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Risk of perforation increases with delay in recognition and surgery for acute appendicitis

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Abstract

Background—Appendicitis remains a common indication for urgent surgical intervention in the United States, and early appendectomy has long been advocated to mitigate the risk of appendiceal perforation. To better quantify the risk of perforation associated with delayed operative timing, this study examines the impact of length of inpatient stay preceding surgery on rates of perforated appendicitis in both adults and children.

Methods—This study was a cross-sectional analysis using the National Inpatient Sample and Kids' Inpatient Database from 1988–2008. We selected patients with a discharge diagnosis of acute appendicitis (perforated or nonperforated) and receiving appendectomy within 7 d after admission. Patients electively admitted or receiving drainage procedures before appendectomy were excluded. We analyzed perforation rates as a function of both age and length of inpatient hospitalization before appendectomy.

Results—Of 683,590 patients with a discharge diagnosis of appendicitis, 30.3% were recorded as perforated. Over 80% of patients underwent appendectomy on the day of admission, approximately 18% of operations were performed on hospital days 2–4, and later operations accounted for <1% of cases. During appendectomy on the day of admission, the perforation rate was 28.8%; this increased to 33.3% for surgeries on hospital day 2 and 78.8% by hospital day 8 ($P < 0.001$). Adjusted for patient, procedure, and hospital characteristics, odds of perforation increased from 1.20 for adults and 1.08 for children on hospital day 2 to 4.76 for adults and 15.42 for children by hospital day 8 ($P < 0.001$).

Conclusions—Greater inpatient delay before appendectomy is associated with increased perforation rates for children and adults within this population-based study. These findings align with previous studies and with the conventional progressive pathophysiologic appendicitis model. Randomized prospective studies are needed to determine which patients benefit from nonoperative *versus* surgically aggressive management strategies for acute appendicitis.

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Keywords

Surgical outcomes; National Inpatient Sample; Kids' Inpatient Database; Acute appendicitis; Perforated appendicitis; Appendectomy; Delayed operation

1. Introduction

Acute appendicitis is the most common indication for emergent surgical procedures in the United States. It affects approximately 250,000 patients each year [1], including 77,000 children [2]. Lifetime incidence for appendicitis is 8.6% for males and 6.7% for females, with maximal incidence at age 10–14 y in males and 15–19 in females [3]. After a period in which research focused primarily on options for surgical management, including laparoscopy [4] and selective nonoperative management [5], attention has increasingly turned to operative timing during the index admission. The conventional disease model for acute appendicitis was described in the early 20th century [6,7], which proposes a progressive inflammatory process triggered by luminal obstruction of the appendix and culminating in perforation resulting from infection and ischemic necrosis. The presumptive time-dependent progression from appendiceal inflammation to rupture and abscess formation has served as the primary justification for prompt surgical intervention.

By this paradigm, delay of either antibiotic administration or appendectomy is deleterious, because it permits the pathologic process of appendicitis to proceed unchecked toward perforation. Impediments to immediate treatment may occur at multiple points as the patient proceeds through the health care system: in the pre-hospital setting, patients may not immediately seek treatment for symptoms; in the outpatient clinic or Emergency Department, providers may not diagnose the condition or refer appropriately; and even after diagnosis and hospital admission, facilities may be inadequately equipped or staffed to provide timely surgery. The present study sought to examine the specific interval of delay separating hospital admission and appendectomy using a nationwide discharge database. In comparing patients receiving same-day appendectomy with those whose operation was delayed, we were able to attempt to quantify the increased risk of an operative finding of perforated appendicitis resulting from delay in surgical treatment after hospital presentation.

2. Methods

2.1. Data acquisition

We performed a retrospective analysis using a combination of the Nationwide Inpatient Sample (NIS) (1988–2008) and the Kids' Inpatient Database (KID) (1997, 2000, 2003, and 2006). Both the NIS and KID have been developed as part of the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. The NIS is an all-payer database that currently compiles information on up to 8.16 million inpatient discharges across the United States each year. Hospitals are selected to represent a 20% stratified sample of all community hospitals. Data from 759–1056 hospitals located in eight to 42 states were available in the data set under study [8]. The KID contains a sample of pediatric (age < 20) discharges from all community, non-rehabilitation hospitals from states

that participate in HCUP. The KID samples 1.91–3.13 million patient discharges, rather than sampling at the hospital level like the NIS. Patient discharges are then weighted to obtain national estimates. The KID contains information from 2521–3739 hospitals in 22–38 states over the period studied [9]. Because of overlap between the NIS and KID for the years 1997, 2000, 2003, and 2006, we used only KID data when selecting pediatric cases for these years.

The Institutional Review Board of Johns Hopkins Medicine deemed this study exempt. The data use agreement from Agency for Healthcare Research and Quality and HCUP does not allow the reporting of information when the number of observations is ≤ 10 , to help maintain patient confidentiality. Therefore, we have entered “ ≤ 10 ” in cases where there were 10 or fewer observations in any category. We calculated the reported P values and confidence intervals using the exact number of observations obtained in the analysis. All statistical analyses were performed using Stata MP, version 11 (College Station, TX).

We initially selected patients from the NIS and KID databases if they had an International Classification of Diseases, 9th Revision (ICD-9) diagnosis code corresponding to acute appendicitis, with (540 and 540.9) or without evidence of perforation (540.0 and 540.1), and International Classification of Diseases, Clinical Modification (ICD-9-CM) procedure codes for therapeutic open or laparoscopic appendectomy (470, 470.1, and 470.9). We excluded patients with admission types designated as other than “emergent” or “urgent,” as well as patients who underwent simple abdominal drainage before appendectomy (ICD-9 CM procedure codes 472, 472.0, and 54.91). Both NIS and KID report the interval (in calendar days) that separates hospital admission from inpatient surgical procedures; we excluded patients receiving surgery more than 7 d after admission to avoid capturing interval appendectomy.

2.2. Data analysis

We performed a descriptive analysis using variables of gender, race, insurance status (uninsured or insured), geographic region (Northeast, Midwest, South, or West), type of hospital (urban teaching, urban non-teaching, or rural) and type of surgical procedure performed (laparoscopic or open appendectomy). We performed comparisons between groups (perforated and nonperforated) using Pearson's chi-square for categorical variables and the Kruskal-Wallis test for non-normally distributed continuous variables.

For analysis of outcome associated with increasing delay of surgery after admission, we performed multiple logistic regression to assess the risk of perforation associated with each interval. This multivariate analysis controlled for the variables of age, gender, race, insurance status, geographic region, type of hospital, type of surgical procedure (laparoscopic or open appendectomy), and comorbid conditions. We assessed the number of comorbid conditions by counting the number of unique ICD-9 codes associated with each admission. We calculated odds ratios using the immediate operation (occurring on the same day as admission) as the reference group.

3. Results

3.1. Patient demographics and hospital characteristics

We identified a total of 683,590 discharged patients who met inclusion criteria; of these, 450,858 (66%) were adults (age >18 y) and 232,732 were children. Figure 1 provide age distributions for perforated and nonperforated cases. A total of 400,352 patients (59%) were male, and 388,879 patients (57%) were white (Table 1). Most patients were treated in hospitals in the South (34%) and Northeast (25%); 85% of admissions were to urban hospitals, most of which were non-teaching institutions (47% of all discharges).

3.2. Case characteristics

Most patients (70%; $n = 476,192$) were discharged with a diagnosis of uncomplicated acute appendicitis; 207,346 were discharged with a diagnosis of acute appendicitis complicated by peritonitis or intra-abdominal abscess. A total of 72% of patients ($n = 493,191$) were treated with open appendectomy and 190,399 patients received laparoscopic appendectomy. A total of 554,368 procedures (81.1%) were performed on the day of admission and 107,989 (15.8%) were performed on the second hospital day. Thereafter, the number of procedures decreased from 11,638 (1.7%) on the third hospital day to 560 (0.1%) by hospital day 8. The proportion of appendectomies performed on the day of admission ranged from 79.0%–82.5% for each of the years studied, with a significant trend toward earlier appendectomy in more recent admission years ($P = 0.015$).

Pediatric patients were significantly more likely to have perforation at the time of operation, and were more likely to receive open appendectomy than were adult patients ($P < 0.001$); children also received surgical intervention earlier in their hospital course than did adults ($P < 0.001$). Examined separately, patients at both extremes of age were significantly more likely to have perforated appendicitis at operation. Male patients were more likely to experience perforation, independent of age (Table 1). With respect to hospitals, most patients were seen in the South region and in urban, non-teaching hospitals. Patients with perforated appendicitis had longer inpatient admissions, with a median length of stay of 5 d (interquartile range [IQR] 3–7 d), versus 2 d (IQR 1–3 d) for patients with uncomplicated appendicitis. Patients with perforated appendicitis also had higher total hospital charges (adjusted for inflation to 2008 US dollars); median charges were \$18,034 (IQR 11,869–27,786) versus \$11,081 (IQR 7327–16,925) for patients with uncomplicated appendicitis.

Patients undergoing appendectomy on the day of admission had an overall rate of perforation of 28.8%. The rate of perforation progressively increased with each additional interval day between admission and appendectomy, reaching 78.8% by the eighth hospital day ($P < 0.001$). This association was independent of patient age, with the proportion of perforated cases rising from 28.7% to 77.4% for adult patients (Fig. 2A) and from 28.9% to 83.8% for children (Fig. 2B). After adjusting for patient, procedural, and hospital factors, as well as for year of admission, the odds ratio for perforation when appendectomy was performed on the second hospital day was 1.10 (95% confidence interval [CI]: 1.08–1.13) for adults and 0.96 (95% CI: 0.92–1.01) for children, relative to appendectomy performed at admission. We observed increasing odds ratios for perforation for each additional

intervening day between admission and operation. Relative to immediate appendectomy, a delay of 7 d was associated with an odds ratio of 2.79 (95% CI: 2.12–3.67) for adults and 9.53 (95% CI: 5.03–18.05) for children (Table 2).

4. Discussion

The present study demonstrates a significant rise in the risk of perforation in cases of acute appendicitis associated with delay in inpatient surgical management. Results are drawn from the largest sample of inpatient records, 683,590 cases, representing clinical progression of appendicitis, which represent a nationwide sample over a 20-y period. The use of all-payer administrative databases avoids management biases that may exist in single-center retrospective studies or patient registries, and therefore reflects the outcomes generated by the US health care system in aggregate. We observed an overall rate of perforation of 30.3% in the present study, which is similar to rates previously reported in studies at the population level [10].

Delay to surgery independently predicted increased odds of perforation, with escalating risk associated with appendectomy undertaken at progressively later times after admission. This is consistent with the findings of previous single-institution investigations in both adult and pediatric patients. Golladay and Sarrett [11] examined delayed diagnosis in 422 pediatric patients over 7.5 y in the 1980s, finding an 81% perforation rate for patients with delayed diagnosis, *versus* 28% for those who received a timely diagnosis. Bickell *et al* [12] reviewed the records of 219 cases of appendicitis treated between 1996 and 1998, and found that perforation rates rose in association with increasing delay between symptom onset and treatment. In that study, patients with untreated symptoms for >36 h had a relative risk of perforation 6.6 times greater than did patients with a shorter symptomatic interval. Ditillo and colleagues [13] similarly examined the interval between onset of symptoms and operation in 1081 adult patients with acute appendicitis between 1998 and 2004, and found that greater delay was associated with worsening pathologic grade of the appendix at appendectomy. Busch *et al* [14] examined in-hospital delay in 1827 cases of adult appendicitis between 2003 and 2006, and observed a significantly increased perforation rate (29.7% *versus* 22.7%) when appendectomy was delayed >12 h. In-graham and colleagues [15] analyzed 32,782 patient records from the American College of Surgeons National Surgical Quality Improvement Program database and reported significant differences in perforation rates between when appendectomy was delayed for >12 h *versus* <6 h, although overall perioperative morbidity was unchanged.

Within the context of the historical model describing the time-dependent pathogenesis of appendicitis, the finding of increased perforation risk with greater delay comes as no surprise. This phenomenon, taken together with the increased morbidity and cost associated with perforation [14,16–22], serves for many as the primary justification for prompt surgical intervention in all cases of acute appendicitis. Indeed, differential perforation rates have been proposed by multiple investigators as a proxy for timely referral and operative intervention and, by extension, as a means to estimate disparities in health care access and quality of care [23–32]. Differences in the rate of escalation of odds ratios between adults and children in this temporal analysis suggest that a more individualized approach in future

research examining discrete risk factors for perforation may yield important insights necessary to reconcile conflicting perspectives in the literature.

Alternative models have been proposed that call into question the value of early intervention. The existence of spontaneous resolution of nonperforated appendicitis is acknowledged, but estimates of its incidence relative to progressive disease vary widely [33,34], as do accounts of recurrent disease [35]. Some authors have hypothesized the existence of two distinct disease variants, one with greater propensity for perforation [36–38]. Considering the low morbidity of appendectomy, the relative magnitude of risk associated with urgent intervention for nonperforated appendicitis *versus* the risk entailed with failure of nonoperative management with antibiotic therapy alone remains the subject of active inquiry [5,39,40]. Two recent meta-analyses of randomized prospective studies comparing antibiotic and operative therapy conducted between 1995 and 2011 reached different conclusions regarding the practical implications of the overall findings: One reported that the extant data were inconclusive, and the other determined that management with antibiotics alone is safe and effective [41,42]. Ingraham and colleagues [15] reported no difference in 30-d morbidity when treatment was delayed, despite the increased perforation rate. These data are difficult to reconcile with the traditional understanding of appendicitis and data supporting the desirability of early intervention. Given the breadth of literature supporting a progressive pathophysiologic model and lack of prospectively validated clinical criteria to employ in selecting patients who might benefit from nonoperative management, this debate will likely continue.

Reporting patterns from administrative databases is always susceptible to bias; however, we attempted to control for recognizable factors in this analysis. Changing clinical patterns over time are apparent (e.g., ratio of open to laparoscopic appendectomies), but the question of whether delay in recognition or intervention leads to perforation should not be greatly confounded by advances in practice. Conversely, and to the advantage of these data, the national databases are presumably free of unquantified geographic variation and institutional practice patterns, perhaps relating more directly to an unbiased natural history of appendicitis.

Other limitations of this study are largely attributable to the data reporting within the NIS and KID databases. The present study used days from the date of admission as the time variable for its association with perforation. However, this is unable to account for the time of day a patient is admitted or receives an operation. For example, a patient admitted at 10:00 PM who underwent appendectomy 3 h later at 1:00 AM would be assigned to the “second hospital day” category, whereas a patient admitted at 1:00 AM and receiving appendectomy at 10:00 PM on the same calendar day would be assigned to the “day of admission” group. This increases the uncertainty of the findings because it may lead to misclassification of operative intervention as “early” *versus* “late” and introduce bias into the results reported here. In addition, operative timing was not universally reported, and we excluded approximately 17% of all patients receiving appendectomy for missing data. A post hoc comparison of this excluded cohort revealed no difference in perforation rates ($P = 0.351$) after controlling for demographic and clinical differences.

A second important limitation is a confounding effect from patients who present to the hospital with appendicitis that has already progressed to perforation. The findings of investigators suggest that perforation in the pre-hospital setting is common and may represent the most significant interval of risk [36–38]. These patients may have been managed differently as inpatients, although it is not possible to identify these cases or adjust for such an effect in our analysis. Although many factors, including diagnostic uncertainty, surgeon availability, or clinical judgment, likely contribute to delays in surgery observed in the present study, it is not possible to ascertain their relative contributions from the data used. Details regarding antibiotic administration are likewise unavailable. The proportionately small numbers of patients receiving appendectomy after the fourth hospital day (0.75%; $N = 5101$) also raises the question as to whether the association observed between perforation and delay reflects intrinsic differences in this narrow subpopulation. The addition of concurrent diagnoses to adjust the multivariate analysis for patient complexity resulted in smaller odds ratios for perforation, but the association of escalating odds of perforation with greater delay persisted in the results reported here.

Other factors that may influence the patient outcomes were not specifically addressed in this analysis, but are relevant to medical decision making in cases of suspected appendicitis. We included only patients who received an appendectomy, but further review of the NIS and KID data reveal that nonoperative management of acute appendicitis was rare in the population selected. Only 4% of patients admitted with acute appendicitis did not have procedure codes for appendectomy, but over half of these patients received other invasive procedures, such as abdominal drainage, cecectomy, and hemicolectomy. Up to 15% of appendectomy specimens do not reveal appendicitis, and negative appendectomy is associated with significant health care costs as well as peri-operative morbidity [43]; however, the present study did not consider the rates of negative appendectomy.

Whereas a growing body of evidence has demonstrated some success in the nonoperative management of patients with appendicitis, to the benefit of selected patients who may safely avoid the risks of surgery [5,39,44], this option has its own inherent risk. Patients receiving appendectomy fare better in this analysis when the operation is performed early, even after adjusting for other factors. These data demonstrate a significant association between inpatient delay preceding operation and the outcome of perforation, which may or may not be causal. Prompt diagnosis of acute appendicitis should be emphasized, irrespective of the ultimate management strategy, to make the safest and most informed decisions regarding patient care.

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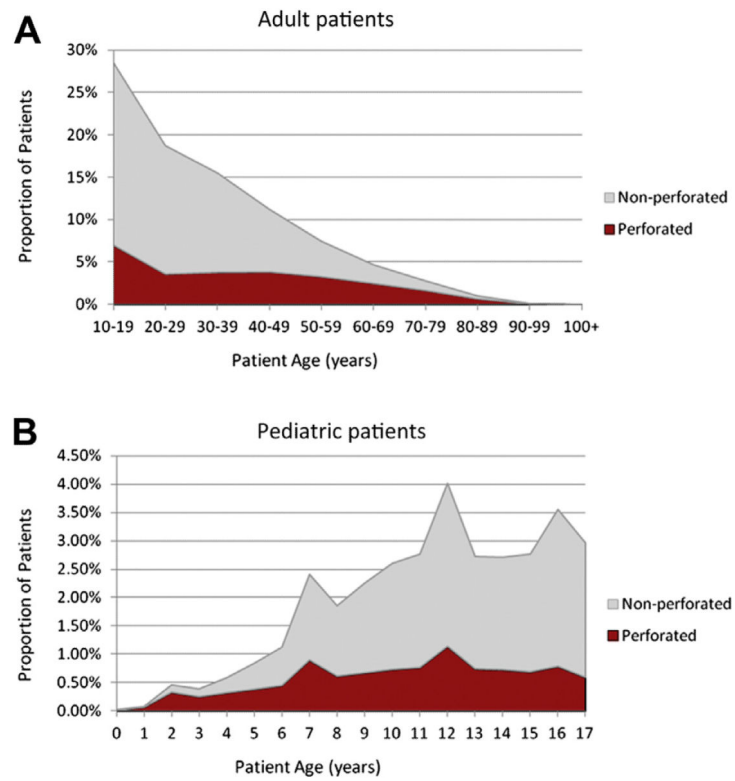


Fig. 1. Age at presentation for acute perforated and nonperforated appendicitis. (A) Adult patients. (B) Pediatric patients. (Color version of figure is available online.)

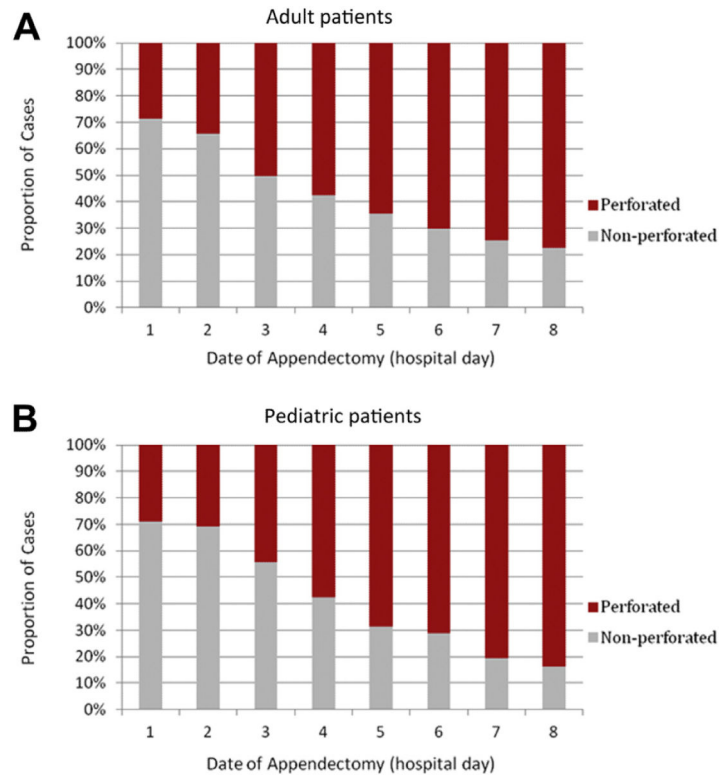


Fig. 2. Proportion of perforated and nonperforated appendicitis displayed by interval between admission and appendectomy. (A) Adult patients. (B) Pediatric patients. (Color version of figure is available online.)

Table 1

Patient characteristics.

	Nonperforated		Perforated		P value
Adult					
Male, <i>n</i> (%)	176,101	(56.3)	81,760	(59.2)	<0.001
Age, <i>y</i> , mean (SD)	36.0	(14.6)	45.9	(17.8)	<0.001
Race, <i>n</i> (%)					<0.001
White	181,415	(58.0)	83,339	(60.3)	
Black	17,300	(5.5)	8012	(5.8)	
Hispanic	36,838	(11.8)	13,189	(9.5)	
Other/unspecified	77,078	(24.7)	33,687	(24.4)	
Insured, <i>n</i> (%)	248,028	(79.3)	111,884	(80.9)	<0.001
Comorbid diagnoses, mean (SD)	2.19	(1.89)	3.73	(2.88)	<0.001
Total	312,631	(69.3)	138,227	(30.7)	
Pediatric					
Male, <i>n</i> (%)	100,018	(61.1)	42,473	(61.4)	0.174
Age, <i>y</i> , mean (SD)	12.0	(3.6)	10.5	(4.1)	<0.001
Race, <i>n</i> (%)					<0.001
White	90,432	(55.3)	33,693	(48.7)	
Black	9099	(5.6)	5080	(7.4)	
Hispanic	25,578	(15.6)	13,507	(19.5)	
Other/unspecified	38,487	(23.5)	16,856	(24.4)	
Insured, <i>n</i> (%)	144,062	(88.1)	59,787	(86.5)	<0.001
Comorbid diagnoses, mean (SD)	1.46	(0.93)	2.31	(1.72)	<0.001
Total	163,596	(70.3)	69,136	(29.7)	

SD = standard deviation.

Table 2

Adjusted risk of perforation.*

	Adult	Pediatric
	odds ratio (95% CI)	odds ratio (95% CI)
Day of admission (1)	Ref	Ref
Hospital day 2	1.10 (1.08-1.13)	0.96 (0.92-1.01)
Hospital day 3	1.63 (1.54-1.73)	1.33 (1.20-1.48)
Hospital day 4	1.79 (1.64-1.96)	2.47 (2.02-3.04)
Hospital day 5	2.25 (1.98-2.54)	3.35 (2.58-4.35)
Hospital day 6	2.74 (2.32-3.23)	3.67 (2.52-5.34)
Hospital day 7	2.52 (2.04-3.11)	8.29 (4.86-14.16)
Hospital day 8	2.79 (2.12-3.67)	9.53 (5.03-18.05)

* Logistic regression, adjusting for procedures performed (open versus laparoscopic appendectomy), patient demographics, number of comorbid diagnoses, hospital characteristics, and admission year.

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