Antibiotics for appendicitis! Not so fast

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BACKGROUND: Emerging literature in acute appendicitis favors the nonoperative management of acute appendicitis. However, the actual use of this practice on a national level is not assessed. The aim of this study was to assess the changing trends in nonoperative management of acute appendicitis and its effects on patient outcomes.

METHODS: We did an 8-year (2004–2011) retrospective analysis of the National Inpatient Sample database. We included all inpatients with the diagnosis of acute appendicitis. Patients with a diagnosis of appendiceal abscess or patients who underwent surgery for any other pathology were excluded from the analysis. Jonckheere-Terpstra trend analysis was performed for operative versus nonoperative management and outcomes.

RESULTS: A total of 436,400 cases of acute appendicitis were identified. Mean age of the population was 33 ± 19.5 years, and 54.5% were male. There was no significant change in the number of acute appendicitis diagnosed over the study period ($p = 0.2$). During the study period, nonoperative management of acute appendicitis increased significantly from 4.5% in 2004 to 6% in 2011 ($p < 0.001$). When compared with operatively managed patients, conservatively managed patients had a significantly longer hospital length of stay (3 [2–6] vs. 2 [1–3] days, $p < 0.001$), and in-hospital complications (27.8% vs. 7%, $p < 0.001$). On comparison of open and laparoscopic appendectomy, both had shorter hospital length of stay and rate of in-hospital complications. Overall hospital charges were lower in patients managed conservatively (15,441 [8,070–31,688] vs. 20,062 [13,672–29,928] USD, $p < 0.001$).

CONCLUSIONS: Nonoperative management of appendicitis has increased over time; however, outcomes of nonoperative management did not improve over the study period. A more in-depth analysis of patient and system demographics may reveal this disparity in trends. (*J Trauma Acute Care Surg.* 2016;80: 923–932. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Epidemiologic/prognostic study, level III.
KEY WORDS: Acute appendicitis; antibiotics; appendectomy; conservative management; nonoperative management.

Acute appendicitis is one of the most commonly diagnosed emergency surgical diseases resulting in more than 300,000 appendectomies annually in the United States.[1] Appendectomy is a relatively safe procedure with a very low morbidity. With the common understanding that natural progression of acute appendicitis leads to perforation and pelvic abscess formation, common surgical principle remains to surgically remove the appendix before the disease progresses to more advanced stages. Furthermore, appendectomy provides a definitive cure with an excellent safety profile with very low morbidity and mortality.

With the better understanding of the disease principle and significant advancements in the antibiotic coverage, the role of appendectomy as the only definitive cure for appendicitis has been challenged.[2] The use of antibiotic therapy alone for treatment of uncomplicated acute appendicitis has been rejuvenated recently. Several clinical trials and prospective studies have put forth a battery of evidence on the effectiveness of both treatment options. However, data still remain unequivocal in favor of any of these regimens.

The concept of treating appendicitis with antibiotics is not new; however, because of fear of disease progression to more ominous stages, it has never gained widespread acceptance. The recent emerging literature brings into question the surgical treatment as the only standard-of-care treatment for acute appendicitis. Randomized controlled trials and retrospective studies have looked at the comparison of these treatment regimens; however, the utility and outcome differences at a national level have never been assessed. The aim of our study was to assess the use and outcome differences of two treatment approaches, that is, appendectomy and antibiotic therapy, for treatment of acute appendicitis.

METHODS

Data Source

We performed an 8-year (2004–2011) retrospective analysis of National Inpatient Sample (NIS) database. The NIS is a part of the family of tools and databases developed for the Healthcare Cost and Utilization Project, maintained by the Agency for Healthcare Research and Quality. It is the largest all-payer publicly available database in the United States, yielding national estimates from more than 7 million inpatient stays. The NIS is the 20% weighted sample of all participating hospitals across 44 states. It includes more than 100 clinical and nonclinical data points encompassing patient demographics, admission profiles, in-hospital diagnoses and procedures, complications, socioeconomic factors, total hospital charges, length of stay, and hospital profile. This study was exempted from institutional review board and patient consent requirement.

Study Population

We included all patients who were admitted to the hospital with the diagnosis of acute appendicitis using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes 540, 540.0, 540.1, 540.9, 541, and 542. We excluded patients with appendiceal abscess (*ICD-9-CM* diagnosis codes 540.1 and *ICD-9-CM* procedure code 47.2) and patients who underwent any other major operative procedures during the hospital stay.

We divided our study population into two groups based on the management strategy: operative and nonoperative. Operative intervention was defined as appendectomy, identified by using *ICD-9-CM* procedure codes 47.0, 47.09, and 47.01. For the purpose of subanalysis into different age categories, population was arbitrarily divided into pediatrics (aged ≤18 years), adults (aged 19–64 years), and elderly (aged ≥65 years). The pediatrics group was further subdivided into 12 years or younger and 13 to 18 years old. The adult group was further subdivided into 19 to 35, 36 to 55, and 56 to 65 years old.

Variables and Definitions

We abstracted data on patients' demographics (age, race, and gender), mode of presentation (elective vs. nonelective), insurance status, teaching status of the hospital, location of the hospital (urban vs. rural), weekend admission, operative approach, all patient-refined diagnosis-related groups (APR-DRG), severity of illness, complications, length of stay, and total hospital charges, which were defined as the prices a hospital sets for its services.

We classified operative approach as either laparoscopic or open. The laparoscopic procedures were identified using *ICD-9-CM* procedure codes 47.02 and 54.21. Severity of illness was classified based on APR-DRG classification into four subclasses: minor, moderate, major, or extreme. All patient-refined diagnosis-related group classification reflects severity of illness in terms of physiologic and organ dysfunction and takes into account patient demographics, concomitant illnesses, and nature of operative and nonoperative procedures.

We defined complications as urinary tract infection (UTI) (*ICD-9-CM* diagnosis code 599.0), sepsis (*ICD-9-CM* diagnosis codes 995.91 and 995.92), pneumonia (*ICD-9-CM* diagnosis codes 480.0–480.9, 481, 482.0–482.9, 483.0–483.8, 485–487, and 507), deep venous thrombosis and pulmonary embolism (*ICD-9-CM* diagnosis codes 453.40–453.42, and 415.1), respiratory dysfunction (*ICD-9-CM* diagnosis codes 518.51–518.53 and 518.81), acute renal failure (ARF) (*ICD-9-CM* diagnosis codes 584.5–584.9 and 593.9), cardiac/cerebrovascular (*ICD-9-CM* diagnosis codes 410, 427.5, and 434.91), and *Clostridium difficile* infection (*ICD-9-CM* diagnosis codes 008.45). For the patients who underwent an operative management, surgery-related complications, such as surgical site infection (*ICD-9-CM* diagnosis codes 998.5, 998.51, and 998.59) and reoperation, were identified. We assumed intention to treat for the following diagnoses and created the category of reoperation: disruption of surgical wound (*ICD-9-CM* diagnosis codes 998.3, and 998.31–998.32), postsurgical hematoma (*ICD-9-CM* diagnosis code 998.11), and abdominal abscess (*ICD-9-CM* diagnosis code 567.22).

Outcomes

The outcome of our study was to assess the differences in complications, hospital length of stay, and hospital charges between operative and nonoperative management of acute appendicitis. We also assessed the trends in the use of

TABLE 1. Demographics and Outcomes

Variable	Total Population (n = 436,400)	Appendectomy (n = 414,846): Laparoscopic (n = 266,590)	Open (n = 148,256)	Total (n = 414,846)	Nonoperative (n = 21,554)
A. Demographics					
Age, mean (SD), y	33 ± 19.5	32.8 ± 18	33 ± 20	32.88 ± 19	36 ± 26
Gender (male)*	54.5% (231,229)	53% (141,292)	56% (83,023)	54.8% (220,876)	48.6% (10,353)
Pediatric (≤18 y)*	27.9% (121,955)	26% (69,325)	30.5% (48,285)	27.6% (114,610)	34.1% (7,345)
≤12 y	15.4% (67,298)	12.6% (33,698)	18.8% (27,934)	14.9% (61,632)	26.3% (5,666)
13–18 y	12.5% (54,631)	13.8% (35,610)	11.7% (17,344)	12.8% (52,954)	7.8% (1,677)
Adult (19–65 y)*	64.8% (282,607)	68.2% (181,942)	61% (90,311)	65.5% (272,253)	48% (10,354)
19–35 y	31.5% (137,421)	34.3% (91,523)	28.4% (42,126)	32.2% (133,649)	17.5% (3,772)
36–55 y	25.7% (112,146)	26.7% (71,127)	24.6% (36,533)	26% (107,660)	20.8% (4,486)
56–65 y	7.6% (33,040)	7.2% (19,292)	8% (11,652)	7.5% (30,944)	9.7% (2,096)
Elderly (>65 y)*	7.2% (31,638)	5.7% (15,222)	8.5% (12,572)	6.7% (27,794)	17.8% (3,844)
APR-DRG severity of illness*					
Minor	62% (168,356)	66.7% (177,815)	56.2% (83,319)	63.7% (164,056)	30.6% (4,300)
Moderate	31% (84,162)	29.3% (788,110)	33.8% (50,110)	30.6% (78,808)	38% (5,354)
Major	5.1% (13,927)	3.4% (9,064)	6.6% (9,784)	4.3% (110,011)	20.8% (2,926)
Extreme	1.9% (5,183)	0.7% (1,866)	3.4% (5,040)	1.4% (3,693)	10.6% (1,490)
B. Outcomes					
In-hospital complications*					
Total	8% (34,982)	4.8% (12,730)	11% (16,270)	7% (29,000)	27.8% (5,982)
UTI	1.7% (7,433)	1.3% (3,585)	1.7% (2,548)	1.5% (6,133)	6% (1,298)
Sepsis	1.3% (5,560)	0.6% (1,643)	1.7% (2,558)	1% (4,201)	6.3% (1,357)
Pneumonia	0.2% (1,108)	0.15 (334)	0.3% (455)	0.2% (789)	1.5% (319)
Respiratory dysfunction	0.6% (2,559)	0.2% (524)	0.9% (1,352)	0.5% (1,876)	3.2% (680)
ARF	1.6% (7,001)	0.9% (2,465)	2% (2,944)	1.3% (5,409)	7.4% (1,589)
Cardiac/cerebrovascular	0.3% (1,199)	0.1% (322)	0.4% (588)	0.2% (910)	1.3% (277)
C. difficile infection	0.3% (1,309)	0.13% (350)	0.3% (497)	0.2% (847)	2.1% (462)
Reoperation	1.25% (5,464)	0.9% (2,294)	2.1% (3,169)	1.3% (5,463)	—
Surgical site infection	0.7% (3,372)	0.5% (1,213)	1.5% (2,159)	0.8% (3,372)	—
Hospital length of stay**	2 (1–3)	1 (1–2)	2 (1–4)	2 (1–3)	3 (2–6)
Total charges**	26,052 (17,875–38,669)	21,267 (15,078–30,651)	17,413 (11,388–28,184)	20,062 (13,672–29,928	15,441 (8,070–31,688)

All values are statistically significant at $p < 0.001$.
*Unit is percentage (n).
**Unit is median (interquartile range).

nonoperative and operative managements of acute appendicitis over the study period.

Statistical Analysis

To account for the missing data on patient demographics, insurance status, location, and teaching status of the hospital, we performed a missing value analysis. The original data were analyzed for random missing points using Little's MCAR test, and data were treated as missing at random. We imputed the missing data using multiple imputations technique. The procedure for multiple imputations was the Markov Chain Monte Carlo method. The Markov Chain Monte Carlo method refers to a collection of methods for simulating random draws from nonstandard distributions. All data presentations and statistical analyses were performed after accounting for the missing data.

Data are presented as mean (SD) for continuous variables and as proportions for categorical variables. We performed χ^2 test to compare the differences for categorical variables, Student *t* test for continuous descriptive variables, and test of median for nonparametric variables. To assess the trends of operative and nonoperative management of acute appendicitis over time, we performed Jonckheere-Terpstra trend analysis. Moreover, to assess the association between each variable and the complications, we performed a multivariate regression analysis. We performed a binary logistic regression analysis for predictors of in-hospital complications and linear regression analysis for hospital length of stay and total charges. The output of regression analyses is presented as odds ratio (OR) and 95% confidence interval (CI). $p < 0.05$ was considered statistically significant. We used Statistical Package for Social Sciences version 22 (SPSS Inc., Armonk, NY) for the statistical analyses.[3–5]

RESULTS

A total of 436,400 patients with the diagnosis of acute appendicitis were included in the study over the period of 8 years (2004–2011). Mean age of the population was 33 ± 19.5 years, 54.5 % were male, 95% underwent operative intervention (laparoscopic: 64%, open: 36%), and 5% were managed conservatively. Patients who got operative intervention were younger (32.9 ± 19 years vs. 36 ± 26 years, $p < 0.001$), were more likely

TABLE 2. Subanalysis of Pediatrics

		Appendectomy (n = 114,610)			
Variable	**Total Pediatric (n = 121,955)**	**Laparoscopic (n = 69,325)**	**Open (n = 45,285)**	**Total (n = 114,610)**	**Nonoperative (n = 7,345)**
Pediatrics					
1 to ≤12 y	67,298	33,698	27,934	61,632	5,666
In-hospital complications					
Total	3.4% (2,291)	2.3% (777)	4% (1,106)	3% (1,883)	7.2% (408)
UTI	0.8% (532)	0.6% (210)*	0.7% (209)*	0.7% (419)	2% (113)
Sepsis	0.4% (274)	0.2% (64)	0.4% (111)	0.3% (175)	1.7% (99)
Pneumonia	0.1% (65)	0.03% (11)*	0.1% (15)*	0.02% (26)	0.7% (39)
Respiratory dysfunction	0.1% (84)	0.03% (11)	0.1% (31)	0.1% (42)	0.7% (42)
Renal	0.2% (103)	0.1% (28)*	0.1% (36)*	0.1% (64)	0.7% (39)
Cardiac/cerebrovascular					
C. difficile infection	0.2% (165)	0.1% (37)	0.2% (52)	0.1% (89)	1.3% (76)
Reoperation	0.87% (591)	0.7% (242)	1.2% (349)	0.95% (591)	—
Surgical site infection	0.7% (477)	0.5% (174)	1.1% (303)	0.77% (477)	—
Hospital length of stay	2.91 ± 4.63	2.49 ± 2.5	3.08 ± 5.9	2.76 ± 4.40	4.56 ± 6.38
Total charges	22,749 ± 35,171	24,095 ± 19,094	21,229 ± 43,621*	22,796 ± 32,618	22,246 ± 55,685*
13–18 y	54,631	35,610	17,344	52,954	1,677
In-hospital complications					
Total	2.8% (1,553)	2.1% (770)	3.4% (594)	2.6% (1,364)	11.2% (189)
UTI	0.8% (452)	0.8% (293)	0.6% (111)	0.8% (404)	2.9% (48)
Sepsis	0.4% (243)	0.3% (95)	0.5% (85)	0.3% (180)	3.8% (63)
Pneumonia	0.1% (58)	0.07% (27)**	0.09% (16)*,**	0.08% (43)	0.9% (15)*
Respiratory dysfunction	0.1% (50)	0.04% (15)	0.1% (20)	0.1% (35)	0.9% (15)
Renal	0.2% (112)	0.1% (36)	0.2% (41)	0.1% (77)	2.1% (35)
Cardiac/cerebrovascular					
C. difficile infection	0.09% (51)	0.1% (23)*	0.1% (15)*	0.07% (38)	0.8% (13)
Reoperation	0.6% (352)	0.5% (175)	1% (177)	0.6% (352)	—
Surgical site infection	0.46% (235)	0.3% (106)	0.7% (129)	0.4% (235)	—
Hospital length of stay	2.19 ± 3.13	1.87 ± 1.92	2.52 ± 3.55	2.08 ± 2.59	5.68 ± 9.69
Total charges	21,828 ± 24,473	22,564 ± 15,531	19,079 ± 25,057	21,417 ± 20,138	34,830 ± 80,899

*Statistically significant difference between the groups. Units: Hospital length of stay in days and Total charges in USD, expressed as median (interquartile range), all others as percentage (n).
**No statistical difference between the subgroups.

TABLE 3. Subanalysis of Adults

Variable	Total Population (n = 314,245)	Appendectomy (n = 300,047)			Nonoperative (n = 14,198)
		Laparoscopic (n = 1,97,164)	Open (n = 102,883)	Total (n = 300,047)	
Adults (19–65 y)	282,607	181,942	90,311	272,253	10,354
In-hospital complications					
Total	4.9% (19,525)	3.5% (8,071)	6.2% (8,849)	4.4% (16,920)	17.3% (2,605)
UTI	1.6% (4,404)	1.3% (2,447)	1.6% (1,401)	1.4% (3,848)	5.4% (556)
Sepsis	1.1% (3,007)	0.6% (1,034)	1.5% (1,365)	0.9% (2,399)	5.9% (608)
Pneumonia	0.2% (517)	0.1% (197)	0.2% (197)	0.1% (394)	1.2% (123)
Respiratory dysfunction	0.4% (1,223)	0.2% (291)	0.7% (629)	0.3% (920)	2.9% (303)
Renal	1.2% (3,527)	0.8% (1,370)	1.6% (1,439)	1% (2,809)	6.9% (718)
Cardiac/cerebrovascular	0.2% (482)	0.1% (139)	0.3% (253)	0.1% (392)	0.9% (90)
C. difficile infection	0.2% (655)	0.1% (207)	0.3% (241)	0.16% (448)	2% (207)
Reoperation	1.1% (3,575)	0.9% (1,589)	2.2% (1,986)	1.3% (3,575)	—
Surgical site infection	0.75% (2,135)	0.4% (797)	1.5% (1,338)	0.78% (2,135)	—
Hospital length of stay	2.58 ± 3.80	2.01 ± 2.29	3.39 ± 4.89	2.47 ± 3.44	5.64 ± 8.55
Total charges	26,100 ± 31,447	25,489 ± 19,546	26,216 ± 41,517	25,731 ± 28,787	35,822 ± 71,507
Elderly (>65 y)	31,638	15,222	12,572	27,794	3,844
In-hospital complications					
Total	36.7% (11,613)	20.4% (3,112)	20.5% (5,721)	20% (8,833)	72% (2,780)
UTI	6.5% (2,042)	4.2% (635)	6.6% (827)	5.3% (1,462)	15% (580)
Sepsis	6.4% (2,034)	3% (450)	7.9% (997)	5.2% (1,447)	15.3% (587)
Pneumonia	1.5% (480)	0.7% (99)	1.8% (227)	1.2% (326)	4% (154)
Respiratory dysfunction	3.8% (1,199)	1.4% (207)	5.3% (672)	3.2% (879)	8.3% (320)
Renal	10.3% (3,256)	6.8% (1,031)	11.4% (1,428)	8.8% (2,459)	20.7% (797)
Cardiac/cerebrovascular	2.2% (694)	1.2% (183)	2.7% (335)	1.9% (518)	4.6% (176)
C. difficile infection	1.4% (438)	0.5% (83)	1.5% (189)	0.97% (272)	4.3% (166)
Reoperation	3% (954)	1.9% (288)	5.2% (657)	3.4% (945)	—
Surgical site infection	1.6% (525)	0.9% (136)	3.1% (389)	1.8% (525)	—
Hospital length of stay	5.85 ± 7.03	3.82 ± 4.35	7.49 ± 8.28	5.48 ± 6.68	8.55 ± 8.727
Total charges	44,928 ± 61,714	36,324 ± 37,110	53,162 ± 76,214*	43,957 ± 58,788	51,954 ± 79,396*

All values are statistically significant unless otherwise mentioned.
*No statistical difference. Units: Hospital length of stay in days and Total charges in USD, expressed as median (interquartile range), all others as percentage (n).

to be male (54.8% (n = 220,876) vs. 48.6% (n = 10,353), $p < 0.001$), and had less severe disease process (moderate, 30.6% vs. 38%, Major, 4.3% vs. 20.8%, and Extreme, 1.4% vs. 10.6%) compared with nonoperative group. In addition, patients in the operative group were more likely to be admitted on weekends (25.6% vs. 23.5%) and in a teaching hospital (56.7% vs. 41.3%). Table 1*A* reflects the results of comparison for the demographics between the groups.

Over the study period, the rate of nonoperative management increased steadily from 4.5% in 2004 to 6% in 2011 ($p < 0.001$). After controlling for age, gender, and severity of illness in a linear regression analysis, there were significantly increased odds of having a nonoperative management with increasing year (OR [95% CI], 0.059 [0.034–0.083]; $p < 0.001$]. On comparison of operative approach, the rate of laparoscopic appendectomy increased significantly over the years from 44.4% in 2004 to 74.2% in 2011 ($p < 0.001$). After controlling for age, gender, and severity of illness in a linear regression analysis, the odds of having an appendectomy done with laparoscopic approach increased significantly with increasing year (OR [95% CI], 0.362 [0.35–0.37]; $p < 0.001$]. SDC 1 (see Figure, Supplemental Digital Content 1, http://links.lww.com/TA/A744) demonstrates the trends of operative versus nonoperative approaches over the years from 2004 to 2011.

Overall, 8% of the patients developed in-hospital complications. Urinary tract infection (1.7%), followed by ARF (1.6%), was the most common complication Patients in the operative intervention group were less likely to have complications compared with nonoperative group (7% vs. 27.8%, $p < 0.001$). The overall rate of reoperation was 1.3% (n = 5,464) in patients who underwent operative intervention. The open appendectomy group had a higher rate of reoperation compared with the laparoscopic group (2.1% vs. 0.9%; $p < 0.001$). The overall rate of surgical site infections was 0.8% (n = 3,372). The rate of surgical site infection was significantly higher in open approach compared with the laparoscopic approach (1.5% vs. 0.5%, $p < 0.001$). The median hospital length of stay was 2 (1–3) days, and median total hospital charges were 19,908 (13,420–29,980) USD. The hospital length of stay was significantly shorter in the operative group (2 [1–3] days vs. 3 [2–6] days; $p < 0.001$), while total hospital charges were significantly lower in the nonoperative group (15,441 [8,070–31,688] vs. 20,062 [13,672–29,928] USD; $p < 0.001$). On comparison between the groups, both laparoscopic and open procedures had shorter hospital

TABLE 4. Regression Analysis for Predictors of Complications

Variable	OR	95% CI	p
Appendectomy vs. conservative management			
Age in years	1.034	1.033–1.034	<0.001
Male gender	0.788	0.759–0.818	<0.001
Severity of illness*			
Moderate	1.191	1.149–1.235	<0.001
Major	7.875	7.543–8.221	<0.001
Extreme	77	70.74–83.99	<0.001
Appendectomy	0.376	0.355–0.399	<0.001
Laparoscopic appendectomy vs. conservative management			
Age in years	1.037	1.036–1.038	<0.001
Male gender	0.81	0.77–0.84	<0.001
Severity of illness*			
Moderate	1.061	1.016–1.109	0.008
Major	8.935	8.46–9.43	<0.001
Extreme	67.6	60–76	<0.001
Laparoscopic appendectomy	0.20	0.19–0.21	<0.001
Open appendectomy vs. conservative management			
Age in years	1.044	1.043–1.045	<0.001
Male gender	0.95	0.90–0.99	0.038
Severity of illness*			
Moderate	2.247	2.128–2.372	<0.001
Major	3.886	3.665–4.120	<0.001
Extreme	51.4	46.6–56.7	<0.001
Open appendectomy	0.420	0.398–0.444	<0.001

*Minor severity = control.

length of stay (laparoscopic: open: nonoperative; 1 [1–2] days vs. 2 [1–4] days vs. 2 [1–3] days; $p < 0.001$) compared with the nonoperative group. The laparoscopic group had a shorter hospital length of stay ($p < 0.001$ and $p < 0.001$) compared with the open and nonoperative groups, while the nonoperative group had the lowest cost ($p < 0.001$ and $p < 0.001$). Table 1*B* demonstrates the comparison of outcomes between the groups.

On subanalysis of population, overall rate of complications was 3.4% in the pediatric population. The rate of complications was significantly lower in the operative group compared with the nonoperative group (2.8% vs. 8%, $p < 0.001$). On subanalysis of operative approach, both open and laparoscopic groups had lower complication rates compared with the nonoperative management in children ($p < 0.001$). Between the operative groups, the rate of complications was lower in the laparoscopic group in children compared with open ($p < 0.001$) and nonoperative management ($p < 0.001$). The hospital length of stay (2 [1–3] days vs. 3 [2–5] days; $p < 0.001$) was significantly lower in children who underwent operative intervention compared with nonoperative management. The total hospital charges were lower in the nonoperative group compared with the operative group (10,887 [5,774–21,270] vs. 17,878 [12,190–26,360] USD; $p < 0.001$). Table 2 further highlights the differences between subsets of pediatric population based on their age and type of operative approach.

Table 3 reflects the results of subanalysis for operative and nonoperative groups in adult patients. Overall rate of in-hospital complications was 4.9% in the adults. Urinary tract infection (1.6%), followed by ARF (1.2%), was the most common complication. The rate of in-hospital complications was significantly lower in the operative group compared with the nonoperative group (4.4% vs. 17.3%, $p < 0.001$). The laparoscopic group had the lowest rate of complications compared with the open ($p < 0.001$) and the nonoperative group ($p < 0.001$). The hospital length of stay was significantly shorter in adults who underwent operative management (2 [1–3] days vs. 3 [2–6] days; $p < 0.001$), while total hospital charges were lower in nonoperative management (16,500 [9,222–31,685] vs. 204,229 [14,052–30,184] USD, $p < 0.001$).

In the elderly population, overall complication rate was 36.7%. Acute renal failure (10.3%), followed by UTI (6.5%), was the most common complication. The rate of complications was significantly lower in the operative group compared with the nonoperative management group (20% vs. 72%, $p < 0.001$). The laparoscopic approach had the lowest complication rates compared with the open ($p < 0.001$) and nonoperative management ($p < 0.001$) groups. The overall hospital length of stay was shorter in the operative group (3 [2–7] days vs. 6 [3–11] days; $p < 0.001$), while total hospital charges were lower in the nonoperative group (26,510 [13,248–58,431] vs. 28,263 [18,403–47,313] USD; $p < 0.008$). Table 3 provides further details into the subanalysis of adult population.

We performed a multivariate regression analysis for overall complications. Table 4 summarizes the results of our multivariate analysis for overall complications. Appendectomy procedure (OR [95% CI], 0.376 [0.355–0.399]; $p < 0.001$),

TABLE 5. Regression Analysis for Predictors of Hospital Length of Stay

Variable	β Coefficient	95% CI	p
Appendectomy vs. conservative management			
Age in years	0.065	0.063–0.067	<0.001
Male gender	0.124	0.034–0.213	0.007
Severity of illness*			
Moderate	−0.330	−0.424 to −0.237	<0.001
Major	3.947	3.788–4.107	<0.001
Extreme	15.11	14.92–15.30	<0.001
Appendectomy	−2.092	−2.12 to −1.972	<0.001
Laparoscopic appendectomy vs. conservative management			
Age in years	.022	0.022–0.023	<0.001
Male gender	0.109	0.080–0.138	<0.001
Severity of illness*			
Moderate	0.773	0.741–0.805	<0.001
Major	3.438	3.368–3.508	<0.001
Extreme	11.526	11.408–11.643	<0.001
Laparoscopic appendectomy	−3.831	−3.887 to −3.775	<0.001
Open appendectomy vs. conservative management			
Age in years	0.030	0.028 to −0.032	<0.001
Male gender	−0.032	−0.111 to 0.048	0.434
Severity of illness*			
Moderate	−0.330	−0.424 to −0.0237	<0.001
Major	3.947	3.788 to 4.107	<0.001
Extreme	15.11	14.92 to 15.3	<0.001
Open appendectomy	−2.092	−2.212 to −1.972	<0.001

*Minor severity = control.

TABLE 6. Regression Analysis for Total Charges

Variable	β Coefficient	95% CI	*p*
Appendectomy vs. conservative management			
Age in years	316	309–324	<0.001
Male gender	906	603–1,208	<0.001
Severity of illness*			
Moderate	−1,059	−1,385 to −732	<0.001
Major	23,273	22,582–23,964	<0.001
Extreme	131,160	130,170–132,149	<0.001
Appendectomy	1,330	724–1,935	<0.001
Laparoscopic appendectomy vs. conservative management			
Age in years	125.5	119–132	<0.001
Male gender	121.3	−125 to 368	0.335
Severity of illness*			
Moderate	592	297–887	<0.001
Major	20,213	19,558–20,868	<0.001
Extreme	106,503	105,420–107,585	<0.001
Laparoscopic appendectomy	−1,532	−2,019 to −1,044	<0.001
Open appendectomy vs. conservative management			
Age in years	528	0.028 to −0.032	<0.001
Male gender	1,647	−0.111 to 0.048	0.434
Severity of illness*			
Moderate	−6,522	−0.424 to −0.0237	<0.001
Major	21,554	20,054–23,055	<0.001
Extreme	143,850	142,073–145,626	<0.001
Open appendectomy	2,994	2,007–3,982	<0.001

*Minor severity = control.

laparoscopic appendectomy (OR [95% CI], 0.20 [0.19–0.21]; $p < 0.001$), and open appendectomy (OR [95% CI], 0.420 [0.398–0.444]; $p < 0.001$) had a significant protective impact for overall complications.

The regression analysis for the predictors of hospital length of stay demonstrated that appendectomy procedure (β [95% CI], −2.092 [−2.12 to −1.972]; $p < 0.001$), laparoscopic appendectomy (β [95% CI], −3.831 [−3.887 to −3.775]; $p < 0.001$), and open appendectomy (β [95% CI], −2.092 [−2.212 to −1.972]; $p < 0.001$) were associated with lower hospital length of stay. Table 5 reflects the results of the regression analysis for the predictors of hospital length of stay.

In the regression analysis of factors contributing to total hospital charges, operative procedures were associated with higher total charges (β [95% CI], 1,330 [724–1,935]; $p < 0.001$). On subanalysis of types of procedure, laparoscopic appendectomy (β [95% CI], −1,532 [−2,019 to −1,044]; $p < 0.001$) was associated with lower total hospital charges compared with nonoperative management. Table 6 shows the association of the predictors for total hospital charges and comparison between operative and conservative management.

DISCUSSION

The conservative nonoperative management of acute appendicitis with antibiotics has been gaining renewed interest, and the results of our study indicate an increasing trend in the use of nonoperative management. The nonoperative management is proposed as an equal, if not better, alternative to the operative management of appendicitis; however, the results of our study indicate higher complication rate and longer hospital length of stay for patients managed nonoperatively. The findings of our study also point out that the elderly and sicker patients are more likely to get a trial of nonoperative management compared with younger otherwise healthy patients.

The debate of operative versus nonoperative management of appendicitis is not new, with the earliest evidence dating back to 1956 when Coldrey demonstrated the efficacy of antibiotic therapy in the management of acute appendicitis.[2] Later on, several authors have tried to assess the efficacy of nonoperative management of appendicitis with variable success rates. One of the most important concerns limiting wider applicability of available data on the use of nonoperative management is the very select group of patient population reported in these studies. The majority of these studies include noncomplicated appendicitis in young and otherwise healthy subjects. However, the data on the comparison of general population with mixed disease severity and comorbid risk factors are very limited. Our study provides a snapshot of national practice on the use of nonoperative management of acute appendicitis. It appears from the results of our study that the patient group that usually undergoes nonoperative management is the slightly older population with associated risk factors and more advanced disease process.

The question of nonoperative management of acute appendicitis has gained a great interest in recent times, and several randomized controlled trials and prospective studies have tried to answer this age-long question. Recently, Salminen et al.,[2] in a randomized controlled trial, reported favorable outcome with antibiotic therapy alone; however, this trial failed to demonstrate the noninferiority of antibiotic therapy compared with the operative management.

The literature still remains divided on the efficacy of antibiotic therapy alone for the treatment of acute appendicitis. In our study, we observed a significantly higher rate of complications in the nonoperative group compared with the operative group. Similar to our study, Whyte et al.[6] reported a higher complication rate with the nonoperative management and concluded in favor of early appendectomy. We believe that, although antibiotics do carry an important therapeutic role in the select group of patients, they only delay operative intervention in the majority of the patients and can actually complicate the disease process. Furthermore, disease processes such as mechanical obstruction of the appendix (fecalith) and appendiceal perforation may not be amenable to antibiotic therapy alone.[7]

There is a vast body of literature with contrasting results to our findings. Peter et al.[8] in their study demonstrated no difference regarding complications such as recurrent abscess rates between laparoscopic appendectomy and nonoperative antibiotic therapy groups. In a matched cohort analysis, Henry et al.[9] suggested that in comparison with operatively managed patients nonoperative group had fewer complications (43% vs. 19%). Moreover, in a meta-analysis of randomized controlled trials of antibiotic therapy versus surgery, Varadhan et al.[10] showed a trend toward a reduced risk of complications in the antibiotic-treated group (RR [95% CI], 0.43 [0.16–1.18]; $p = 0.10$). However, they concluded that antibiotic therapy was unlikely to supersede appendectomy at present. Although recent evidence seems to favor more toward nonoperative management, it is fraught with limitations, most important of which is a very selective patient population, thus limiting the wider acceptability of this practice.

In our study, we also found that hospital length of stay was significantly higher in the nonoperative group compared with the operatively managed patients. Wilms et al.[11] in their study had similar results. They demonstrated that patients who underwent appendectomy had a significantly shorter hospital stay than did the patients who were treated with antibiotics. One of the reasons for this longer hospital length of stay can be attributed to the disease severity itself because sicker patients were likely to undergo a trial of nonoperative management in our study. Another important plausible explanation can be failure to respond to the therapy and higher rate of complications. The published literature also concurs with this observation as failure of therapy leads to longer hospital length of stay.[6,12] The laparoscopic group remained to be the group with the shortest overall hospital length of stay compared with the operative and the nonoperative group. This difference can be attributed to relatively less complicated postoperative care of a laparoscopic procedure and lower complication rates.

Although nonoperative management strategy for acute appendicitis was associated with higher complication rates and longer hospital length of stays, overall hospital charges were significantly lower in the nonoperative group. This difference in total hospital charges remained valid in a subgroup analysis of operative approach and age-based population subsets. The data on cost benefit of nonoperative management are currently limited. Only a few studies have compared the impact of operative and conservative management of acute appendicitis on total hospital charges. Minneci et al. in their study found no significant difference in total hospital charges between the two groups.[13] This difference in hospital charges seems counterintuitive considering that the operative group had lower complications and shorter hospital length of stay. The limited information on total hospital charges in NIS limits our ability to further delineate this disparity; however, this finding sets up an interesting question for future studies.

In a subanalysis of differences in outcomes between operative and nonoperative management of acute appendicitis in pediatric patients, overall in-hospital complications and overall hospital LOS were significantly higher in the nonoperative management compared with the operative management. These results reflect that operative management of acute appendicitis in pediatric patients still remains the standard-of-care treatment option. The results of a study on pediatric patients with perforated appendicitis similarly suggested higher complication rates in the nonoperative group and do not consider conservative nonoperative management as the first line of treatment.[6]

On comparison of operative approach, that is, open and laparoscopic, our results were not surprising. The majority of patients in our study underwent laparoscopic appendectomy. Over the years, there was a significant increase in the proportion of operative cases being done laparoscopically. Similar to the published literature, laparoscopic appendectomy afforded better outcomes compared with both open appendectomy and nonoperative management.[14] These improved outcomes resulted in increasing number of laparoscopic cases with each passing year over the study period. However, still a significant number of patients required open appendectomy and may actually represent a different subset of patients altogether. In-depth analysis on this very important subject remains beyond the scope of this article, and future research will elucidate more in this area.

Limitations

The results of our study need to be interpreted with its limitations. Our study is derived from NIS, which is limited by data reporting errors. Furthermore, it is a retrospective study with many disease and patient factors left unaccounted. An important outcome of nonoperative management of appendicitis is interval appendectomy; however, because of incident nature of the database and lack of follow-up information, we cannot comment on this very important concern. However, our study is first of its kind to assess the trends and outcomes of nonoperative management of appendicitis at a national level.

CONCLUSIONS

The nonoperative management of appendicitis is becoming more frequent nationally. The results of our study suggest that at current stage national practice favors nonoperative management of appendicitis in older and sicker patients with higher overall complication rates. The results of our study demand further investigation and more in-depth analysis of patient and disease factors responsible for these findings.

AUTHORSHIP

M.K., B.J., T.O.J., P.R., and N.K. conceived and designed this study. B.J., M. K., A.H., K.V., A.T., and R.L. acquired the data. M.K., T.O.J., P.R., A.H., and A.T. contributed to data analysis and interpretation. M.K., B.J., T.O.J., A. H., and L.G. drafted the manuscript. B.J., M.K., T.O.J., T.O, and P.R. performed critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

Dr. Robert Sawyer (Charlottesville, Virginia): Khalil et al have performed an interesting review of the National In-Patient Sample Data Base from 2004 to 2011, analyzing patients who were admitted with a diagnosis of appendicitis, comparing those who underwent an appendectomy to those who did not.

I think we can safely summarize their data as follows: (i) More patients are being treated non-operatively. (ii) Patients who are treated non-operatively tend to be older and sicker than patients who are treated operatively, and patients who are treated non-operatively have a higher rate of complications and longer hospital stays than those treated operatively.

I did not find the results surprising, but they are important to document in the literature and I recommend the published manuscript to all acute care surgeons.

To place this paper in context, one really needs to review the randomized trials regarding the use of antibiotics alone versus appendectomy in non-perforated appendicitis, including the paper which was referenced just recently this year in *JAMA* by Salminen et al. Some say the literature is controversial, but I disagree. The literature is very consistent. Antibiotics alone are successful in about two-thirds of patients but fail in about a third. Meaning, the patient ends up undergoing appendectomy within the following year or so.

What *is* controversial is the question of how to use these data to guide physician and patient choices. I have four questions for the authors:

Why do you think your data appear to be so different from multiple randomized, controlled trials that show relatively similar outcomes between operative and non-operative patients with appendicitis?

Do you think a multivariable analysis would have been worthwhile, allowing you to adjust for differences in age and comorbidities? I don't think so since I doubt one can ever ferret out retrospectively from administrative data the reasons why a surgeon decided to offer a non-operative approach to one patient but not the next. But I am interested in your opinion.

Do you think there are patients who should be treated non-operatively? Or do you believe that an appendectomy should be performed on any patient with appendicitis who has a detectible heart rate and blood pressure?

Finally, presuming the answer to the third question is yes, how do we set about determining which patients should be treated non-operatively for appendicitis?

In other words, can we figure out who those two-thirds of patients are who can receive antibiotics alone and never require an appendectomy and the third of patients who clearly benefit from an appendectomy?

I thank the Association for the privilege of the floor and the honor of being a new member. Thank you.

Dr. Dennis Vane (Saint Louis, Missouri): Two quick questions. The first question, for pediatric patients, the adolescents and younger pediatric patients, historically we have switched to treating the patients with complicated appendicitis or suspected complicated appendicitis—high white counts, relatively septic, palpable mass in the abdomen—with an interval appendectomy which means initially they are admitted for antibiotics, when they are stable they are sent home and they come back for their appendectomy, depending on what institution you are, up to six weeks later.

So how did you separate out those patients in your study because a lot of them would have been treated initially without appendectomy and then later with appendectomy?

Dr. Paula Ferrada (Richmond, Virginia): I was wondering if you looked back on comorbidities, especially in the elderly, and adding immunosuppression as well. Thanks.

Dr. Therese Duane (Fort Worth, Texas): We are in a post-antibiotic era, at this point. The two complications you don't really look at are the length of antimicrobial therapy, which is always longer in the non-operative case, and the impact on that. The one thing you cannot measure—and I want to know what you think about being able to measure it—is the impact on antibiograms by using longer duration of therapy. Thanks.

Dr. W. Slate Wilson (Portland, Oregon): Given the fact that many of our pediatric patients are treated with antibiotics alone and no interval appendectomy, I'd like to know if there have been any long-term follow-ups on recurrent appendicitis years later?

Maybe it's something like taking the gallstones out and leaving the gallbladder—a silly comparison. But I would be very interested in any long-term studies.

Dr. Mazhar Khalil (Tucson, Arizona): Thank you very much for all your questions and comments. I start with Dr. Sawyer's comments. Thank you very much, sir, for reviewing our paper and providing your feedback.

Regarding your first question that why the results of our study are different from the results of randomized, controlled trials. I believe, the answer lies in the patient selection.

All the randomized, controlled trials, they report non-complicated, simple, acute appendicitis while in the real practice as reflected in the data we presented—and I believe that most of us will agree—that we tend to treat sicker patients with antibiotics rather than the young and healthy patients that come at night with new onset abdominal pain. We tend to take them directly to operating room.

And the other thing that influences decision is hospital resources. Most of the centers that publish randomized, controlled trials, they are well-equipped. They have CT scans available 24 hours and they have a team of acute care surgeons available all the time, in contrast to a smaller community hospitals where the resources are limited and they tend to approach aggressively rather than keep the patient in-hospital and observe them over two or three days.

I think the primary reason for the difference we observed from the trials is that the patients we treat with antibiotics in real practice are different from the patients that are reported in the randomized, controlled trials.

Regarding your second question about multivariate analysis, I agree with the limitations you proposed. We don't have the factors in the database that can answer this question. Even though we can include demographics and some comorbidities in our multivariate model, but these are not the decision-making factors. We don't have the findings on CT scan that are usually the most important factor along with time to presentation. In reality they are the more important factors that play a critical role in decision making.

Your other question was: should most of our patients have undergone non-operative management? We don't want to introduce our bias into the results and I would say that still it is an open field. There are a lot of surgeons that still believe that appendicitis is a surgical disorder requiring surgery. The literature in favor of antibiotics is still emerging. I would argue that it all depends on patient selection. Slowly and gradually we are moving forward towards more appropriate patient selection and probably we will be able to get the results that we hope for.

Regarding question about interval appendectomy in pediatric patients. We don't have that data available in the National In-Patient Sample. And it can only be done through a prospective study.

Dr. Ferrada mentioned immunosuppression in older patients and comorbidities. We, at that time we don't have that analysis but I am sure that we can get some of that data from the National In-Patient Sample. And the paper that we are going to publish will definitely include such analysis to show that how immunosuppression or other comorbidities affect outcomes in elderly patients.

Regarding the length of antibiotics, due to limitations of the dataset, we can not extract that data from the National In-Patient Sample. The data that are available regarding the use of antibiotics is limited. The only information we can extract in this regard is whether antibiotics were used or not. But this is an extremely important point and whoever is moving forward with this study design, should also consider the length of antibiotics because inappropriate antibiotic therapy can also lead to the failure of the treatment and can bias the results and opinions about the antibiotic treatment.

Dr. Wilson mentioned recurrent appendicitis. Again, due to limitations of dataset, we don't have that data available from the National In-Patient Sample.

Thank you very much for your comments.