

# Hospital- and Patient-Level Characteristics and the Risk of Appendiceal Rupture and Negative Appendectomy in Children

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**T**HE PRIMARY ADVERSE OUTCOME of appendicitis is appendiceal rupture. Patients with an appendiceal rupture at the time of surgical exploration have as high as a 39% chance of having a postsurgical complication, such as intra-abdominal abscess, wound infection, and postoperative paralytic ileus, compared with an approximately 8% chance if the appendix is not perforated.<sup>1,2</sup> It has been assumed that the natural history of appendiceal rupture is within the control of the hospital or physician and that a high rate of rupture reflects a failure of medical care. As a result, appendiceal rupture rates have been proposed as a measure of intrinsic hospital quality. Given the difficulty of diagnosing appendicitis in both children and adults, the traditional approach by hospitals to decrease the rupture rate has been to encourage early surgical exploration. In fact, high rates of negative exploration for appendicitis have been tolerated to lessen the likelihood of appendiceal rupture and its attendant complications.<sup>1,2</sup> In essence, one complication (a negative exploration) is encouraged to decrease the incidence of another complication (appendiceal rupture). Negative

**Context** The rates of appendiceal rupture and negative appendectomy in children remain high despite efforts to reduce them. Both outcomes are used as measures of hospital quality. Little is known about the factors that influence these rates.

**Objective** To investigate the association between hospital- and patient-level characteristics and the rates of appendiceal rupture and negative appendectomy in children.

**Design, Setting, and Patients** Retrospective review using the Pediatric Health Information System database containing information on 24 411 appendectomies performed on children aged 5 to 17 years at 36 pediatric hospitals in the United States between 1997 and 2002.

**Main Outcome Measures** Rates of negative appendectomy and appendiceal rupture; the odds ratio (OR) of negative appendectomy and appendiceal rupture by hospital, patient age, race, and health insurance status, and hospital fiscal year and appendectomy volume. Negative appendectomy rate was defined as the number of patients with appendectomy but without appendicitis divided by the total number of appendectomies.

**Results** The median negative appendectomy rate was 3.06% (range, 1%-12%) and the median appendiceal rupture rate was 35.08% (range, 22%-62%). The adjusted OR for appendiceal rupture was higher in Asian children (1.66; 95% confidence interval [CI], 1.24-2.23) and black children (1.13; 95% CI, 1.01-1.30) compared with white children. Children without health insurance and children with public insurance had increased odds of appendiceal rupture compared with children who had private health insurance (adjusted OR, 1.36; 95% CI, 1.22-1.53 for self-insured; adjusted OR, 1.48; 95% CI, 1.34-1.64 for public insurance). No correlation existed between negative appendectomy rate and race, health insurance status, or hospital appendiceal rupture rate. The negative appendectomy rate improved as the hospital appendectomy volume increased.

**Conclusion** The rate of appendiceal rupture in school-aged children was associated with race and health insurance status and not with negative appendectomy rate and therefore is more likely to be associated with prehospitalization factors such as access to care, quality of care, and patient or physician education.

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hospital appendectomy rates as high as 26% have been reported.<sup>3</sup>

Despite efforts by hospitals and physicians and the advent of new diagnostic techniques such as ultrasonography and computed tomography, the appendiceal rupture rate remains high among children and ranges from 30%

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to 74%.<sup>4</sup> Recently, some have argued that high rupture rates may be unrelated to hospital-level care and that delay in diagnosis and treatment due to inadequate access to health care may instead be the major factor.<sup>3-8</sup>

In this study, we examined the patterns of diagnosis and care of children aged 5 to 17 years with appendicitis at 36 major children's hospitals to assess the contributions of race, health insurance status, age, sex, and hospital volume on the appendiceal rupture rate. We also evaluated the correlation between rupture rate and negative appendectomy rate.

## METHODS

### Study Population

Data in this study were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient and selected outpatient data from 36 not-for-profit, free-standing US pediatric hospitals that are affiliated with Child Health Corporation of America (Overland Park, Kan), a business alliance of children's hospitals. The database was created in 1992 and quality and accuracy is a joint effort between participating hospitals, Child Health Corporation of America, and Solucient LLC (Evanston, Ill). Solucient is a leading source of health care business intelligence that maintains the nation's largest health care database composed of more than 22.6 million discharges annually from 2900 hospitals, representing 77.5% of all discharges.<sup>9</sup> Solucient manages the data warehouse function for the PHIS database. The number of hospitals participating in PHIS has grown from 12 to 36 hospitals. Eighty percent of the participating hospitals provide daily resource use data that is used in comparing clinical practice. From a demographic perspective, 17 of the 20 major metropolitan areas in the United States are represented in the PHIS database. The National Association of Children's Hospitals and Related Institutions (Alexandria, Va) estimates that there are 50 to 55 freestanding pediatric general acute care hospitals in the United States. Seventy percent of

these hospitals submit data to the PHIS database.

Information on 24 411 appendectomies performed on children aged 5 to 17 years was abstracted. Although information on infants and young children to age 4 years was abstracted and is included in the population overview, this age group was excluded from detailed analysis because of an appendiceal rupture rate that was significantly higher than older age groups. Inclusion of these infants and young children would skew the results. All patients were discharged between January 1, 1997, and June 30, 2002. The PHIS uses all patient-refined diagnosis related groups to classify patients. The criterion for inclusion was any child with a principal diagnosis of appendectomy and a principal *International Statistical Classification of Diseases, 9th Revision (ICD-9)* procedure code of 47.01 (laparoscopic appendectomy) or 47.09 (other appendectomy). Children undergoing an incidental appendectomy performed during another abdominal surgical procedure were excluded. Children with appendicitis who were treated initially by drainage followed by a subsequent admission for an interval appendectomy were included.

The results were blinded to the identity of the hospitals, which is consistent with PHIS policies. This study received an exemption from the institutional review board at Children's National Medical Center, Washington, DC.

### Outcome Measures

Patients were stratified into 3 groups: appendiceal rupture (*ICD-9* codes 540.0 and 540.1), nonruptured appendicitis (*ICD-9* codes 540.9, 541, 542), and negative appendectomy (other *ICD-9* codes). *Rupture rate* was defined as the total number of patients with appendiceal rupture divided by the number of patients with acute appendicitis. *Negative appendectomy rate* was defined as the number of patients with appendectomy but without appendicitis divided by the total number of appendectomies. Independent variables included age (5-12 years and 13-17 years), sex, race (white, black, Asian, or other), and health insurance

status (private insurance, self-insured, or public insurance). These independent variables were the most complete variables from the PHIS database that characterize the population. Ninety percent of the children in the public health insurance category had Medicaid insurance; the other 10% included title 4 and other government-sponsored insurance, such as Champus or nontraditional Medicaid (Medicaid health maintenance organization). Other race includes all individuals who were not Asian, black, or white. If race was not indicated in the database, it was coded as missing. Race was included as a variable because it has been cited as an issue in many studies of disparities in quality and access to health care for children. Hospital-level independent variables were fiscal year (1997-2002), hospital negative appendectomy rate, and hospital volume (number of appendectomies performed per year). These hospital-level characteristics were chosen as independent variables because they were likely to affect patient outcome.

### Statistical Analysis

The rates of negative appendectomy and appendiceal rupture were computed for each age, race, health insurance status, and fiscal year group. Intergroup differences were tested for significance using the  $\chi^2$  test at the individual level. The odds of rupture and negative appendectomy by hospital appendectomy volume group, age, sex, race, and health insurance status were then modeled with multivariable logistic regressions. The logistic regressions were adjusted for interhospital correlations using generalized estimating equation models in PROC GENMOD of SAS statistical software (version 8.02, SAS Institute Inc, Cary, NC).<sup>10,11</sup> In the multivariable model for rupture, the negative appendectomy rate was also adjusted as a hospital characteristic. Rates of radiological procedures were not used as covariates in the analysis because of difficulty interpreting the results. A Pearson correlation analysis was performed to assess if any correlation existed between negative appendectomy rate and rupture rate among each race.

A multivariate analysis was also performed to assess the association between negative appendectomy rate and appendiceal rupture rate. Because appendicitis cases from the same hospital cannot be considered independent observations, generalized estimating equation models in PROC GENMOD were used to adjust for the effect of case clustering by hospital.<sup>12</sup> The *P* value cutoff for significance for this study was .05.

## RESULTS

### Patient Demographics

Of children with appendectomies discharged between January 1, 1997, and June 30, 2002, 10.6% were infants and children to age 4 years; 64.8%, 5 to 12 years; and 24.6%, 13 to 17 years. Infants and children to age 4 years had a higher appendiceal rupture rate (70.5%) compared with older children (37.1%) and were excluded from further analysis. Previous studies have shown similar rates of rupture in this age group.<sup>13</sup> Of those between ages 5 and 17 years, 61% were male and 39% were female. Seventy-seven percent were white; 12%, black; 2%, Asian; and 9%, other races. Fifty-three percent had private health

insurance; 39% had public health insurance; and 8% were self-insured.

To assess the representativeness of the study population, we compared the demographic profile of all appendectomy discharges within the PHIS database from July 1, 2001, to June 30, 2002, with the demographic profile of all pediatric appendectomy discharges for 5- to 17-year-olds during the same period in the Solucient database. Sixty percent of the PHIS appendectomy discharges were male, 40% were female, and 29% had public insurance. Fifty-eight percent of the Solucient population was male, 42% was female, and 25% had public insurance.<sup>9</sup> Because patient race was not available from the Solucient database, the racial profile of the PHIS database for all diagnoses from July 1, 2001, to June 30, 2002, was compared with the Solucient 2003 population projections based on the 2000 US Census. Seventy-two percent of the individuals in the PHIS database were white; 25%, black; and 2%, Asian. The Solucient population projections were 71% white; 16%, black; and 3.8%, Asian.<sup>14</sup>

The groups with the highest frequencies of negative appendectomies were females (aged 13-17 years), blacks, those with private health insurance, and those

who had appendectomies in 1997 (TABLE 1). The groups with the highest frequencies of appendiceal ruptures were children aged 5 to 12 years, Asians, those with public health insurance, and those with appendectomies in 1997.

Surgical exploration was performed in 81% of the children on the day of presentation to the hospital and 15% on the next calendar day. Because the PHIS database includes date but not time of admission, some of these 15% may actually have been operated on within the first 24 hours of presentation. The probability of having an appendectomy on the first day of presentation to the hospital was similar in all health insurance groups: private insurance (83.4%), self-insured (84.3%), and public insurance (82.3%); and in all race groups: Asian (84.2%), black (82.1%), and white (83.3%).

Overall, 49% of children in this study underwent a radiological procedure prior to surgery, including computed tomography, ultrasound, fluoroscopy, or magnetic resonance imaging. The percentage of children who underwent a radiological procedure was lower for Asian children (41.0%) compared with blacks (52.9%) and whites (50.1%; *P* < .001). The percentage of children who

**Table 1.** Frequency of Outcome by Demographic and Patient Characteristics

	Appendectomy			Appendicitis			Total No. of Patients
	No. (%) Negative	No. (%) Positive	<i>P</i> Value	No. (%) Ruptured	No. (%) Nonruptured	<i>P</i> Value	
Age							
≤1 mo to 4 y*	142 (4.89)	2764 (95.1)	<.001	1950 (70.5)	814 (29.5)	<.001	2906
5-12 y	503 (2.84)	17 192 (97.16)		7009 (40.7)	10 686 (62.16)		17 695
13-17 y	245 (3.65)	6471 (96.35)		2040 (30.37)	4505 (69.63)		6716
Sex							
Male	372 (2.48)	14 648 (97.52)	<.001	5508 (36.67)	9512 (63.33)	.10	15 020
Female	375 (3.99)	9016 (96.01)		3544 (37.74)	5847 (62.26)		9391
Race							
White	546 (3.37)	15 669 (96.63)	.03	5700 (35.15)	10 515 (64.85)	<.001	16 215
Black	97 (3.73)	2505 (96.27)		1053 (40.48)	1549 (59.52)		2602
Asian	10 (1.96)	501 (98.04)		264 (51.70)	247 (48.30)		511
Other	45 (2.44)	1799 (97.56)		751 (40.74)	1093 (59.26)		1844
Insurance							
Private	298 (3.06)	9431 (96.94)	<.001	3085 (31.71)	6644 (68.29)	<.001	9729
Self	42 (2.74)	1492 (97.26)		633 (41.29)	901 (58.71)		1534
Public	175 (2.48)	6874 (97.52)		3171 (44.98)	3878 (55.02)		7049
Year							
1997	91 (3.45)	2544 (96.55)	.46	1104 (41.92)	1530 (58.08)	<.001	2635
1998	123 (3.18)	3746 (96.82)		1502 (38.81)	2367 (61.19)		3869
1999	119 (2.96)	3906 (97.04)		1546 (38.40)	2479 (61.60)		4025
2000	152 (3.21)	4579 (96.79)		1662 (35.12)	3069 (64.88)		4731
2001	158 (3.07)	4995 (96.93)		1857 (36.04)	3296 (63.96)		5153
2002	105 (2.63)	3894 (97.37)		1382 (34.57)	2617 (65.43)		3999

\*The group consisting of infants and children to age 4 years were excluded from the remainder of the table and from further analysis.

underwent a radiological procedure prior to surgery varied by health insurance status: 49.0% were self-insured, 44.1% had private health insurance, and 47.3% had public insurance ( $P < .001$ ). However, a higher frequency of radiological tests was not associated with a lower rupture rate: 43.8% of children with appendiceal rupture had a radiological test compared with 35.9% of children with nonruptured appendicitis ( $P < .001$ ).

**Appendiceal Rupture Rate**

The median rupture rate was 35.08% (range, 22%-62%) among the 36 hospitals studied. The quarterly incidence rate of appendiceal rupture decreased 7% during the 5 years studied from 42% to 35% ( $P < .001$ , FIGURE 1).

Asian children had a greater chance of having an appendiceal rupture compared with white children (adjusted odds ratio [AOR], 1.66; 95% confidence in-

terval [CI], 1.24-2.23) as did black children (AOR, 1.13; 95% CI, 1.01-1.30) (TABLE 2). Children with public health insurance had a greater chance of having an appendiceal rupture compared with children with private health insurance (AOR, 1.48; 95% CI, 1.34-1.64), as did children who were classified as self-insured (AOR, 1.36; 95% CI, 1.22-1.53). Children aged 5 to 12 years had an AOR of 1.41 (95% CI, 1.30-1.53) for having an appendiceal rupture compared with children aged 13 to 17 years. There was no statistical difference in rupture rate between male and female children. Hospital experience, defined by the volume of appendectomies performed, was not associated with appendiceal rupture rate ( $r = 0.03$ ;  $P = .86$ ) regardless of adjustments for race, sex, age, and health insurance status.

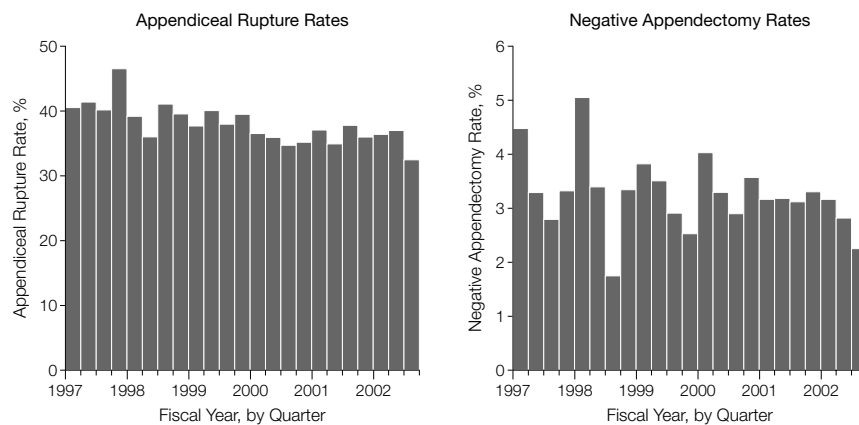
**Negative Appendectomy Rate**

The median negative appendectomy rate was 3.03% (range, 1%-12%) in the 36 hospitals studied. The incidence of negative appendectomy did not change during the 5 years of the study ( $P = .46$ ; Figure 1).

Race and health insurance status had no statistically significant impact on negative appendectomy rates (TABLE 3). Children aged 5 to 12 years had a lower chance of having a negative appendectomy compared with children aged 13 to 17 years (AOR, 0.80; 95% CI, 0.69-0.94). Girls had a 58% greater chance of having a negative appendectomy compared with boys (AOR, 1.58; 95% CI, 1.30-1.92). A significant interaction was found between age and sex with regard to negative appendectomy rate. A stratified analysis showed no association between age and negative appendectomy rate for boys (2.74% negative appendectomy rate in the 13- to 17-year age group compared with 2.39% in the 5- to 12-year age group;  $P = .22$ ). For girls, however, the older group had a higher negative appendectomy rate (5.06% compared with 3.58%;  $P = .001$ ).

The principal diagnoses for the negative appendectomy group were right lower quadrant abdominal pain (30%); diseases of the appendix not else-

**Figure 1.** Trends in Negative Appendectomy Rate and Appendiceal Rupture Rate



Appendiceal rupture rate decreased 7% during the 5 years studied from 42% to 35% ( $P < .001$ ). The decline in the negative appendectomy rate was not statistically significant.

**Table 2.** Odds Ratio of Appendiceal Rupture

	OR (95% CI)	Adjusted OR (95% CI)*
<b>Hospital</b>		
Negative appendectomy rate (per 1000 patients)	1.00 (1.00-1.01)	1.00 (1.00-1.01)
Volume (per 1000 patients)	0.96 (0.70-1.31)	0.96 (0.71-1.28)
<b>Patients</b>		
Age, y		
5-12	1.42 (1.31-1.54)	1.41 (1.30-1.53)
13-17	1.00	1.00
Sex		
Male	1.00	1.00
Female	1.04 (0.98-1.10)	1.04 (0.98-1.11)
Race		
White	1.00	1.00
Black	1.24 (1.09-1.41)	1.13 (1.01-1.30)
Asian	1.74 (1.26-2.40)	1.66 (1.24-2.23)
Other	1.17 (0.98-1.40)	1.12 (0.94-1.33)
Insurance		
Private	1.00	1.00
Self	1.40 (1.25-1.57)	1.36 (1.22-1.53)
Public	1.53 (1.39-1.69)	1.48 (1.34-1.64)

Abbreviations: CI, confidence interval; OR, odds ratio.

\*In addition to adjusting for hospital as a cluster variable, the multivariable models were adjusted for patient age, sex, race, health insurance status, and hospital volume.

where classified (27%); mesenteric lymphadenitis (8%); abdominal pain site not otherwise specified (7%); non-infectious gastroenteritis (5%); and hyperplasia of the appendix (3%). These diagnoses accounted for 80% of the negative appendectomies.

Negative appendectomy rate was influenced by hospital volume (Table 3). As the total number of appendectomies performed at a given hospital increased by 1000, there was a 50% reduction in the negative appendectomy rate (AOR, 0.50; 95% CI, 0.35-0.71).

### Association of Negative Appendectomy Rate and Appendiceal Rupture Rate

There was no correlation between negative appendectomy rate and appendiceal rupture rate by hospital ( $r = 0.08$ ;  $P = .65$ ) (FIGURE 2) or among the individual races ( $P = .65$ ). The rupture rate was not associated with negative appendectomy rate either before or after adjustments for race, sex, age, health insurance status, and hospital volume (Table 2).

### COMMENT

The data presented herein suggest that hospital-level characteristics may not be associated with the rate of appendiceal rupture. Hospitals with increased negative appendectomy rates did not necessarily have lower appendiceal rupture rates. In addition, no association was found between hospital volume and appendiceal rupture rate. Evidence supports a relationship between hospital case volume and quality of outcomes, and in this study, an increased hospital volume was inversely associated with negative appendectomy rate.<sup>15</sup> The absence of a relationship between hospital volume and appendiceal rupture rate and the lack of correlation between the negative appendectomy rate and appendiceal rupture rate suggest that hospital characteristics have little influence on appendiceal rupture.

The only factors associated with appendiceal rupture in this study were race, health insurance status, and age. These findings corroborate previous

**Table 3.** Odds Ratio of Negative Appendectomy

	OR (95% CI)	Adjusted OR (95% CI)*
	<b>Hospital</b>	
Volume (per 1000 patients)	0.55 (0.37-0.82)	0.50 (0.35-0.71)
	<b>Patients</b>	
Age, y		
5-12	0.80 (0.69-0.92)	0.80 (0.69-0.94)
13-17	1.00	1.00
Sex		
Male	1.00	1.00
Female	1.57 (1.31-1.87)	1.58 (1.30-1.92)
Race		
White	1.00	1.00
Black	0.97 (0.72-1.31)	0.98 (0.72-1.34)
Asian	0.62 (0.38-1.01)	0.65 (0.36-1.19)
Insurance		
Private	1.00	1.00
Self	0.91 (0.66-1.26)	0.93 (0.65-1.34)
Public	0.94 (0.77-1.14)	0.94 (0.76-1.16)

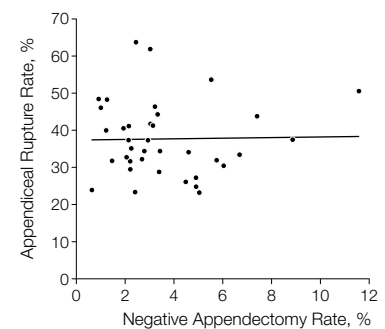
Abbreviations: CI, confidence interval; OR, odds ratio.

\*In addition to adjusting for hospital as a cluster variable, the multivariable models were adjusted for patient age, sex, race, health insurance status, and hospital volume.

studies linking appendiceal rupture in both children<sup>8</sup> and adults to certain risk factors including extremes of age, Medicaid insurance, and nonwhite race.<sup>3,5,16,17</sup> Asian and black children had a significantly higher likelihood of appendiceal rupture than white children. Moreover, children with public insurance had a 48% greater chance of having an appendiceal rupture than children with private insurance. While the racial disparities may represent language barriers, cultural variances, or a genetic etiology, the association of appendiceal rupture rate with health insurance status suggests that the incidence of rupture may be related to medical care access or quality. Finally, the finding of a higher appendiceal rupture rate in younger children is a well-established phenomenon and correlates with the difficulty in parental or physician recognition of abdominal symptoms in this age group.

These findings are consistent with previous articles suggesting that appendiceal rupture typically occurs prior to hospital presentation. Hale et al<sup>18</sup> reported that 68% of all ruptures occur prior to surgical evaluation. These authors found that a delay in outpatient management or diagnosis resulted in a doubling of the appendiceal rupture rate. Furthermore, the number of ap-

**Figure 2.** Negative Appendectomy Rate Compared With Appendiceal Rupture Rate



Rates shown are the mean rates during the 5 years studied. There was no correlation between negative appendectomy rate and appendiceal rupture rate ( $r = 0.08$ ,  $P = .65$ ). The regression line was created using a least squares fit model.

pendiceal ruptures related to in-hospital delay was not statistically significant.<sup>18</sup> There are several reports that document that prehospital delay increases the rate of complicated appendicitis.<sup>4,7,11,19</sup> In their prospective analysis of 5755 children and adults, Pittman-Waller et al<sup>19</sup> determined that the time from the onset of symptoms to first seeking medical attention is a significant predictor of complicated appendicitis (39.8 vs 16.5 hours for acute appendicitis), whereas the time from surgical evaluation to operative intervention was significantly shorter for

complicated appendicitis (3.8 vs 4.7 hours for acute appendicitis).

Unlike the appendiceal rupture rate, the negative appendectomy rate was related to hospital-level characteristics. The negative appendectomy rate was not associated with race or health insurance status but did improve as hospital volume increased. The mean negative appendectomy rate among the 36 hospitals was 3%, which was much lower than that previously reported.<sup>4</sup> The beneficial effects of imaging advances such as computed tomography and ultrasound probably contributed to the low rate.<sup>16,20</sup>

The higher negative appendectomy rate in girls and adolescent females is most likely related to the gynecologic sources of pain after puberty that often mimic appendicitis. This theory is supported by the intergroup comparisons showing that adolescent girls but not adolescent boys had a higher negative appendectomy rate.

If a relationship between negative appendectomy rate and appendiceal rupture rate exists, a decline in the negative appendectomy rate over time should result in an increased rupture rate. However, several recent studies<sup>6,16,20-27</sup> performed in the era of improved diagnostic imaging show stable or declining appendiceal rupture rates in the face of declining negative appendectomy rates in both children and young adults. Some reports have noted no change in either rate over time.<sup>28,29</sup>

The data presented herein demonstrate that the appendiceal rupture rate did decline by 7% during the years studied without a statistically significant change in negative appendectomy rate.

The use of an administrative database created several limitations. For example, there is a lack of data concerning the prehospital experience of the patients, including whether patients were transferred from other hospitals. Additionally, race was provided subjectively by either an admitting clerk or the patient's family. Ethnicity is not captured in the database and the Hispanic patient population, therefore, cannot be evaluated separately. The PHIS database slightly overrepresented blacks, but

appears to be similar to the national pediatric demographic profile for sex and health insurance status. Studies using different data sets may further elucidate the racial, ethnic, and health insurance status disparities. This study also was limited by the inability to analyze physician-specific practice variation. The negative appendectomy rates and appendiceal rupture rates may not be representative of all hospitals because all of the institutions were children's hospitals.

These findings present a dual challenge for improving the outcomes of children with appendicitis. The low negative appendectomy rates and the relationship between hospital volume and negative appendectomy rate suggest potential opportunities for improvement at the hospital level. Efforts to reduce the incidence of appendiceal rupture should focus on prehospital care. The findings of disparate care by race and health insurance status are troubling. A public health paradigm with concentration on access to care and quality-of-care issues as well as family and physician education might facilitate earlier diagnosis and intervention. The excessively high rates of appendiceal rupture in children should no longer be tolerated.

**Author Contributions:** Dr Newman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Ponsky, Kittle, Gilbert, Newman.

**Acquisition of data:** Ponsky, Kittle, Gilbert, Newman. **Analysis and interpretation of data:** Ponsky, Huang, Eichelberger, Gilbert, Brody, Newman.

**Drafting of the manuscript:** Ponsky, Gilbert, Newman. **Critical revision of the manuscript for important intellectual content:** Ponsky, Huang, Kittle, Eichelberger, Gilbert, Brody, Newman.

**Statistical analysis:** Ponsky, Huang.

**Administrative, technical, or material support:** Ponsky, Kittle, Gilbert, Newman.

**Study supervision:** Eichelberger, Gilbert, Brody, Newman.

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