The Clinical and Economic Correlates of Misdiagnosed Appendicitis

Nationwide Analysis

David R. Flum, MD; Thomas Koepsell, MD, MPH

Background: Negative appendectomy (NA)—the nonincidental removal of a normal appendix—occurs commonly but the associated clinical- and system-level costs are not well studied.

Hypothesis: The frequency of adverse clinical outcomes and associated financial burden of hospitalizations during which NA is performed is greater than previously recognized and varies widely among demographic groups.

Design: Population-based, retrospective cohort study.

Setting: The 1997 Nationwide Inpatient Sample of the Health Care Utilization Project.

Patients: All surveyed patients assigned *International Classification of Diseases, Ninth Revision* procedure codes for appendectomy but without an associated diagnosis of acute appendicitis.

Main Outcome Measures: The age- and sex-stratified rates of NA, the incidence of associated infectious complications and case fatality, and the average length of stay and hospitalization charges during those admissions.

Results: Nationwide, an estimated 261 134 patients underwent nonincidental appendectomies in 1997, and 39 901 (15.3%) were negative for appendicitis. Women had a higher rate of NA as did patients younger than 5 years and older than 60 years. When compared with patients with appendicitis, NA was associated with a significantly longer length of stay (5.8 vs 3.6 days, $P<.001$), total charge-admission ($18 780 vs $10 584, $P<.001$), case fatality rate (1.5% vs 0.2%, $P<.001$), and rate of infectious complications (2.6% vs 1.8%, $P<.001$). An estimated $741.5 million in total hospital charges resulted from admissions in which a NA was performed.

Conclusions: There are significant clinical and financial costs incurred by patients undergoing NA during the treatment of presumed appendicitis. These should be considered when evaluating system-level interventions to improve the management of appendicitis.

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THE LIFETIME risk of appendectomy is 12% for men and 25% for women, making it the most commonly performed emergency operation in the world.[1,2] Though considered a straightforward diagnosis by clinicians, a high rate of misdiagnosis—often referred to as *negative appendectomy* (NA)—suggests otherwise. A recent population-based analysis[3] has confirmed the findings of smaller clinical studies[2,4,5] that in more than 15% of appendectomies performed there is no pathologic evidence of appendicitis. In some high-risk populations, such as women of reproductive ages, the population-based rate of unnecessary appendectomy is as high as 26%.[3] While computed tomographic scanning, ultrasonography, and laparoscopy have been advocated to improve accuracy in the diagnosis of appendicitis, the benefit of these modalities in clinical trials[6] has not been realized in general practice.[4] In fact, diagnostic accuracy on a population level has not improved during the last 15 years despite the widespread availability of such testing.[3]

See Invited Critique at end of article

Classically, this rate of NA has been accepted by the clinical community because the frequency of appendiceal perforation is considered by many to be inversely linked to the rate of NA.[7] It has been suggested[7] that a higher than zero (10%-15%) rate of unnecessary appendectomy must be tolerated to assure a low threshold for operation, such that diagnostic delays that might result in perforation are

From the Robert Wood Johnson Clinical Scholars Program (Drs Flum and Koepsell) and the Departments of Surgery (Dr Flum) and Epidemiology and Health Services (Dr Koepsell), University of Washington, Seattle.

SUBJECTS AND METHODS

STUDY DESIGN

A retrospective cohort study was conducted, using a national, population-based hospital discharge database. The University of Washington Human Subject Review Committee exempted this study from human subjects review because the dataset includes only anonymous data and is considered within the public domain.

DATA SOURCES AND CHARACTERISTICS

Data were obtained from the Nationwide Inpatient Sample of the Health Care Utilization Project (release 6) for 1997. The Health Care Utilization Project is funded by the Agency for Healthcare Research and Quality. The dataset is a 20% sample of hospital discharges from US nonfederal hospitals based on a stratified probability sample of hospitals. Data are obtained from 22 states and contain information on all inpatient stays from more than 900 hospitals. Anonymous inpatient records contain clinical and resource use information. Hospital and patient discharge weights allow national estimates to be computed.

SUBJECTS

All discharge reports from January 1, 1997, to December 31, 1997, were searched for *International Classification of Diseases, Ninth Revision (ICD-9)*, procedure codes pertaining to appendectomy (see box on page 803). This group was then evaluated based on associated *ICD-9* diagnostic codes that described appendiceal disease.

VARIABLE DEFINITION

A case of appendicitis was defined as any patient undergoing NA with an associated diagnostic code of appendicitis or related appendiceal disease, and NA was defined as those having the surgery without an associated diagnostic code of appendicitis. Women aged 15 to 45 years were considered to be of reproductive age. Infectious complications included postoperative wound infections and pelvic abscesses and were defined by appropriate *ICD-9* codes. A comorbidity index (0-3, with 3 indicating greatest comorbidity) was calculated for each patient based on *ICD-9* diagnostic codes.[11]

STATISTICAL ANALYSIS

Statistical analysis was performed using Stata statistical analysis software (Stata Corp, College Station, Tex). The survey data analysis features of Stata incorporated probability weighting, adjustment for clustering by sampling unit, and the stratification strategy. The procedure-based proportions of NA for the entire cohort and for demographic subgroups considered at expected higher risk for NA were calculated and compared using univariate analysis. A survey estimator for linear combinations of variables was used to compare survey estimates of continuous data and a test of independence appropriate for complex survey design was used to compare categorical data.

Two multivariate, unconditional logistic regression models were constructed. The first grouped together the variables positively associated with NA in the univariate analysis. This model considered NA as the response variable, and female sex, age group, comorbidity index, Medicaid payer status, teaching hospital, and rural location as predictor variables when controlling for one another. A separate model was created to evaluate the predictors of adverse outcome. In this second logistic regression model, adverse outcome (prolonged length of stay, increased charge of admission, case fatality, and infectious complications) was the response variable and NA was considered the predictor variable. This model excluded patients at the extremes of age and considered the effect of NA on adverse outcome adjusted for age, sex, and comorbidity index.

avoided. Recent reports,[2,4,8] however, from clinical- and population-based analyses[3] have found no link between the frequency of perforation and misdiagnosis. Indeed, perforation is often a "prehospital" event that may be caused by a more aggressive infectious agent.[5,9] Another common justification for this rate of NA is that removal of a noninflamed appendix is considered a relatively benign intervention. Among surgeons, conventional wisdom suggests that if there is a question of appendicitis, appendectomy should be performed because the intervention may prevent perforation and because there will be little cost to the patient or to the system.[9,10] The purpose of this study was to address the nationwide frequency, clinical characteristics, outcomes, and economic burdens of NA.

RESULTS

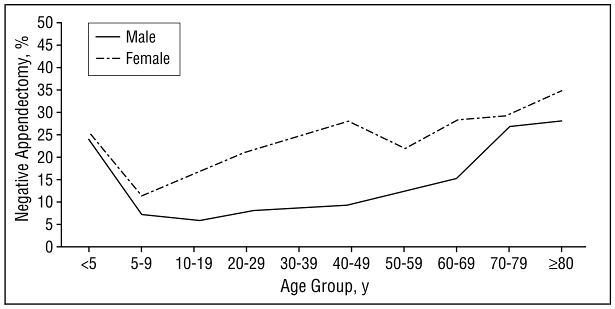
The Nationwide Inpatient Sample contained 52 969 patient discharge records consistent with NA. Based on the sampling weights, an estimated 261 134 such patient discharges occurred nationwide in 1997. The results that follow are estimates for the full survey population. Overall, 53.8% of patients were men with a mean age of 31.3 years (SD, 18.7 years) and a mean comorbidity index of 0.15. Negative appendectomy was performed in 39 901 (15.3%). Women had a higher rate of NA at all ages (**Table 1**) as did patients younger than 5 years and older than 60 years. The **Figure** depicts the rate of NA based on the age and sex of the patient. A bimodal age distribution was noted among males with highest rates of NA among those younger than 5 years and older than 80 years. Of all patients, the lowest rate of NA (6%) was found in males in the age group most commonly undergoing appendectomy (those between ages 10 and 19 years). Negative appendectomy occurred at a higher frequency among females of all ages, with a rate of 25% in those younger than 5 years, but increased with age essentially monotonically (a decrease in the 50- to 59-year-old age group was noted). Differences in the rate of NA by sex were statistically significant for all age groups except those younger than 5 years. Negative appendectomy occurred in 23.2% of women of reproductive ages, with the highest rates identified in women aged 40 to 49 years (28.2%) and those older than 80 years (35.2%). Patients undergoing NA had

Table 1. Patient and Hospital Demographics

Characteristics	No. Estimated (Actual)	Appendicitis, %	Not Appendicitis, %
All	261 134 (52 969)	84.7	15.3
Sex			
Male	140 092 (28 489)	90.7	9.3
Female*	121 033 (24 478)	77.8	22.2
Age group, y			
<5	3783 (803)	75.1	24.9
Male	2179 (465)	75.7	24.3
Female	1604 (338)	74.9	25.0
5-9	17 407 (3575)	91.2	8.9
Male	10 198 (2105)	92.7	7.3
Female	7205 (1469)	88.7	11.3
10-19	63 085 (12 806)	89.6	10.4
Male	36 504 (7430)	93.9	6.1
Female	26 576 (5375)	83.7	16.3
20-29	52 477 (10 677)	85.9	14.1
Male	27 821 (5699)	92.4	7.6
Female	24 656 (4978)	78.5	21.5
30-39	47 331 (9609)	83.6	16.4
Male	24 609 (4998)	91.5	8.5
Female	22 723 (4611)	74.8	25.2
40-49	32 392 (6533)	81.2	18.8
Male	16 188 (3256)	90.7	9.3
Female	16 203 (3277)	71.8	28.2
50-59	18 922 (3802)	83.1	16.9
Male	9505 (1910)	87.8	12.2
Female	9418 (1892)	78.1	21.9
60-69	13 109 (2632)	78.6	21.4
Male	6791 (1363)	84.7	15.3
Female	6318 (1269)	71.9	28.2
70-79	9104 (1828)	71.9	28.1
Male	4654 (935)	84.7	26.7
Female	4451 (893)	70.3	29.7
≥80	3495 (699)	67.9	32.1
Male	1677 (325)	73.3	28.3
Female	1868 (374)	64.8	35.2
Women of reproductive years (15-45 y)	71 623 (14 617)	76.8	23.2
Women not of reproductive years (15-45 y)*	48 319 (9 864)	79.3	20.7
Comorbidity index†			
0	234 798 (47 641)	86.7	13.3
1	16 963 (3303)	80.8	19.1
2	4591 (919)	53.9	46.0
3	4780 (959)	24.8	75.2
Race			
White	152 823 (31 041)	83.6	16.5
Nonwhite*	108 311 (21 928)	86.2	13.8
Insurance type			
Non-Medicaid	225 910 (45 760)	84.8	15.2
Medicaid*	35 222 (7209)	83.5	16.5
Hospital type			
Nonteaching hospital	181 824 (36 856)	85.3	14.7
Teaching hospital*	79 309 (16 113)	83.3	16.7
Not rural	210 988 (43 144)	84.7	15.4
Rural	50 144 (9825)	84.7	15.3
Not for profit	229 847 (46 291)	84.6	15.4
For profit	31 285 (6678)	84.8	15.2

*Statistically significant difference in rate of negative appendectomy when compared with the corresponding variable ($P<.05$). This applies to females of all age groups, unless otherwise indicated.

†Significant test of trend.



Nationwide rates of negative appendectomy, by age and sex of patient. Based on an estimated population of 261 134 patients undergoing appendectomy.

significantly higher comorbidity indexes than those undergoing appendectomy for appendicitis (0.45 vs 0.09, $P<.001$). The unadjusted rate of NA was slightly higher in white patients, patients whose primary or secondary payer was Medicaid, and those undergoing the procedure at teaching institutions. Patients treated at rural hospitals and those with "for profit" status did not have a higher rate of misdiagnosis.

The length of stay, total charges, case fatality, and infectious complication (wound infections and pelvic abscesses) rates are listed in **Table 2**. Negative appendectomy was associated with a significantly longer length of stay (5.8 vs 3.6 days, $P<.001$), total charge-admission ($18 825 vs $10 535, $P<.001$), case fatality rate (1.5% vs 0.2%, $P<.001$), and rate of infectious complications (2.5% vs 1.8%, $P<.001$). An estimated $741.5 million (95% confidence interval, $653 million-$830 million, expressed in 1997 US dollars) in total hospital charges were generated by hospital admissions in which NA was performed. Average charges, length of stay, case fatality, and the incidence of infectious complications were higher in the youngest and older patients, with extremely low rates of case fatality in the groups most commonly undergoing the procedure.

When considered in logistic regression analysis (**Table 3**), female sex was strongly associated with NA (odds ratio, 2.7; 95% confidence interval, 2.6-2.9). Additionally, advancing age, comorbidity index, teaching hospital status, and rural locations had significant positive associations with NA when controlling for other covariates. All adverse outcomes (prolonged length of stay, increased charge of admission, case fatality, and infectious complications) were more likely (**Table 4**) if a patient had undergone NA; however, for all adverse outcomes, these increases were considerably diminished when adjusting for sex, age, and comorbidity index.

COMMENT

While appendicitis is a common diagnosis, it is by no means a simple one to establish. There are few surgical procedures performed in which 15% to 25% of the time it is expected that the target organ will not be diseased. A component of the acceptance of this rate of NA is that removing the appendix from a patient without appendicitis is viewed as a benign error with limited clinical- or system-level costs.

This study defines the nationwide rate of NA, confirming many of the demographic findings identified in

Table 2. Adverse Outcome After Appendectomy, by Diagnosis and Demographics*

Patient Type	Length of Stay, Mean	Median Hospital Charges/Admission, $	Case Fatality	Infectious Complications
All appendicitis	3.6	10 584	0.21	1.78
All not appendicitis	5.8†	18 780†	1.59†	2.56†
Total	3.9	11 841	0.42	1.90
By age group, y				
<5				
Appendicitis	5.4	13 597	0.13	3.75
Not appendicitis	24.1†	81 387†	5.05†	1.89†
5-9				
Appendicitis	3.6	9286	0.01	2.34
Not appendicitis	3.1†	8932	0.23†	1.67
10-19				
Appendicitis	2.9	8481	0.01	1.30
Not appendicitis	3.1	9689	0.00	1.82
20-29				
Appendicitis	2.7	8863	0.01	1.25
Not appendicitis	3.3†	11 643†	0.16†	1.90†
30-39				
Appendicitis	3.2	10 237	0.03	1.67
Not appendicitis	4.1	13 006	0.21	2.72†
40-49				
Appendicitis	3.8	11 658	0.14	2.08
Not appendicitis	5.4†	16 703†	0.33	2.68
50-59				
Appendicitis	4.6	13 553	0.25	2.48
Not appendicitis	7.4†	23 039†	1.33†	3.29
60-69				
Appendicitis	5.9	16 608	0.74	3.20
Not appendicitis	9.5†	30 123	5.50†	2.60
70-79				
Appendicitis	6.9	19 255	1.73	2.79
Not appendicitis	11.5†	39 222	8.79†	5.73†
≥80				
Appendicitis	8.1	22 357	6.83	2.16
Not appendicitis	13.7†	43 278†	10.29	2.12
By sex				
Male: appendicitis	3.5	10 358	0.22	1.74
Male: not appendicitis	7.4†	25 138†	2.59†	2.53†
Female: appendicitis	3.6	10 885	0.19	1.83
Female: not appendicitis	5.4†	15 682†	1.11†	2.59†

*Data based on national estimates.
†Statistically significant difference in rate of negative appendectomy when compared with the corresponding variable ($P<.05$).

Table 3. Multivariate Regression Model of Variables Associated With Misdiagnosis*

	Misdiagnosis, Odds Ratio (95% Confidence Interval)
Female sex	2.7 (2.6-2.9)
Age group, y†	
0-4	3.0 (2.5-3.6)
5-9	0.9 (0.7-0.9)
10-19	1.0 (Reference)
20-29	1.3 (1.3-1.5)
30-39	1.6 (1.5-1.8)
40-49	1.6 (1.5-1.7)
50-59	1.2 (1.1-1.3)
60-69	1.3 (1.1-1.5)
70-79	1.7 (1.5-1.9)
≥80	1.9 (1.7-2.4)
Each unit of increase in comorbidity index	2.3 (2.2-2.4)
Procedure performed in teaching hospital	1.1 (1.1-1.3)
Procedure performed in rural location	1.2 (1.1-1.3)

*Each variable controlling for other variables.
†Odds of negative appendectomy for each age group compared with 10- to 19-year-old age group.

retrospective reviews.[2,4,5] Misdiagnosis resulting in NA occurred more commonly in the very young and very old, among women more than men, and in patients with higher levels of comorbid illnesses. As expected, women had a higher rate of NA at all ages, even when controlling for advanced comorbid illness. The highest rate of NA, however, was not among women in their third and fourth decades, as has been suggested by others,[4] but among women older than 70 years. Elderly patients undergoing appendectomy have not previously been thought to have such high rates of misdiagnosis.[12]

Patients undergoing NA have prolonged hospitalizations (5.8 days), increased infectious complications (2.5%), and higher rates of case fatality (1.5%) when compared with patients with appendicitis. The national cost of hospitalizations with NA (more than $740 million) is significant. Hospitalizations with NA had higher overall charges ($18 780) compared with $10 584 for hospitalizations during which appendicitis was diagnosed.

The finding that NA is associated with greater clinical and financial costs than appendectomy for correctly diagnosed appendicitis may not be causally related to the

Table 4. Multivariate Regression Model of Variables Associated With Adverse Outcome*

Variables	Prolonged LOS, OR (95% CI)†	Increased Hospital Charge, OR (95% CI)†	Case Fatality, OR (95% CI)	Infectious Complications, OR (95% CI)
Negative appendectomy (unadjusted)	1.3 (1.3-1.4)	1.4 (1.4-1.5)	6.5 (3.9-10.8)	1.4 (1.2-1.6)
Negative appendectomy (adjusted for age, sex, and comorbidity index)	1.0 (1.0-1.1)	1.1 (1.0-1.2)	3.1 (1.7-5.7)	1.2 (1.0-1.5)

*LOS indicates length of stay; OR, odds ratio; and CI, confidence interval. Excludes patients younger than 5 years and older than 65 years.
†Greater than mean LOS (3.9 days) and median hospital charge ($11 841).

NA but rather linked to the clinical and administrative sequelae of caring for patients with clinical conditions that are mistaken for appendicitis. For example, the increased length of stay associated with NA may be the result of additional testing and/or observation used to identify the source of the patient's symptoms. The increased charges linked to admissions with NA when compared with patients who had appendicitis may be the result of this increased length of stay. The higher rate of infectious complications found among patients with NA in this study may be the result of increased hospitalization time among patients with NA. The Health Care Utilization Project dataset captures in-hospital events only. Wound infections and pelvic abscesses are likely to be occurring at equal if not higher rates in patients who had appendicitis (a percentage of whom also had appendiceal perforation and are therefore at greater risk for infectious complications), but may be occurring in the outpatient environment and not captured in this dataset. Differences in the rates of in-hospital mortality are difficult to explain but are highest in the very young and very old, suggesting that the disease mistaken for appendicitis may be linked to higher mortality.

After controlling for age and comorbidity index, much of the increase in the odds of all adverse outcomes is reduced, suggesting that the contributing causes of the increase in these adverse events include not only the appendectomy itself, but other clinical factors, some of which may not be completely measured in this dataset. The odds of in-hospital death remain more than 3 times greater among patients who have undergone a NA after adjusting for measured patient factors. These increased odds of death may reflect the effects of the underlying disease process that is mistaken for appendicitis rather than a causal relationship of the operation itself. A priori, there is no reason to believe that NA is associated with greater morbidity and mortality than appendectomy for appendicitis. Indeed, a prior observational study examined complications of NA and found little difference when compared with appendectomy performed for appendicitis.

There are several limitations to this study. Most importantly, the use of administrative data to answer clinical questions is dependent on an accurate translation of clinical information into codes used for billing purposes. The first researchers to use administrative data to characterize NA and other components of appendicitis were Addiss et al.[1] Their results corresponded closely to data gathered in large clinical datasets[4,5] and have been used for a decade to describe the epidemiology of appendicitis. It should be noted, however, that in the study by Addiss et al[1] and in our study, there is an uncertain relationship between the administrative determination of NA and histopathologic data. Limitations of this sort are likely to occur equally among all demographic groups so that comparisons between groups may be reasonable. Additionally, because this dataset includes only in-hospital events, data about computed tomographic scan use and prehospital delay, which are important in understanding adverse outcomes in appendectomy, are not available. Also, administrative coding of pelvic abscess and wound infection has an unclear temporal relationship to appendectomy. Indeed, infectious complications described in this analysis may be diagnosed before an appendectomy is performed rather than following appendectomy. The eventual administrative record does not reflect such temporal relationships. If this were the case, however, a higher rate of infectious complications in patients with appendicitis would be expected, which was not demonstrated in this survey.

By demonstrating the clinical costs and system level charges associated with NA, this study emphasizes the importance of developing more effective diagnostic strategies in the management of presumed appendicitis. While advanced diagnostic testing may decrease NA in study environments,[6] it does not seem to have made an impact on the rate of NA on a population level[3] or in a recent retrospective review.[4] In clinical practice, the rate of equivocal tests[13] and delayed reporting[14] remains high and may render these tests less useful. One must conclude that either the diagnostic modalities currently available to improve the diagnosis of appendicitis are underused, or their benefit significantly overestimated. A

Codes

International Classification of Diseases, Ninth Revision, ICD-9 Codes

***ICD-9* Procedure Codes for Appendectomy**

47 Operations on appendix, excludes incidental
47.0 Appendectomy, excludes incidental
47.01 Laparoscopic appendectomy
47.09 Other appendectomy

***ICD-9* Diagnostic Codes for Appendicitis**

540 Acute appendicitis
540.0 With perforation, peritonitis, rupture
540.1 Abscess with generalized peritonitis
540.9 Without mention of perforation, peritonitis, rupture
541 Appendicitis unqualified
542 Other appendicitis

randomized trial should be considered to understand the practical benefits of advanced diagnostic testing in typical clinical practice. This information will help in developing the optimal diagnostic pathway for patients with presumed appendicitis.

In conclusion, NA is commonly performed in patients who do not have appendicitis. This high rate of unnecessary surgery is likely caused by limitations in our diagnostic abilities. Negative appendectomy is not a benign intervention, but rather has significant clinical and cost implications. These costs should be considered when evaluating system level interventions to improve the management of appendicitis.

Corresponding author and reprints: David R. Flum, MD, Department of Surgery, Robert Wood Johnson Clinical Scholars Program, University of Washington, H-220 Health Sciences Center, Box 357183, Seattle, WA 98195-7183 (e-mail: daveflum@u.washington.edu).

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Invited Critique

The mere act of the well-intended surgeon knowingly removing a normal appendix is of no immediate therapeutic benefit to the patient diagnosed as having appendicitis. This of course is always predicated on clinical and, more often than not, imaging information that suggest appendicitis.

A "negative appendectomy"—removal of an uninflamed appendix in a patient with a clinical diagnosis of appendicitis—results in an average length of hospital stay of 5.8 days, a charge of $18825, a fatality rate of 1.5%, and an infectious complications rate of 2.6%. If the surgeon removes an inflamed appendix in a patient with the same clinical diagnosis, the respective values are more favorable at 3.6 days, $10535, 0.2%, and 1.8%. The annual cost of a negative appendectomy to the health system is calculated to be $742 million.

Negative appendectomy, simply viewed by the statisticians, is an operation that has great untoward consequences, not least a fatality rate 7 to 8 times that of appendicitis. The course for the clinically naive to follow, so as not to incur the wrath of those among the bean counters who muse over the surgeon's outcome data, is to operate only when the diagnosis of appendicitis is irrefutable. A negative appendectomy rate close to zero, hinted at as desirable in the article by Flum and Koepsell, is a quality assurance dream! Following this clinical pathway would increase the observation time and length of hospital stay, the number of imaging studies taken, and perhaps the percentage of patients with ruptured appendix, along with a higher mortality rate—not to mention the resultant further-increased financial burden to the health care system. The ire of the keepers of the purse strings would surely descend on such a wayward surgeon.

Whom should the surgeon then please? Silly—the patient, of course! What a novel concept today.

A negative appendectomy in an otherwise "well" patient has a lower infection rate than appendectomy for appendicitis. The infection rates for the various classes of bowel operations are well established. The mortality of an otherwise healthy patient undergoing a negative appendectomy relates to the infectious complications. It is the disease that mimicked appendicitis, or comorbid ills extant at appendectomy, that explain the increased mortality in patients with a negative appendectomy—an observation that was more striking in patients with a negative appendectomy who were younger than 5 years and older than 60 years. Do not let this, a quirk of statistics, be attributed to removal of the bystander appendix and enshrined in surgical dogma.

At first glance the article by Flum and Koepsell suggests to the reader that a negative appendectomy is the genesis of much expense and fatal ills. One wonders if the normal appendix should always be left unsullied in patients undergoing surgery for appendicitis. Certainly this is more likely to be the case if the operation is performed laparoscopically. If this were to become the practice in *laparatomie blanche* for appendicitis, the data on it gleaned from statistics dredging would remain almost the same as for negative appendectomy.

So, please don't blame the normal appendix, knave of the intestine, for the increased cost and mortality of a negative appendectomy. There is good reason to banish the hapless knave, not least to avoid the same conundrum at the patient's next presentation with appendicitis.

Russell A. Williams, MD
Orange, Calif