$).

We also evaluated the association between time to appendectomy and postoperative complications. For every day delay of surgery, the relative risk of postoperative abscess increases by 8 per cent (RR 1.08 [95% CI: 1.01, 1.15], $P = 0.027$) (Table 3). Time to appendectomy was not significantly associated with an increased relative risk for wound infection. However, patients who had a perforated appendix on pathology were more likely to have postoperative complications, including abscess (19.4% vs 2.5%, $P < 0.001$) and wound infections (4.6% vs 1%, $P = 0.001$) (Table 4).

Discussion

In this study, we demonstrate a 9 per cent increase in relative risk with each day delay from onset of symptoms to time of appendectomy, after controlling for pertinent covariates. We also determined that increasing patient age, male gender, elevated temperature at the time of admission to the hospital, and the presence of a fecalith were all statistically significantly associated with increased risk of appendiceal perforation. These characteristics are important to consider when advising

patients about the risk of perforation associated with both NOM and nonemergent appendectomy. In particular, patients with a fecalith have an 89 per cent increased relative risk for appendiceal perforation.

Our findings are supported by the current literature. A recent study by Sammalkorpi et al.¹⁰ found that the incidence of appendiceal perforation doubled from 9.5 to 18.9 per cent when the in-hospital delay to appendectomy increased from less than 6 hours to greater than 12 hours. Similarly, Busch et al. demonstrated that time delays greater than 12 hours were associated with a higher frequency of perforated appendicitis (29.7% vs 22.7%).¹¹ Because we report time to appendectomy in the format of days instead of hours, it is difficult for us to make a case against urgent management of appendicitis. However, we believe our results make a strong argument against delayed operative management of acute appendicitis greater than 24 hours, particularly in the presence of fecalith, given the risk for progression to perforation.

Our results also demonstrate an 8 per cent increase in the relative risk of postoperative abscess for each day delay of appendectomy. Furthermore, complicated appendicitis is shown to be correlated with postoperative complications, including abscess and wound infection. A study by Jeon et al.¹² reviewed more than 4000 patients who underwent appendectomy for suspected appendicitis and found that those patients whose surgery was delayed for >18 hours had more postoperative complications. Similarly, Bhangu et al.¹³ demonstrated that after 48 hours of surgical delay, the risk of surgical site infection and 30-day adverse events increased (adjusted OR 2.24 and 1.71, respectively). A more

recent study by Patel et al.¹⁴ evaluated delays in surgery for patients with acute appendicitis. They show that the risk of complications was associated with time from triage to surgery of more than 24 hours. Furthermore, Saar et al.¹⁵ evaluated 255 patients with acute appendicitis and demonstrated that delay to surgery in 12-hour increments showed a stepwise adjusted increase in complications. Delay to appendectomy also significantly increased duration of surgery and hospital length of stay (LOS), respectively.

There are significant implications of a delayed operative strategy for acute appendicitis, especially in regard to cost. A recent retrospective study by Sibia et al. evaluated the financial sequelae after appendectomy.¹⁶ Of the 741 patients they evaluated with appendicitis, 42.1 per cent were diagnosed with complicated acute appendicitis. The median LOS was one day (range, 0–21 days). The median hospital cost was \$4,183 (range, \$2,075–\$71,023). Increasing cost was attributable to abscess formation and the subsequent diagnostic workup, including repeat imaging, interventional radiology procedures, and associated pharmacotherapy. In addition, Sibia et al. showed that the 90-day readmission rate was 3.2 per cent.¹⁶ This varied significantly for patients who presented early (2.1%), without perforation or abscess, *versus* those who presented late with generalized peritonitis (8.8%) and were found to have gangrene, perforation, or an abscess. The mean cost per readmission was \$5,025 (range, \$1,595–\$10,795). LOS, hospital costs, and 90-day readmissions were significantly higher for complicated *versus* uncomplicated acute appendicitis. The cost implications associated with perforated appendicitis during both the initial hospitalization and readmissions were impressive and should be strongly considered when contemplating delaying surgical intervention for a patient with acute appendicitis.

Conclusion

There is a 9 per cent increased relative risk for appendiceal perforation per day delay of appendectomy with a resultant 8 per cent increase in relative risk of postoperative abscess. The associated cost implications for delay in appendectomy for both the patient and the health-care system are high, particularly after considering both the initial hospitalization and the increased potential for readmission to the hospital. We recommend prompt appendectomy for all patients presenting with acute appendicitis. Patient characteristics that increase the risk of appendiceal perforation include increasing patient age, male gender, and higher temperature at the time of admission to the hospital. However, patients with a fecalith identified on abdominal imaging are at the highest risk for perforation

and should continue to have their appendectomy performed as an emergent procedure.

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