

Time to Appendectomy and Risk of Complicated Appendicitis and Adverse Outcomes in Children

Stephanie K. Serres, MD, PhD; Danielle B. Cameron, MD, MPH; Charity C. Glass, MD, MPP; Dionne A. Graham, PhD; David Zurakowski, PhD; Mahima Karki, BA; Seema P. Anandalwar, MD; Shawn J. Rangel, MD, MSCE

← Editorial

IMPORTANCE Management of appendicitis as an urgent rather than emergency procedure has become an increasingly common practice in children. Controversy remains as to whether this practice is associated with increased risk of complicated appendicitis and adverse events.

OBJECTIVE To examine the association between time to appendectomy (TTA) and risk of complicated appendicitis and postoperative complications.

DESIGN, SETTING, AND PARTICIPANTS In this retrospective cohort study using the Pediatric National Surgical Quality Improvement Program appendectomy pilot database, 2429 children younger than 18 years who underwent appendectomy within 24 hours of presentation at 23 children's hospitals from January 1, 2013, through December 31, 2014, were studied.

EXPOSURES The main exposure was TTA, defined as the time from emergency department presentation to appendectomy. Patients were further categorized into early and late TTA groups based on whether their TTA was shorter or longer than their hospital's median TTA. Exposures were defined in this manner to compare rates of complicated appendicitis within a time frame sensitive to each hospital's existing infrastructure and diagnostic practices.

MAIN OUTCOMES AND MEASURES The primary outcome was complicated appendicitis documented at operation. The association between treatment delay and complicated appendicitis was examined across all hospitals by using TTA as a continuous variable and at the level of individual hospitals by using TTA as a categorical variable comparing outcomes between late and early TTA groups. Secondary outcomes included length of stay (LOS) and postoperative complications (incisional and organ space infections, percutaneous drainage procedures, unplanned reoperation, and hospital revisits).

RESULTS Of the 6767 patients who met the inclusion criteria, 2429 were included in the analysis (median age, 10 years; interquartile range, 8-13 years; 1467 [60.4%] male). Median hospital TTA was 7.4 hours (range, 5.0-19.2 hours), and 574 patients (23.6%) were diagnosed with complicated appendicitis (range, 5.2%-51.1% across hospitals). In multivariable analyses, increasing TTA was not associated with risk of complicated appendicitis (odds ratio per 1-hour increase in TTA, 0.99; 95% CI, 0.97-1.02). The odds ratios of complicated appendicitis for late vs early TTA across hospitals ranged from 0.39 to 9.63, and only 1 of the 23 hospitals had a statistically significant increase in their late TTA group (odds ratio, 9.63; 95% CI, 1.08-86.17; $P = .03$). Increasing TTA was associated with longer LOS (increase in mean LOS for each additional hour of TTA, 0.06 days; 95% CI, 0.03-0.08 days; $P < .001$) but was not associated with increased risk of any of the other secondary outcomes.

CONCLUSIONS AND RELEVANCE Delay of appendectomy within 24 hours of presentation was not associated with increased risk of complicated appendicitis or adverse outcomes. These results support the premise that appendectomy can be safely performed as an urgent rather than emergency procedure.

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Author Affiliations: Department of Surgery, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (Serres, Cameron, Glass, Karki, Anandalwar, Rangel); Center for Applied Quality Analytics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (Graham); Department of Anesthesiology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (Zurakowski).

Corresponding Author: Shawn J. Rangel, MD, MSCE, Department of Surgery, Boston Children's Hospital, Harvard Medical School, 300 Longwood Ave, Fegan-3, Boston, MA 02115 (shawn.rangel@childrens.harvard.edu).

Appendicitis is the most common gastrointestinal condition that requires surgical management in the pediatric age group.¹⁻³ Approximately 70 000 cases are diagnosed annually in children, and appendicitis is the most costly surgical disease treated in the pediatric population.⁴⁻⁶ Complicated appendicitis is found in up to 30% of patients treated operatively and represents a particularly resource-intensive condition.^{2,7-10} Children with complicated appendicitis have a longer length of stay (LOS), greater hospital cost, and higher risk of subsequent hospital visits compared with those with uncomplicated disease.^{2,8,11-14} Despite significant advancements in the diagnostic evaluation of children with suspected appendicitis during the past few decades, the rates of complicated appendicitis have remained unchanged.^{2,7-10,15}

Several factors have been identified that affect complicated appendicitis, including age, sex, ethnicity, and insurance status.^{2,3,7-9} Despite extensive investigation, the association between treatment delay and risk of complicated appendicitis after hospital presentation remains inconclusive.^{2,7-14,16-24} Several studies^{2,7,11,16-19} have reported that longer time to appendectomy (TTA) increases the risk of perforation, whereas others^{9,10,12,20-23} have not found this association. This heterogeneity may reflect limitations in the methods and data quality of available studies, as well as variation in the definitions used for exposures and outcomes. In this regard, reports from single-center experiences^{2,11,16} are often underpowered and suffer from a lack of generalizability, whereas multicenter studies^{7-10,21,22} have been limited by the use of subjective, administrative-based definitions (eg, *International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* diagnostic codes) for defining outcomes. The relevance of multicenter studies derived from administrative data to contemporary clinical practice have been further limited by measuring treatment delay in the context of calendar days rather than hours and therefore have not been calibrated to answer the key question relevant to contemporary clinical practice. In patients who present with appendicitis, does management as an urgent rather than emergency condition (eg, performing appendectomy within 24 hours of presentation) increase the risk of complicated appendicitis?⁸

With these considerations in mind, the primary goal of this study was to explore the association between treatment delay and complicated appendicitis by using standardized definitions and a rigorous medical record review process to confirm exposures and outcomes across a collaboration of children's hospitals. We sought to explore this association across all hospitals with TTA analyzed as a continuous variable for a broader public health perspective and at the level of each hospital as a categorical variable to provide a more granular (and complementary) analysis. In the latter analysis, patients were categorized into early and late groups for comparison based on whether their TTA was shorter or longer than the hospital's median TTA for all patients treated at their hospital during the study period. Exposures were defined in this manner to compare rates of complicated disease within a time frame sensitive to each hospital's existing infrastructure and diagnostic practices, and we sought to provide insight into whether a hospital could potentially reduce its rate of complicated disease by decreasing its TTA. The influence of TTA on LOS and

Key Points

Question In children diagnosed with appendicitis, does delay in appendectomy within 24 hours of hospital presentation increase the risk of complicated appendicitis or adverse events?

Findings In this retrospective cohort study of 2429 patients from 23 children's hospitals, delay of appendectomy within 24 hours of presentation was not associated with increased risk of complicated disease or postoperative complications.

Meaning These results support the premise that appendectomy can be performed as an urgent rather than emergency procedure.

rates of postoperative complications was also explored to provide further insight into the potential association between treatment delay and progression of disease.

Methods

Study Design and Data Source

This retrospective analysis used the American College of Surgeons Pediatric National Surgical Quality Improvement Program (NSQIP-Pediatric) database. The NSQIP-Pediatric database includes a broad array of clinical and laboratory data for the purpose of comparing risk-adjusted adverse event data among its 82 member hospitals.²⁵⁻²⁷ Data are procured at each hospital by dedicated, full-time medical record abstractors using standardized search criteria and a rigorous medical record review process. Accuracy and consistency of data collection are facilitated through periodic auditing of participating hospitals, mandatory recertification training for medical record abstractors, and availability of an American College of Surgeons clinical support team to address questions surrounding data definitions and data collection protocol. The Boston Children's Hospital Institutional Review Board deemed that the study did not require informed consent; all data were deidentified.

In 2013, the NSQIP-Pediatric appendectomy collaborative pilot project was launched, which included 29 NSQIP-Pediatric hospitals with the goal of collecting an extended set of disease-specific outcome measures in patients with suspected appendicitis.²⁸ These data included preoperative imaging use, pathology report findings, time points of care (including time of emergency department registration and time of incision), measures of postoperative resource use, and an encrypted unique identifier for each participating hospital. A manual of operations to ensure consistency and accuracy of data collection was distributed to all participating hospitals and reviewed via webinar before the initiation of data collection.

Study Cohort

All patients younger than 18 years undergoing an appendectomy for suspected appendicitis at 1 of the 29 hospitals participating in the collaborative from January 1, 2013, through December 31, 2014, were considered for inclusion. Hospitals were included if they contributed at least 20 patients into each comparison group during the study period (eg, at least 40 patients undergoing appendectomy in total). Patients were excluded if they were missing data on time points of care (emergency department registration or time of incision), operative findings, or pathology report

findings. To minimize variation in the influence of prehospital treatment delay on outcomes, patients evaluated at referring hospitals before transfer to the NSQIP-Pediatric hospital for definitive care were excluded.^{9,23} Patients undergoing interval appendectomy and those without appendicitis documented in the final pathology report were also excluded.

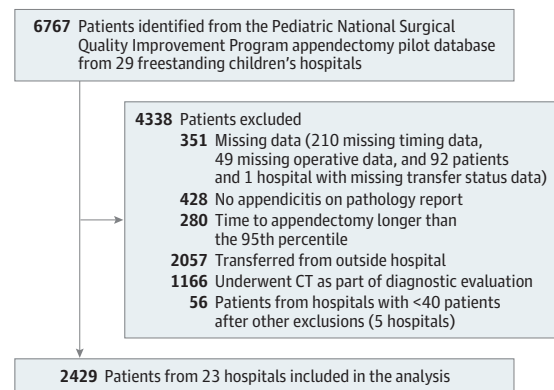
We further excluded patients who underwent computed tomography (CT) as part of their diagnostic evaluation to reduce the influence of knowledge surrounding the presence and extent of perforated appendicitis on the decision to treat operatively vs nonoperatively. Such decision making surrounding operative vs nonoperative management may become relevant to the present analysis based on 3 considerations: (1) CT is more likely than ultrasonography to provide data surrounding the severity and extent of complicated appendicitis (if present), (2) CT is frequently obtained as a follow-up imaging study when an initial attempt at ultrasonography provides equivocal results, and (3) preliminary analysis of our study data demonstrating that the median TTA for patients undergoing serial imaging (CT and ultrasonography) was 2.9 hours longer than those undergoing ultrasonography only.^{25,29-34} When considering the longer TTA associated with serial imaging and the potential that patients with advanced disease who undergo CT may be more likely to be treated nonoperatively, a disproportionate censoring of patients with complicated disease and longer relative TTAs could potentially occur. The result of such censorship could bias the analysis toward the null (no association between TTA and risk of complicated disease) even if such an association actually existed.

Finally, we limited the analyses to patients with a time from emergency department admission to appendectomy within the 95th percentile across all hospitals (24 hours). This was done to focus the analysis within a period representative of contemporary practice and to capture the window of treatment delay associated with the practice of managing appendicitis as an urgent rather than emergency condition. Furthermore, this approach served to minimize the inclusion of patients who may have failed an initial attempt at medical management in which antibiotics were used as definitive treatment.

Exposure Classification and Outcomes

Time to appendectomy was defined as the time from emergency department registration to operative incision. Patients were categorized into early and late appendectomy groups based on whether their TTA was shorter or longer than their hospital's median TTA for all patients treated during the study period. The primary outcome was complicated appendicitis. The diagnosis of appendicitis was determined by the final pathology report, and the presence or absence of complicated disease was established from review of the operative note by using a set of standardized criteria developed by NSQIP-Pediatric's Data Definitions Committee. Specifically, patients were categorized as having complicated appendicitis if any of the following findings were documented: (1) a visible hole in the appendix, (2) diffuse fibrinopurulent exudate throughout the peritoneal cavity, (3) intra-abdominal abscess, or (4) a fecalith in the peritoneal cavity outside the appendix. Patients without any of these 4 findings were categorized as having uncomplicated appendicitis. Secondary outcomes included LOS and rates of postoperative adverse events (incisional and

Figure 1. Assembly of Study Cohort From 23 Children's Hospitals



Inclusion criteria for consideration included age younger than 18 years; discharged from the hospital between January 1, 2013, and December 31, 2014; and underwent appendectomy for suspected appendicitis. CT indicates computed tomography.

organ space surgical site infections [SSIs], percutaneous drainage procedures, unplanned reoperation, and hospital revisits to the emergency department or inpatient setting).

Statistical Analysis

We used χ^2 tests to compare patient characteristics between the early and late appendectomy groups and between patients with and without complicated appendicitis. For each hospital, we estimated the unadjusted odds of complicated disease for patients undergoing appendectomy in the late group relative to early group.

A mixed-effects logistic regression model was used to estimate the association between TTA and the risk of complicated appendicitis while adjusting for relevant covariates. Covariates identified from previous studies^{2,7-10} to have influence on the rate of complicated appendicitis were included in the regression model. These covariates included sex, race, insurance status, and age divided into tertiles and treated as a categorical variable (≤ 7 , 8-12, and 13-17 years). We used a linear mixed model to evaluate the adjusted association between TTA and LOS. In both models, we included random intercepts and slopes for TTA to control for clustering within the hospital. We modeled the adjusted effect of TTA on organ space SSI and hospital revisits by using a logistic model with random intercept for hospital. We used logistic regression to model the adjusted associations between TTA and incisional SSI, percutaneous drainage procedures, and reoperation because small numbers of events prevented inclusion of random effects.

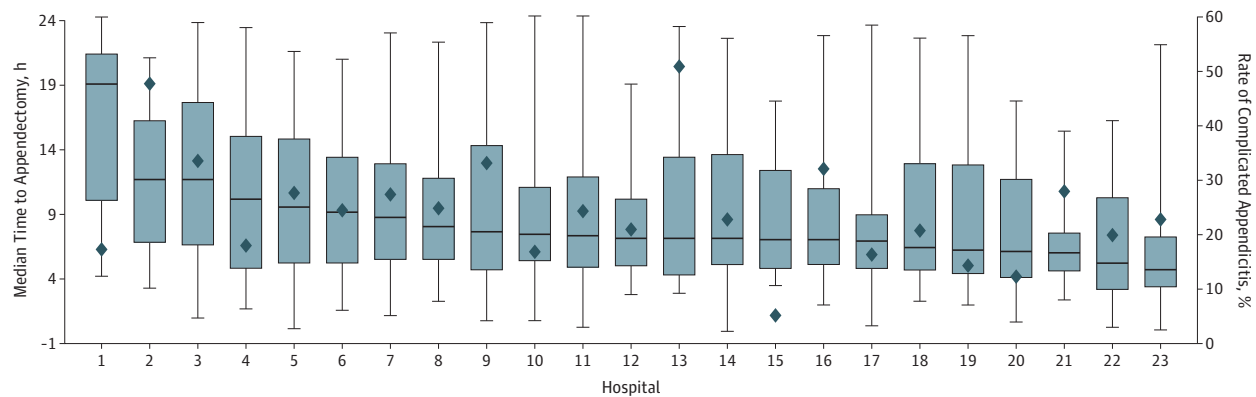
The α value was set at .05, and all statistical tests were 2-tailed. Statistical analyses were performed using SAS Enterprise Guide software, version 7.1 (SAS Institute Inc).

Results

Study Cohort

Of the 6767 patients who met the inclusion criteria in 29 hospitals, 2429 children from 23 hospitals were ultimately included in the analysis after applying exclusion criteria (Figure 1). The median number of patients per hospital was 90

Figure 2. Variation in the Time to Appendectomy (TTA) and Rates of Complicated Disease at 23 Children's Hospitals From January 1, 2013, Through December 31, 2014



Boxplots indicate TTA; diamonds, rates of complicated disease; and error bars, minimum and maximum values.

Table 1. Patient Characteristics Associated With Delayed Time to Appendectomy at 23 Hospitals From January 1, 2013, Through December 31, 2014

Characteristic	Exposure Analysis, No. (%)		P Value ^a
	Early Group	Late Group	
Age, y			
≤7	307 (25.2)	474 (22.8)	.35
8-12	558 (45.7)	577 (47.9)	
13-17	355 (29.1)	353 (29.3)	
Sex			
Male	773 (63.2)	694 (57.6)	.01
Female	451 (36.9)	511 (42.4)	
Race			
White	699 (57.1)	654 (54.3)	.56
Black or African American	101 (8.3)	98 (8.1)	
Hispanic	318 (26.0)	345 (28.6)	
Other	38 (3.1)	34 (2.8)	
Unknown	68 (5.6)	74 (6.1)	
Insurance status			
Commercial	624 (51.0)	576 (47.8)	.02
Public	346 (28.3)	399 (33.1)	
Self-pay	54 (4.4)	35 (2.9)	
Unknown	200 (16.3)	195 (16.2)	

^a χ^2 tests were used for significance testing.

Table 2. Patient Characteristics Associated With Complicated Appendicitis at 23 Hospitals From January 1, 2013, Through December 31, 2014

Characteristic	Outcome Analysis, No. (%)		P Value ^a
	Uncomplicated Appendicitis	Complicated Appendicitis	
Age, y			
≤7	382 (20.7)	199 (34.7)	<.001
8-12	872 (47.1)	263 (45.8)	
13-17	596 (32.2)	112 (19.5)	
Sex			
Male	1146 (61.8)	321 (55.9)	.01
Female	709 (38.2)	253 (44.1)	
Race			
White	1081 (58.3)	272 (47.4)	<.001
Black or African American	148 (8.0)	51 (8.9)	
Hispanic	464 (25.0)	199 (34.7)	
Other	55 (3.0)	17 (3.0)	
Unknown	107 (5.8)	35 (6.1)	
Insurance status			
Commercial	956 (51.5)	244 (42.5)	.01
Public	536 (28.9)	209 (36.4)	
Self-pay	68 (3.7)	21 (3.7)	
Unknown	295 (15.9)	100 (17.4)	

^a χ^2 tests were used for significance testing.

(interquartile range [IQR], 57-146). Of the entire study cohort, 1467 patients (60.4%) were male, with an overall median age of 10 years (IQR, 8-13 years).

Time to Appendectomy

The median TTA among all patients from all hospitals was 7.4 hours (IQR, 4.9-12.9). The median TTA among individual hospitals ranged from 5.0 to 19.2 hours, and the differences in the median TTA between the early and late appendectomy groups being compared within hospitals ranged from 2.9 to 11.1 hours (Figure 2). In univariate analyses, female sex and public health insurance were associated with a relative delay in appendectomy (Table 1).

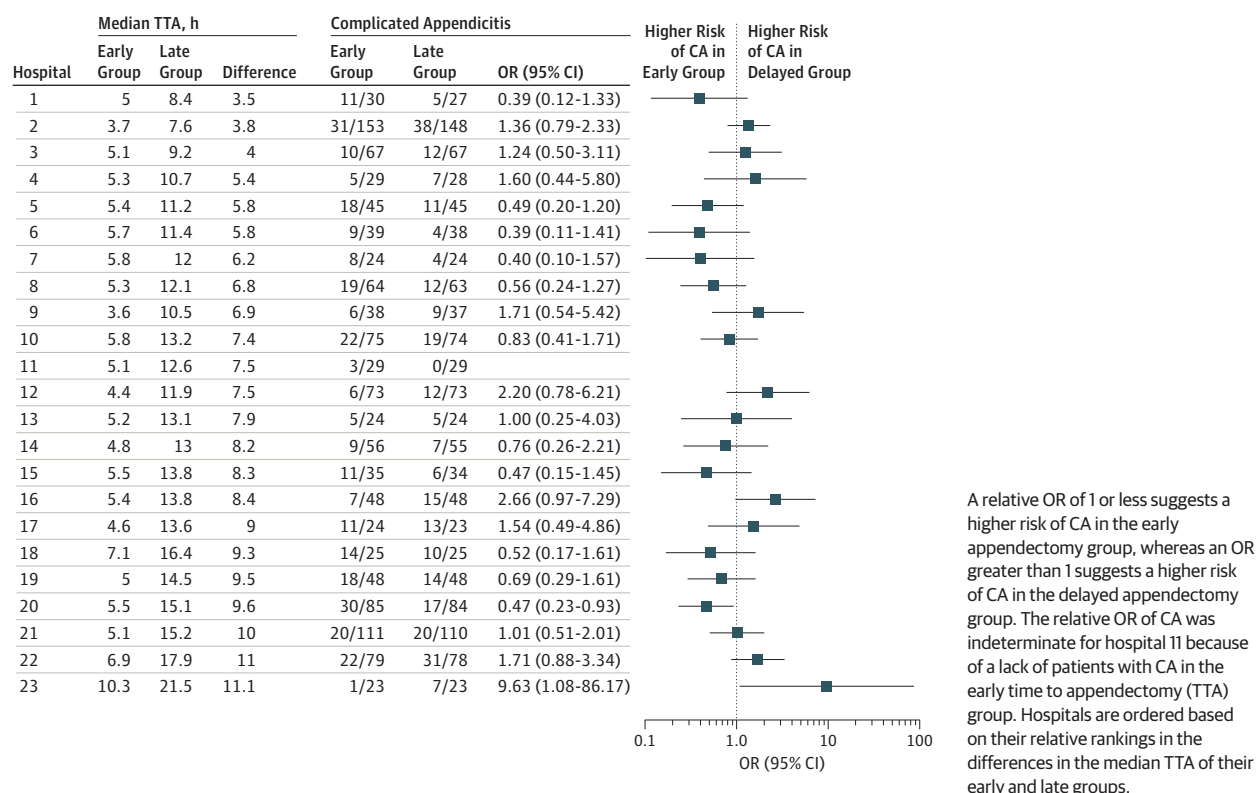
Incidence of Complicated Appendicitis

Among the entire study cohort, 574 patients (23.6%) were diagnosed with complicated appendicitis at exploration, and rates of complicated disease varied from 5.2% to 51.1% across hospitals ($P < .001$) (Figure 2). In univariate analyses, increased risk of complicated appendicitis was associated with age younger than 8 years, female sex, Hispanic ethnicity, and public insurance (Table 2).

Outcomes

In a univariable mixed-effects model, TTA was not associated with an increased risk of complicated appendicitis (odds

Figure 3. Relative Odds Ratios (ORs) of Complicated Appendicitis (CA) in Patients Undergoing Late vs Early Appendectomy at 23 Children's Hospitals From January 1, 2013, Through December 31, 2014



ratio [OR] per 1-hour increase in TTA, 1.00; 95% CI, 0.97-1.02; $P = .76$) and remained nonsignificant in the multivariable analysis (OR, 0.99; 95% CI, 0.97-1.02; $P = .60$). However, in the multivariable analysis, increased risk of complicated appendicitis was associated with younger age (≤ 7 years: OR, 2.59; 95% CI, 1.97-3.41; 8-12 years: OR, 1.60; 95% CI, 1.25-2.06), female sex (OR, 1.56; 95% CI, 1.20-2.01), and Hispanic ethnicity (OR, 1.56; 95% CI, 1.20-2.01).

The odds of complicated disease in the late appendectomy group relative to the early group ranged from 0.39 to 9.63 among hospitals (Figure 3). In 2 of these hospitals, the odds of complicated disease were significantly different, with one demonstrating an increased risk of perforation in the late group (OR, 9.63; 95% CI, 1.08-86.17; $P = .04$) and one demonstrating a decreased risk of perforation in the early group (OR, 0.47; 95% CI, 0.23-0.93; $P = .03$).

Median LOS for the entire cohort was 2 days (IQR, 2-4 days), and longer TTA was associated with prolonged LOS (increase in mean LOS for each additional hour of TTA, 0.06 days; 95% CI, 0.03-0.08 days; $P < .001$). Longer TTA was not associated with increased risk of incisional SSIs (overall cohort rate, 1.0%; OR per 1-hour increase in TTA, 0.96; 95% CI, 0.88-1.04; $P = .29$), organ space SSIs (overall cohort rate, 2.8%; OR, 1.00; 95% CI, 0.96-1.05; $P = .99$), percutaneous drainage procedures (overall cohort rate, 2.6%; OR, 1.02; 95% CI, 0.97-1.07; $P = .40$), unplanned reoperation (overall cohort rate, 1.2%; OR, 1.00; 95% CI, 0.93-1.07; $P = .90$), or hospital revisits (overall cohort rate, 8.9%; OR, 1.01; 95% CI, 0.99-1.04; $P = .39$).

Discussion

In this multicenter study representing a broad range of patient populations and diagnostic practice patterns, longer TTA was not associated with an increased risk of complicated disease or adverse outcomes when appendectomy was performed within 24 hours of presentation. Furthermore, in the context of each hospital's median TTA as a reference point for treatment delay, a significantly higher rate of complicated disease associated with late appendectomy was observed in only 1 of the 23 hospitals examined. This finding may suggest that internal efforts on behalf of individual hospitals to decrease their TTA (eg, to improve the efficiency of the diagnostic process) would not lead to a reduction in the rate of complicated disease. In aggregate, these results suggest that it is unlikely that the timing of appendectomy affects the risk of complicated disease or adverse outcomes if performed within a reasonable time frame, and this assessment is likely to be widely generalizable despite differences in diagnostic practices and patient populations treated at different hospitals.

Previous studies^{2,7-14,16-24} have reported conflicting results in finding an association between appendectomy timing and risk of complicated disease. Single-institutional experiences have been limited by inadequate sample size and lack of generalizability because of differences in patient populations, transfer patterns, and perioperative management.^{2,11-14,16,18-22,24} In this regard, the results and interpretation of this study would

have been quite different (and potentially quite misleading) if the analysis was limited to the 2 hospitals in our cohort in which significant differences were found across exposure groups. Other studies^{8,10} using administrative and registry data have attempted to take into account a broader range of patient populations to improve study power. The major limitation of these studies has been the use of subjective and imprecise ICD-9-CM-based diagnostic codes for defining outcomes and the inability to adjust for hospital-level effects on observed perforation rates.^{8-10,17} In regard to the former, ICD-9-CM-based diagnostic codes are not defined on the presence or absence of complicated (or perforated) disease but rather the presence of localized or generalized peritonitis.³⁵ When results across hospitals are pooled, cross-classification of outcomes is likely to occur (ie, perforated vs nonperforated being classified differently among hospitals and at the level of individual surgeons), which would have the effect of biasing the analysis toward the null hypothesis (no difference between groups) even if an association between treatment delay and complicated disease exists.^{8,10}

The inability to adjust for hospital-level differences in baseline perforation rates in multicenter analyses may further bias the results toward the null hypothesis. In this regard, our analysis found that the rate of perforated disease varied from 5% to 51% among hospitals. When considering the lack of association found between treatment delay and this outcome in the present analysis, we postulate that such variation is attributable to variation in the rate of complicated disease at presentation among hospitals, the application of nonoperative management, or both (most likely). Without the ability to adjust for such differences among hospitals in the analytic modeling (which is only possible through the availability of unique hospital identifiers in the data set), attempts to characterize an association between treatment delay and outcome would be further biased toward the null hypothesis. To our knowledge, no published multicenter study has adjusted for this potential hospital-level effect.^{8-10,17}

When considering the limitations of existing data, we believe that this multicenter study using standardized definitions, a rigorous medical record review process to confirm exposures and outcomes, and a careful analytic process to mitigate potential sources of bias provides the most accurate and generalizable evidence to date as to whether treatment delay leads to an increased risk of complicated appendicitis and adverse outcomes. Furthermore, we sought to limit the analysis to a time frame relevant to contemporary clinical practice and defined exposures in a manner that would provide results reflective of a broad public health relevance (analysis of

TTA as a continuous variable across all hospitals) and a more granular assessment at the level of individual hospitals.

Limitations

The findings of this study must be carefully considered in the context of its limitations. Although data obtained from NSQIP-Pediatric is subject to multiple levels of quality assurance, they were retrospectively collected and errors in medical record documentation and data procurement were possible. Our analysis did not account for differences between patients in the onset of symptoms to hospital presentation, otherwise known as prehospital delay.¹³ Prehospital delay is likely to be an important contributory factor in the development of complicated appendicitis, especially because of the lack of association between TTA and complicated disease found in this study. Data regarding the timing of the antibiotic administration relative to hospital presentation were not available. In this regard, timely administration of antibiotics may play an important role in halting the progression of early appendicitis as evidenced by preliminary studies³⁶⁻³⁹ that reported the efficacy of antibiotics for definitive treatment. Finally, we did not examine the risk of complicated appendicitis in patients with relatively prolonged treatment delay (>24 hours). However, we believe that this magnitude of delay is representative of a different cohort of patients for whom the diagnosis was delayed or remained in question after the initial hospital admission.

Conclusions

Despite these limitations, we conclude that delay of appendectomy does not increase the risk of complicated appendicitis when performed within 24 hours of presentation. In the context of contemporary clinical practice, these data support the premise that treating appendicitis as an urgent (rather than emergency) condition is safe and that delay of appendectomy until the following day in children presenting after hours is an acceptable practice. These findings may have important implications for many hospitals at which performing an appendectomy at night poses significant logistical and fiscal challenges. The ultimate decision surrounding timing of appendectomy should balance the benefits of a timely intervention (eg, potentially lower hospital cost, LOS, and lost days from school and work on behalf of the patient and their family) against a hospital's available resources but should not be influenced by concern for clinically relevant disease progression if it can be performed in a reasonable time frame.

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Study concept and design: Serres, Cameron, Glass, Graham, Anandalwar, Rangel.

Acquisition, analysis, or interpretation of data:

Serres, Graham, Zurakowski, Karki, Rangel.

Drafting of the manuscript: Serres, Graham, Zurakowski, Karki, Rangel.

Critical revision of the manuscript for important intellectual content: Serres, Cameron, Glass, Zurakowski, Anandalwar, Rangel.

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