

Nonoperative Management of Uncomplicated Appendicitis

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abstract

BACKGROUND AND OBJECTIVES: Several studies have revealed the success of nonoperative management (NOM) of uncomplicated appendicitis in children. Large studies of current NOM utilization and its outcomes in children are lacking.

METHODS: We queried the Pediatric Health Information System database to identify children <19 years of age with a diagnosis code for appendicitis. We used linear trend analysis to assess the subsequent utilization and outcomes of NOM in children with nonperforated appendicitis over time. We calculated the proportion of children experiencing treatment failure, defined as either a subsequent appendectomy or hospitalization with a diagnosis code of perforated appendicitis.

RESULTS: We identified 117 705 children with appendicitis over the 9-year study period. Of the 73 544 children with nonperforated appendicitis, 10 394 (14.1%) underwent NOM. The odds of NOM significantly increased (odds ratio 1.10 per study quarter, 95% confidence interval [CI] 1.05–1.15). The 1-year and 5-year failure rates were 18.6% and 23.3%, respectively. Children who experienced failure of NOM had higher rates of perforation at the time of failure than did the general cohort at the time of initial presentation (45.7% vs 37.5%, $P < .001$). Patients undergoing NOM had higher rates of subsequent related emergency department visits (8.0% vs 5.1%, $P < .001$) and hospitalizations (4.2% vs 1.4%, $P < .001$) over a 12-month follow-up period.

CONCLUSIONS: NOM of nonperforated appendicitis in children is increasing. Although the majority of children who undergo NOM remain recurrence-free years later, they carry a substantial risk of perforation at the time of recurrence and may experience a higher rate of postoperative complications than children undergoing an immediate appendectomy.



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WHAT'S KNOWN ON THIS SUBJECT: Primary antibiotic treatment of nonperforated appendicitis in children has revealed a 1-year success rate of ~75%. Previous studies suggest that an increasing number of pediatric appendicitis cases are being managed nonoperatively despite a lack of large-scale long-term follow-up data.

WHAT THIS STUDY ADDS: Despite a lack of large-scale prospective studies, children with nonperforated appendicitis are increasingly being managed nonoperatively. Among US pediatric hospitals, one-third of these children are medically managed and experience higher rates of subsequent healthcare utilization and perforation.

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Although perforated appendicitis may be treated with intravenous antibiotics and interval appendectomy, the current standard of care in nonperforated appendicitis is immediate laparoscopic appendectomy. However, the past decade has brought increasing evidence calling this routine practice into question. The results of randomized controlled trials in adults suggest that nonoperative management (NOM) with antibiotics alone may be a reasonable treatment approach for individuals without appendicolith,¹⁻³ although up to 39% of patients may experience treatment failure by the 5-year mark.⁴ To date, a number of randomized^{5,6} and nonrandomized⁷⁻¹³ prospective trials have been published in children; recently published long-term follow-up data from 2 small prospective pediatric studies have observed a 5-year success rate of NOM of 58% to 70%.^{5,14}

Despite limited evidence, NOM is already being used in children with nonperforated appendicitis at US children's hospitals; we previously found that from 2010 to 2016, the overall rate of NOM in children with nonperforated appendicitis was 6%, with a demonstrable increase in NOM over the study period.^{5,14,15} The World Society of Emergency Surgery recently endorsed NOM as a reasonable management option for children with uncomplicated appendicitis without appendicolith, emphasizing the importance of shared decision-making between surgeons and families.¹⁶

In this study, we examined administrative data from children with nonperforated appendicitis seen at US children's hospitals to (1) assess trends in NOM, (2) determine the early and late treatment failure rates with NOM, (3) compare subsequent healthcare utilization between children undergoing immediate operative management and those undergoing

NOM, and (4) compare rates of perforated appendicitis and postsurgical complications between children undergoing immediate operative management and those who experience failure of NOM.

METHODS

Study Design

We conducted a retrospective cohort study using data obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient, emergency department (ED), ambulatory surgery and observation encounter-level data from >50 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource utilization data (eg pharmaceuticals, imaging, and laboratory) into PHIS. Data are deidentified at the time of data submission and are subjected to reliability and validity checks before being included in the database. For this study, data from the 47 hospitals that contributed emergency department (ED) data during the study period were included.

Study Patients

We reviewed encounters from children <19 years of age seen in one of 47 PHIS EDs from January 2011 through March 2020 who were ascribed a primary diagnosis of appendicitis (*International*

Classification of Diseases, Ninth Revision [ICD-9] 540.0, 540.1, 540.9, 541, 542 or *International Classification of Diseases, Tenth Revision* [ICD-10] K35×, K36, K37). To increase the specificity of our case definition, we only included patients who either underwent appendectomy or received a parenteral antibiotic during the index visit. We excluded children with a complex chronic condition^{17,18} and those with a previous visit with a diagnosis of appendicitis or a procedure code for an appendectomy (for inclusion, all patients had available data for a minimum of 12 months before the index visit).

Definitions

We defined perforated appendicitis by the presence of an ICD-9 or ICD-10 code for perforated appendicitis or a surgical code for an abdominal drainage procedure during the index visit. We defined nonperforated appendicitis by the presence of an ICD-9 or ICD-10 code for nonperforated appendicitis with no surgical code for an abdominal drainage procedure during the index visit. Among children with nonperforated appendicitis, operative management was defined by a surgical code for an appendectomy during the index visit, and NOM was defined by the lack of a surgical code for an appendectomy or abdominal drainage procedure during the index visit and the administration of parenteral antibiotics. All ICD-9 and ICD-10 codes used in the above definitions can be found in Supplemental Table 3.

Outcomes

As most NOM treatment regimens recommend antibiotics for less than 14 days, we defined early failure as a subsequent encounter within 14 days of the index visit with a surgical code for an appendectomy

or a diagnosis code for perforated appendicitis. We defined late failure as a subsequent encounter >14 days after the index visit with a surgical code for an appendectomy or a diagnosis code for perforated appendicitis. A postsurgical complication was defined by a diagnosis code for wound dehiscence, wound infection, incisional hernia, or intestinal obstruction. For purposes of this study, repeat ED visits and hospitalizations were defined as a subsequent ED visit or hospitalization for one of the following primary diagnoses: appendicitis, abdominal pain, intestinal obstruction, vomiting, diarrhea, dehydration, or postsurgical complication. All ICD-9 and ICD-10 codes used in the above definitions are included in Supplemental Table 3.

Data Integrity

Due to the transition from ICD-9 to ICD-10 coding during the study period, we assessed the data for validity before and after the transition by reviewing each hospital's trends. Based on preliminary analyses, several hospitals had dramatic shifts in the rates of perforated appendicitis and NOM not likely attributable to trends in clinical management. To systematically minimize erroneous data, we analyzed hospital-level rates of perforated appendicitis and NOM for 1 year before and after the transition to the ICD-10 system (October 2015). We conservatively excluded hospitals with an absolute change of 50% in the rate of either perforated appendicitis or NOM over this time transition period because a significant change that coincides with the introduction of ICD-10 is possibly related to coding issues.

Analytic Plan

To describe the demographic characteristics of the study cohort,

we used frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. For the remainder of the analyses, we included only children with nonperforated appendicitis as the cohort of interest for assessing trends and outcomes of nonoperative versus operative management of uncomplicated appendicitis.

To assess linear trends over time in the proportion of cases with NOM, we estimated a logistic regression model with NOM as the dependent variable and time (coded in 3-month blocks) as the independent variable, clustering by hospital to account for intrahospital correlation. We analyzed hospital-level rates of NOM over the study period.

We calculated the proportion of patients undergoing NOM who experienced early and late failure during the study period and generated a Kaplan-Meier survival curve to describe the time to failure. We determined the Kaplan-Meier failure function of patients who had failed NOM at discrete time points (1 year, 2 years, and 5 years). For each time point, we included only patients with a minimum of 12 months of follow-up (eg a patient whose index visit occurred in September of 2018 would only be eligible to contribute data to the 1-year failure rate).

To evaluate subsequent healthcare utilization, we considered the 12-month period after the index visit. Using the χ^2 test, we compared the rates of subsequent related ED visits and hospitalizations, as well as the rates of advanced imaging studies of the abdomen, between the two groups. Advanced imaging studies were defined by using Clinical Transaction Classification codes as follows: abdominal/pelvic ultrasound (441041), appendix ultrasound

(444741), abdominal/pelvic computed tomography (CT) scan (441051), abdominal/pelvic MRI (441052).

We employed 2 analyses to investigate whether children with failed NOM had higher rates of complications. First, we determined the proportion of children with failed NOM presenting with perforated appendicitis and compared this to the proportion of the overall cohort presenting with perforated appendicitis at the index visit. Second, we compared the 12-month rates of postsurgical complications between children with nonperforated appendicitis managed operatively at the index visit and those undergoing appendectomy as a result of failed NOM.

Statistical tests were 2-tailed and α was set at 0.05. All analyses were conducted by using the statistical software package Stata 16 (College Station, TX). The institutional review board at the study institution deemed this study exempt from review. The study was approved by the Children's Hospital Association, which administrates the PHIS database.

RESULTS

Study Sample

Over the study period, we identified 159 975 children <19 years of age seen in a PHIS ED with appendicitis who either underwent appendectomy or had parenteral antibiotics administered at the index visit. After excluding 8992 patients meeting exclusion criteria and another 33 159 from 12 hospitals for data quality concerns (all 12 hospitals had >50% absolute change in the rate of perforated appendicitis or NOM during the transition to ICD-10), 117 705 patients remained, of whom 73 544 (62.5%) had nonperforated

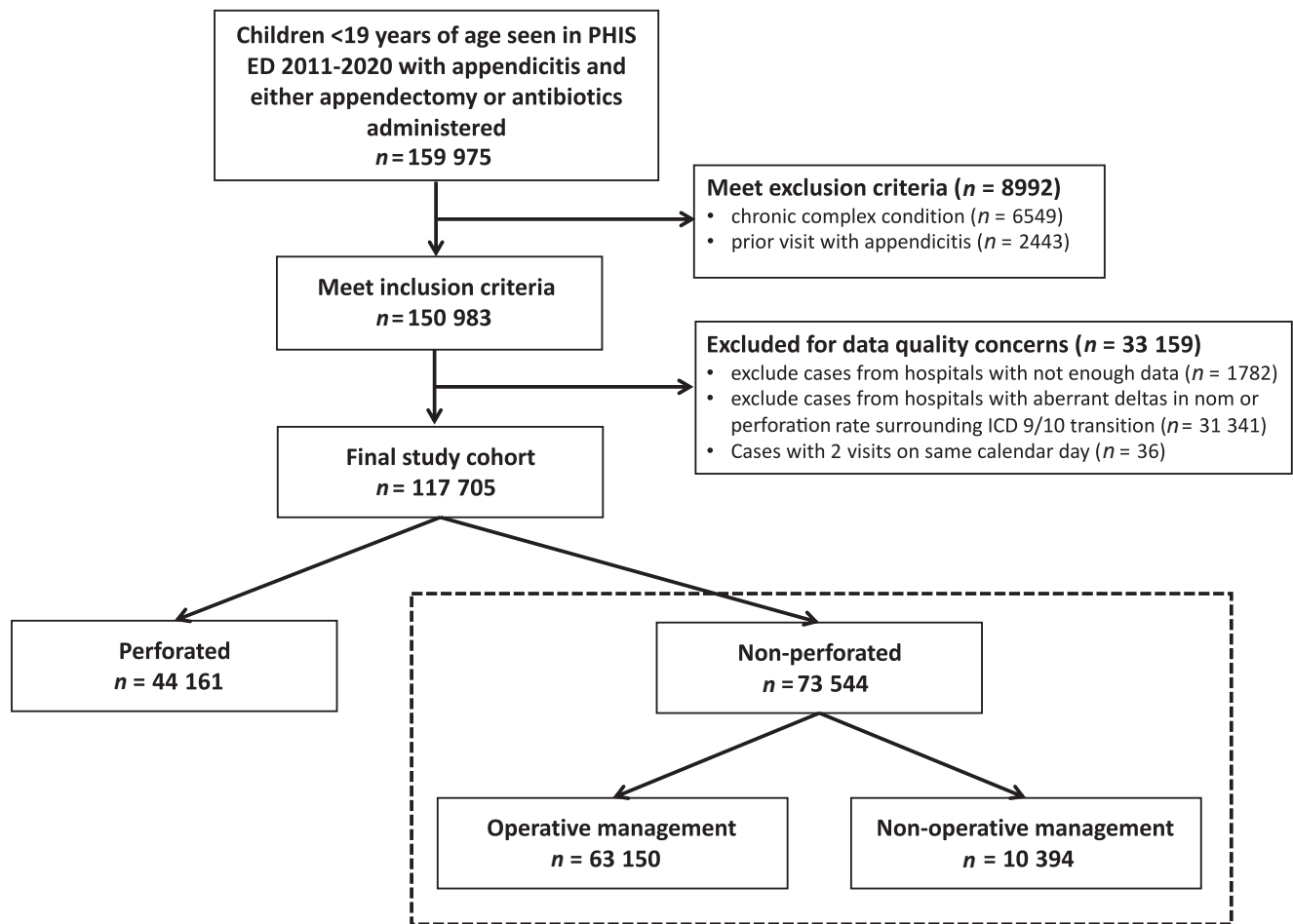


FIGURE 1
Study inclusion. The dashed box indicates the population of interest.

TABLE 1 Demographic and Clinical Characteristics of Children Diagnosed With Nonperforated Appendicitis in the Emergency Department in 35 US Children's Hospitals, 2011 to 2020

	Overall, <i>n</i> = 73 544	Operative Management, <i>n</i> = 63 150		Nonoperative Management, <i>n</i> = 10 394	
Age, y	11.4 (8.8–14.2)	11.4	(8.8–14.2)	11.5	(8.8–14.3)
Female sex	28 544 (38.8)	24 518	(38.8)	4026	(38.8)
Insurance payor					
Private	34 430 (46.8)	29 611	(46.9)	4819	(46.4)
Public	35 538 (48.3)	30 859	(48.9)	4679	(45.0)
Other	2664 (3.6)	2201	(3.5)	463	(4.5)
Missing	912 (1.2)	479	(0.8)	433	(4.2)
Race					
White	48 924 (66.5)	42 244	(66.9)	6680	(64.3)
Black	4552 (6.2)	4056	(6.4)	496	(4.8)
Asian	1803 (2.5)	1581	(2.5)	222	(2.1)
Other	12 158 (16.5)	10 892	(17.3)	1266	(12.2)
Missing	6107 (8.3)	4377	(6.9)	1730	(16.6)
Ethnicity					
Latino	26 160 (35.6)	22 048	(34.9)	4112	(39.6)
Not Latino	41 040 (55.8)	35 443	(56.1)	5597	(53.9)
Missing	6344 (8.6)	5659	(9.0)	685	(6.6)
Length of stay, d	1 (1–1)	1	(1–2)	1	(1–1)

Values in the table represent frequency (percent) or median (interquartile range).

appendicitis and represented the main cohort of interest (Fig 1). The median age of patients was 11.4 years (IQR 8.8–14.2 years), and 44 994 patients (61.2%) were male (Table 1). The median time from the index visit to the end of the study period for the cohort was 4.2 years (IQR 2.0–6.5 years).

Management Modality

Of the 73 544 children presenting with nonperforated appendicitis, 63 150 (85.9%) underwent appendectomy at the index visit and 10 394 (14.1%) were initially managed nonoperatively. The operative and nonoperative groups did not differ in terms of median age, sex, insurance type, race, ethnicity, or length of stay. The proportion of patients managed nonoperatively rose significantly over the study period from 2.7% in the first quarter of 2011 to 32.9% in the first quarter of 2020 (Fig 2). The median hospital rate of NOM was 9.4% (IQR 1.3%–25.4%).

Subsequent Care Utilization in Children Undergoing Operative Versus Nonoperative Management

Among children managed nonoperatively, 2084 (20.1%) had failure during the study period, including 2004 (96.2%) undergoing an appendectomy. The median time to failure among these children was 2 days (IQR 1–5 days). Time to failure is shown in Fig 3; 1909

children (18.4%) experienced early failure and 175 (1.7%) experienced late failure. The cumulative rate of failure at 1 year ($n = 5672$ with follow-up data available) was 18.6% (95% CI, 17.9–19.4), at 2 years ($n = 3437$ with follow-up data available) was 19.2% (95% CI, 18.4–20.0), and at 5 years ($n = 717$ with follow-up data available) was 23.3% (95% CI, 22.1–24.6). Among children with failed NOM, 953 (45.7%) had a diagnosis of perforated appendicitis at the time of failure, compared with 37.5% of children in the overall study cohort presenting with perforated appendicitis at the index visit ($P < .001$).

Subsequent care utilization and performance of imaging studies in children undergoing operative management versus NOM in the 12 months after the index visit are shown in Table 2. As compared with patients undergoing initial operative management, patients undergoing NOM had higher rates of subsequent related ED visits (8.0% vs 5.1%, $P < .001$), hospitalizations (4.2% vs 1.4%, $P < .001$), abdominal ultrasound (0.2% vs 0.03%, $P < .001$) and abdominal CT (3.8% vs 1.7%, $P < .001$). Children with failed NOM requiring a subsequent appendectomy had slightly higher rates of postsurgical complications within 12 months of appendectomy than did children with nonperforated appendicitis

undergoing immediate operative care (1.9% vs 1.2%, respectively, $P = .006$).

DISCUSSION

In this retrospective cohort study of 73 544 children with nonperforated appendicitis managed at US children's hospitals from 2011 to 2020, we found that the use of NOM increased over time, plateauing at ~30% after 2018. Among the 14.1% of children managed nonoperatively over the study period, 20.1% experienced failure of NOM, the vast majority of which occurred within 14 days of the initial presentation. Almost half of the children experiencing failure presented with perforated appendicitis at the time of the recurrence, and rates of postsurgical complications were slightly higher in children undergoing appendectomy after initial NOM than those undergoing immediate operative care. Additionally, children undergoing NOM were more likely to experience a subsequent related ED visit, hospitalization, or advanced imaging study than those undergoing immediate operative care.

Long-term outcomes of nonoperative management of pediatric appendicitis are becoming increasingly available. Recently, Patkova et al⁵ presented 5-year follow-up data on their cohort of 50 children with acute uncomplicated appendicitis randomly assigned to either operative management or NOM. During the follow-up period, 11 of the 26 children managed with NOM (42%) experienced a treatment failure, 9 of which occurred during the first year, although the majority of recurrences were not confirmed histopathologically. No child in the NOM group was diagnosed with perforated appendicitis, mechanical bowel obstruction, or malignancy at

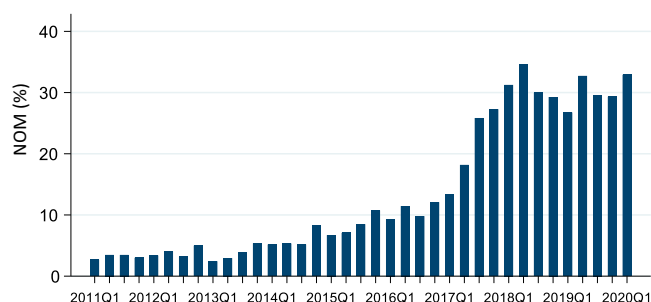


FIGURE 2

Proportion of nonoperative management over time (2011–2020) among ED patients with nonperforated appendicitis. Linear trend analysis by quarter: the odds of NOM significantly increased over time (odds ratio [95% CI] = 1.10 [1.05–1.15])

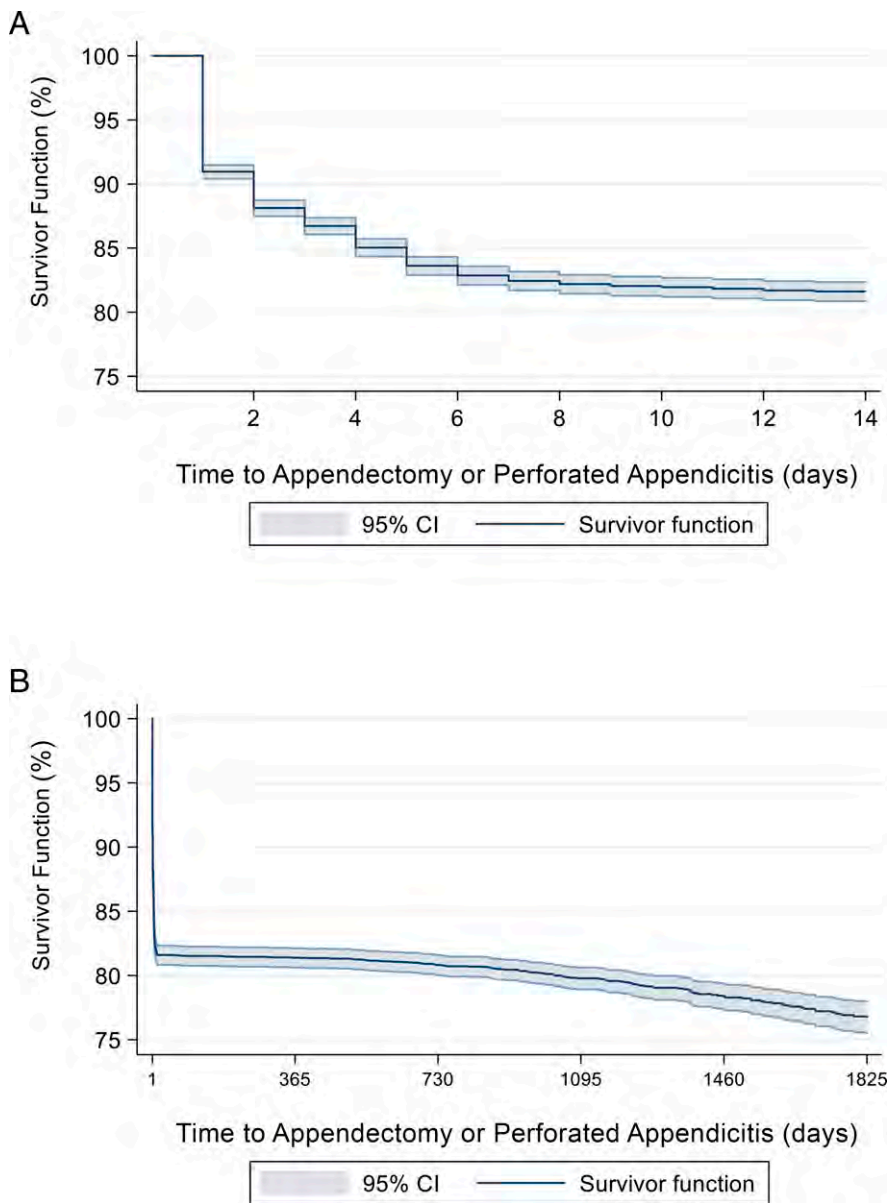


FIGURE 3 Event-free survival (no treatment failure) among 10 409 children with nonperforated appendicitis managed nonoperatively. (A) Time to failure within 14 days of index visit. (B) Time to failure within 5 years of index visit.

the time of recurrence. Knaapen et al¹⁴ published 5-year follow-up data on their cohort of 49 nonrandomly selected children who underwent NOM for acute uncomplicated appendicitis without appendicolith. Of the 47 children contacted for follow-up, 14 (30%) cases experienced treatment failure; no cases of perforated appendicitis were diagnosed. The lower rate of

failure observed in this study as compared with the Patkova study may be due to its nonrandomized nature and its exclusion of children with appendicoliths, which have been shown to increase the risk of treatment failure.^{1,19,20} In 2015, Tanaka et al¹³ published long-term follow-up data on a nonrandomized cohort of 78 children with uncomplicated appendicitis with or

without appendicolith whose caregivers chose NOM. Children were followed for a median of 4.3 years and 22 patients (29%) experienced treatment failure with a 1-year failure rate of 20.8%. There was no difference in the rate of postoperative complications between patients undergoing an immediate appendectomy and those undergoing appendectomy after a recurrence. The lower failure rate in this nonrandomized study may be due to selection bias. Our findings add to the existing literature by analyzing the long-term outcomes of a large number of children undergoing NOM. We observed a lower rate of overall treatment failure in our cohort than in the studies presented above which might indicate a refined selection of NOM-amenable cases, a liberalized diagnosis of appendicitis to include cases with equivocal clinical findings or imaging, or limitations of the dataset for detecting failure based on coding accuracy.

Although we observed a lower rate of treatment failure in our cohort, it is important to note that almost half of the children experiencing treatment failure were diagnosed with perforated appendicitis at the time of failure. This contrasts with a rate of 37% of perforated appendicitis at the time of initial presentation across the entire study cohort. Additionally, there was a slightly higher incidence of postoperative complications in the first year after appendectomy for those experiencing failure of NOM as compared with children undergoing immediate operative treatment. The large sample size of our study, combined with the long follow-up period for some of its patients, may have revealed some disadvantages of NOM that were not previously observed in the smaller studies cited above. The finding of increased perforation in patients with failed

TABLE 2 Subsequent Care Utilization and Imaging Studies in the 12 Months After the Index Visit Among Children With Appendicitis Managed Operatively and Nonoperatively. Limited to Index Cases With Admission Dates Through March 31, 2019 to Allow for a Complete Year of Follow-Up.

	Operative Management, <i>n</i> = 56 569	Nonoperative Management, <i>n</i> = 7415	<i>P</i>
Care utilization			
Subsequent related ED visit ^a	2888 (5.1)	593 (8.0)	<.001
Subsequent related hospitalization ^a	809 (1.4)	313 (4.2)	<.001
Number of subsequent ED visits			<.001
0	53 681 (94.9)	6822 (92.0)	
1	2533 (4.5)	527 (7.1)	
2+	355 (0.6)	66 (0.9)	
Number of subsequent hospitalizations			<.001
0	55 760 (98.6)	7102 (95.8)	
1	759 (1.3)	299 (4.0)	
2+	50 (0.1)	14 (0.2)	
Imaging performed			
Any subsequent imaging ^b	996 (1.8)	294 (4.0)	<.001
Abdominal ultrasound	18 (0.03)	14 (0.2)	<.001
Abdominal CT	958 (1.7)	279 (3.8)	<.001
Abdominal MRI	36 (0.1)	8 (0.1)	.172

Values in the table represent frequency (percent).

^aVisit to the same PHIS institution with one of the following primary diagnoses: appendicitis, abdominal pain, intestinal obstruction, vomiting, diarrhea, dehydration, colitis, or post-surgical complication.

^bUnderwent any abdominal ultrasound, CT, or MRI

NOM has been similarly observed in adults although the meta-analysis included studies that included patients with appendicoliths.²¹ Continued long-term follow-up of children managed nonoperatively, as well as larger randomized controlled trials, are essential to further assess subsequent complications.

The results of our study combined with the recent long-term follow-up data of NOM in children suggest that the majority of children with uncomplicated appendicitis who are managed with NOM will remain recurrence-free for at least 5 years after their initial presentation. For select children, NOM may be a viable first step in the management of appendicitis, with surgery reserved for those who do not respond to antibiotic therapy alone or those with a recurrence of appendicitis after their first episode. It is important to counsel families that children undergoing NOM may have a higher likelihood of perforated appendicitis and postoperative complications if they do fail NOM and may be more likely to experience subsequent ED visits,

hospitalizations, and abdominal imaging than children undergoing immediate operative management. Studies of shared decision-making in pediatric appendicitis have revealed success in the form of fewer disability days and lower healthcare costs in children whose caregivers opt for NOM as compared with those undergoing immediate operative management.^{11,22}

In addition to research aimed at establishing the efficacy of NOM in children, additional studies should focus on a more comprehensive understanding of how NOM will fit into the modern management paradigm: factors making children more or less likely to succeed with NOM, the optimal antibiotic regimen for children undergoing NOM, standardized criteria of treatment failure, cost-effectiveness, and patient/parent satisfaction. Additionally, as NOM becomes more common in children, we should vigilantly monitor for unintended consequences such as diagnostic uncertainty,²³ side effects of increased antibiotic use, and missed appendiceal malignancies.

As with all studies using administrative data, ours must be considered in the context of its limitations. The study definitions and interpretation of the analyses rely on accurate and consistent coding of diagnoses and procedures; although we have previously assessed the accuracy of these codes,^{24,25} we did not attempt to reassess any biases in coding in the current study. Importantly, we do not believe the trends in NOM management, or the analysis of outcomes were influenced by a newly introduced systematic error in coding over the study period. Additionally, the absence of clinical data precludes analysis of differences in clinical, laboratory, or radiographic findings that may have influenced management decisions or more accurately defined treatment failure. Similarly, we do not have access to histologic data to determine if children undergoing subsequent appendectomy truly had appendicitis. Our methods define early failure as occurring after the initial hospitalization but before 14 days. By definition, children experiencing early failure (during

the initial hospitalization) were classified as immediate operative management rather than NOM. This may have led to a lower rate of early failure than would have been observed had failure been evaluated prospectively. With this reliance on coding, some children coded as “perforated appendicitis” may have had small perforations discovered at the time of surgery that were not clinically meaningful, but still coded as such. Finally, we were only able to identify repeat visits to the same PHIS ED as the index visit.

CONCLUSIONS

Nonoperative management of nonperforated pediatric appendicitis has risen at US children’s hospitals between 2011 and 2020. Although the majority of children undergoing NOM are treated successfully, our findings suggest that they have increased rates of subsequent related emergency department revisits and hospitalizations as well as a substantial risk of perforation at the time of failure. Additional rigorous, large-scale studies of NOM in children are needed to determine its optimal usage.

ABBREVIATIONS

CI: confidence interval
 CT: computed tomography
 ED: emergency department
 IQR: interquartile range
 NOM: nonoperative management
 PHIS: Pediatric Health Information Systems

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