Association of Viral Infection and Appendicitis

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Hypothesis: What causes appendicitis is not known; however, studies have suggested a relationship between viral diseases and appendicitis. Building on evidence of cyclic patterns of appendicitis with apparent outbreaks consistent with an infectious etiology, we hypothesized that there is a relationship between population rates of appendicitis and several infectious diseases.

Design: Epidemiologic study.

Setting: The National Hospital Discharge Survey

Patients: Estimated US hospitalized population.

Main Outcome Measures: International Classification of Diseases, Ninth Revision, Clinical Modification discharge diagnosis codes of the National Hospital Discharge Survey were queried from 1970 to 2006 to identify admissions for appendicitis, influenza, rotavirus, and enteric infections. Cointegration analysis of time series data was used to determine if the disease incidence trends for these various disease entities varied over time together.

Results: Rates of influenza and nonperforating appendicitis declined progressively from the late 1970s to 1995 and rose thereafter, but influenza rates exhibited more distinct seasonal variation than appendicitis rates. Rotavirus infection showed no association with the incidence of nonperforating appendicitis. Perforating appendicitis showed a dissimilar trend to both nonperforating appendicitis and viral infection. Hospital admissions for enteric infections substantially increased over the years but were not related to appendicitis cases.

Conclusions: Neither influenza nor rotavirus are likely proximate causes of appendicitis given the lack of a seasonal relationship between these disease entities. However, because of significant cointegration between the annual incidence rates of influenza and nonperforated appendicitis, it is possible that these diseases share common etiologic determinates, pathogenetic mechanisms, or environmental factors that similarly affect their incidence.

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See Invited Critique at end of article

APPENDECTOMY IS THE MOST common emergency general surgical procedure with more than 250,000 operations performed annually in the United States.1 Despite its ubiquitous nature, why appendicitis occurs remains unknown. Several theories exist attempting to explain this disease's cause. At the heart of most appendicitis theories is luminal obstruction. The appendix becomes obstructed either by a fecalith or enlarged lymphoid tissues resulting in high luminal pressures that compromise mucosal integrity leading to infection. Infections are thought to cause appendicitis2 by stimulating lymphoid hyperplasia, which obstructs the appendix. Many viral disorders are associated with lymph node enlargement, which, in turn, can obstruct the appendiceal lumen. Viral infections could cause mucosal ulcerations that could result in subsequent bacterial infection of the appendix.3,4 Appendicitis has been associated with a viral prodrome compatible with a viral illness preceding the first symptoms of appendicitis. Early epidemiologic investigations found that appendicitis was more frequent during months when respiratory infections were present.5

Several epidemiologic patterns suggest a link between appendicitis and infections. Appendicitis outbreaks have been described. In 1 small Texas town, a significant cluster of cases was described over a very short period, suggesting an infectious etiology.6 Larger-scale investigations from Sweden revealed that the disease has a propensity to cluster in time and location.7 A 35-year epidemiologic investigation from our group uncovered apparent appendicitis outbreaks in the United States.8
To develop further evidence possibly linking specific infectious etiologies with appendicitis, we analyzed a national sample of hospital discharge data for associations between rates of appendicitis and certain candidate infectious diseases including influenza, rotavirus, and other intestinal infections.

**METHODS**

The annual National Hospital Discharge Survey (NHDS) databases for 1970 to 2006 were acquired from the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/nchs/nhds.htm) and the Inter-University Consortium for Political and Social Research (http://www.icpsr.umich.edu/icpsrweb/ICPSR) Web sites. The NHDS is the principal database used by the US government for monitoring hospital use. Each year, approximately 300,000 hospital discharges are selected for the NHDS from the 35 million total discharges nationally. The NHDS uses a complex multistage design to ensure that the database is representative of the US hospitalized population. Using US census information, the CDC provides statistical weighting factors for each patient entry in the NHDS database so that incidence and prevalence estimates of hospitalized disease can be made for the entire US population. These weighting factors were used to determine the national prevalence of appendicitis. The estimated US population for each year of the study was obtained from the US Census Bureau as accessed through the CDC Web site (http://wonder.cdc.gov/population.html). Disease incidence per geographic region was determined in regions as defined in the NHDS.

The NHDS converted from International Classification of Diseases Adapted for Use in the United States, Eighth Revision (ICDA-8) encoding to International Classification of Diseases, Ninth Revision (ICD-9) in 1979. Before 1979, codes for the various forms of appendicitis diagnoses were the same in the ICDA-8 system as in the ICD-9. The same was true for enteric infections. For cases in the database occurring from 1970 through 1978, procedures were identified as drainage of appendiceal abscess (code 410), appendectomy (code 411), appendicostomy (code 412), closure of appendiceal fistula (code 413), and other appendectomy (code 419). Hospital admissions for influenza were identified by diagnostic codes ranging from 470 to 474. Abdominal pain was encoded with 785.5.

Beginning in 1979, the ICD-9 coding system was implemented. Appendicitis was defined as a patient having any of the following 7 NHDS discharge diagnostic codes: 540.9 (acute appendicitis), 541.0 (appendicitis-unqualified), 542.0 (other appendicitis), 543.0 (other diseases of the appendix), and 543.0 (unspecified disease of the appendix). Perforated appendicitis

Figure 1. Monthly hospital admission rates for perforated and nonperforated appendicitis and influenza from 1970 to 2006. Data are presented as the number of hospital admissions per month per 10,000 US population. The left axis represents the scale for influenza rates and the right scale, for appendicitis. Influenza occurs almost exclusively in the winter months, whereas appendicitis is present throughout the year.
(code 540.0) or appendiceal abscess (code 540.1) were aggregated into a single category called “perforated appendicitis.” Nonperforated appendicitis was defined as having any appendicitis diagnostic code except for 540.0 or 540.1. Procedures codes used were appendectomy (47.0), laparoscopic appendectomy (47.01), other appendectomy (47.09), incidental appendectomy (47.1), laparoscopic incidental appendectomy (47.11), other incidental appendectomy (47.19), drainage of appendiceal abscess (47.2), “other” appendiceal operation (47.9), appendicostomy (47.91), closure of an appendiceal fistula (47.92), and other appendiceal operation (47.99). Incidental appendectomies were identified if there were any of the following 3 procedure codes: 47.1, 47.11, or 47.19. Nonincidental appendectomies were defined as having any appendectomy procedure codes excluding those for incidental procedures. A negative appendectomy was defined as having any procedure code of 47.0, 47.01, or 47.09 without any diagnostic coding for appendicitis.

A diagnosis of any type of intestinal infectious disease was established if the diagnostic codes ranged from 008.00 to 008.89. Of these, a subset of intestinal viral diseases (ICD-9 code 008.6X) was assessed in greater detail. Only rotavirus (code 008.61) had sufficient numbers of admissions to be analyzed. A specific rotavirus ICD-9 Clinical Modification diagnostic code was introduced in 1993. There were too few cases to assess on a monthly basis. For that reason, rotavirus admissions were aggregated into 3-month quarters. All other data were analyzed by monthly or annual aggregations of the disease incidences.

To determine if inpatient influenza rates approximated those of the outpatient disease, we examined 7 years of CDC survey data of outpatient influenza. Outpatient influenza is tracked by establishing the proportion of all outpatient visits that are caused by influenza (http://www.cdc.gov/flu/weekly/weeklyarchives2006-2007/data/ILI0607.htm). These proportions were found to correlate to annual inpatient admission rates for 2000 to 2007 (p = 0.59).

Disease incidence estimates can be affected by coding changes. When a major change in disease classification occurs, disease entities may be grouped differently, they may have new names or definitions that cause diseases to be classified in other sections of the coding schema than before, or the definitions for a disease may change resulting in its classification into new areas. When this occurs, plotting of the disease incidence over time will have discontinuities at the years in which the coding change was implemented. If the discontinuity is obvious and the trends on either side of the break are reasonably linear, then correction factors can be determined. Correction factors are calculated by dividing the disease incidence ratio for the years before the new code introduction by that for the years after the new codes were used. The resultant ratio is known as the comparability ratio. The ICD system is assessed for this phenomenon with each major update and comparability ratios published. Of the disease entities we studied, only intestinal infections had a significant discontinuity when ICDA-8 was converted to ICD-9 in 1979. We applied a correction factor of 5.49 to the pre-1978 data for intestinal infections, removing the observed 1978 to 1979/ICDA-8 to ICD-9 coding change–induced disease incidence discontinuity.9,11

Similarity in the long-term trending or wandering behavior of 2 disease rates was tested using the technique of cointegration analysis,12 which has been widely used in econometric time series analysis. The analysis was based on an autoregressive modeling of the disease rate time series. In this setting, 2 disease rates were considered to be cointegrated (varying together over time) if each rate was unit-root nonstationary and the processes showed significant indication that they were “tethered together” over time as measured by cointegration analysis. We tested the null hypothesis that the time series had a unit root and, therefore, was nonstationary using the augmented Dickey-Fuller test.13,14 Rejecting the null hypothesis (P ≤ .05) supports stationarity, whereas failing to reject the null hypothesis (P > .05) supports unit-root nonstationarity. Based on the evidence of a unit root, the next step was to test for a cointegrating relationship between nonperforated appendicitis and influenza, both nationally and regionally. We considered panel cointegration tests designed to increase the power of detecting cointegration when cross-section data (ie, regional data in our case) are available. Panel cointegration tests proposed by Pedroni15,16 and by Maddala and Wu17 were also applied. All time series computations in this article were done using the econometrics software package EVIEWS 6 (1997-2007; Quantitative Micro Software, LLC, Irvine, California).

RESULTS

Both nonperforating appendicitis and influenza declined in overall incidence until 1995. After that, the overall incidence of both diseases has been increasing (Figure 1). This U-shaped curve was not observed for perforating appendicitis, which exhibited a slowly rising incidence over the years. Influenza exhibited a sharp increase in incidence in the winter months, with the disease rarely observed during the remaining months of the year (Figure 2). Appendicitis occurred throughout the year, with a slight tendency to occur more frequently in the summer months. Intestinal infections also were observed throughout the year but had a propensity to occur in the winter months. Influenza admissions occurred mostly between December and February and rarely occurred at other times of the year.

Although the strong winter presence of influenza was not observed with appendicitis, the overall annual incidences for these diseases appear to wander in time together (Figure 3). The results of unit root tests for the national and regional data are shown in Table 1 and Table 2 where the national data on nonperforated appendicitis and influenza as well as the regional data on both disease rates show evidence of a unit root since the null hypothesis of a unit root is not rejected in any of the cases. Because of the small sample size of our overall analysis (ie, 36 data points, 1 representing each year’s disease incidence), we also examined the consistency of the appendicitis-influenza disease incidence relationship in the 4 major US regions. In Figure 4, we show normalized overlays of the incidence rates for nonperforated appendicitis and influenza for the 4 regions. From Table 1, the augmented Dickey-Fuller test shows evidence of a unit root for both disease incidence rates in each region. Table 2 shows that both the trace and maximum eigenvalue tests indicate cointegration between nonperforated appendicitis and influenza both nationally and regionally except for the West. When these analyses were repeated by only including influenza admissions for patients older than 40 years and appendicitis admissions for those younger than 20 years, all regions of the country demonstrated statistically significant cointegration. Panel cointegration tests proposed by Pedroni15,16 and by Maddala and Wu17 were also applied, and the results (data not shown) were consistent with those previously obtained in the region-by-region analysis using the Johansen tests. That is,
the panel results, like these Johansen test results, were supportive of cointegration in all the major regions of the United States.

Figure 5 shows the relationship between appendicitis and intestinal rotavirus infection. International Classification of Diseases–specific codes for rotavirus were only available after 1993. Because of the relatively low rotavirus incidence, data were aggregated into quarters rather than months. Rotavirus infection peaked in the winter months, but there was no obvious correlation between

Figure 2. Histograms of the monthly incidence rates of nonperforated and perforated appendicitis, intestinal infection, and influenza. There is a weak tendency for appendicitis to be more common in the summer months, intestinal infections are more common in the winter, and influenza is clearly a winter disease. Data are presented as the average for any given month in all the years between 1970 and 2006. Error bars are too small to be seen because of the very large sample sizes.

Figure 3. Cointegration analysis of appendicitis and influenza rates. A, Both the nonperforated and influenza rates are nonstationary over time. B, The residual rate (annual nonperforated appendicitis rate − 0.788 × the annual influenza rate) as determined by applying ordinary least squares to the cointegrating equation \( app = a + b \times flu + \text{residual} \). This provides the consistent estimates of \( a=6.27 \) and \( b=0.788 \).
What causes appendicitis remains a mystery. Our previous analysis of appendicitis time trends demonstrated that the increasing appendicitis rates observed after 1995 paralleled the rise, and could possibly be related to, increased use of computed tomographic scanning and laparoscopic surgery. However, the year-to-year variation in the nonperforating appendicitis incidence and apparent disease outbreaks suggested that appendicitis is caused by an infectious agent. The current study was performed to further investigate this possibility. We did find that there were epidemiologic similarities between the rates of nonperforating appendicitis and influenza. The annual incidence rates for both diseases progressively fell thereafter both began to rise in parallel. Moreover, time series analysis demonstrated statistically significant cointegration of the wanderings of the annual incidence rates of the 2 diseases. Appendicitis shared no common pattern with intestinal infections or with documented rotavirus infections. These findings suggest that nonperforating appendicitis may be caused by an infectious agent or other process related to influenza virus infection; however, since influenza has a winter peak that is not observed with nonperforating appendicitis, it is unlikely to be a proximate cause. These findings also suggest that our previously observed parallel rise in nonperforating appendicitis after 1995 and in use of laparoscopic appendectomy and/or computed tomographic scanning might be coincidental and not causative.

Further evidence for the likelihood that appendicitis is caused by an infectious disease is the observation that the disease occurs in clusters. Several well-defined disease outbreaks have been identified in addition to our previously described pattern of disease outbreaks. Seasonal changes in appendicitis have also been described; however, we found that although there was a tendency for appendicitis to be more common in the summer months, the seasonal variation was modest, consistent with previous reports. The incidence of perforated appendicitis did not correlate with nonperforating appendicitis or with the other infectious diseases we evaluated, suggesting that perforated appendicitis has causative factors that are more complex than the simple delay in treating acute appendicitis. This has important clinical ramifications since appendectomy is generally performed as an emergency

| National | Appendicitis | -1.8046 | 4 | .37 |
| National | Flu | -1.2019 | 1 | .66 |
| Northeast | Appendicitis | -2.0762 | 1 | .26 |
| Northeast | Flu | -1.6286 | 3 | .46 |
| Midwest | Appendicitis | -1.7036 | 0 | .42 |
| Midwest | Flu | -1.4457 | 2 | .55 |
| South | Appendicitis | -1.6029 | 1 | .47 |
| South | Flu | -1.1253 | 1 | .70 |
| West | Appendicitis | -1.6793 | 2 | .43 |
| West | Flu | -1.5598 | 1 | .49 |

Table 1. Augmented Dickey-Fuller Test Statistic, ADF*, With the Lag Order of the Dickey-Fuller Test Equation and 1-Sided P Values Taken From MacKinnon19, a

| National | Appendicitis | -1.6377 | 0 | .42 |
| National | Flu | -1.4457 | 2 | .55 |
| Northeast | Appendicitis | -2.0762 | 1 | .26 |
| Northeast | Flu | -1.6286 | 3 | .46 |
| Midwest | Appendicitis | -1.7036 | 0 | .42 |
| Midwest | Flu | -1.4457 | 2 | .55 |
| South | Appendicitis | -1.6029 | 1 | .47 |
| South | Flu | -1.1253 | 1 | .70 |
| West | Appendicitis | -1.6793 | 2 | .43 |
| West | Flu | -1.5598 | 1 | .49 |

Table 2. Johansen Multiple Equation Tests for Cointegration a

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operation for fear of causing a perforation if treatment is delayed. Our epidemiologic findings suggest that patients who have perforated appendicitis have a different disease entity than those with nonperforating disease.

Intestinal infections have been increasing with time. In 1989, there was a marked upsurge in their annual peak incidence. These findings appear to contradict a theory explaining changes in the incidence of appendicitis called the hygiene hypothesis. The rising appendicitis rate observed in the early 20th century paralleled an improvement in living conditions with fewer intestinal infections. This observation led to the hygiene hypothesis wherein it was posited that better hygiene caused less exposure to infectious agents, reducing the immune system's ability to prevent appendicitis. Up to 1995, our findings were consistent with this hypothesis since increasing numbers of persons with intestinal infection could result in enhanced immunity to other gastrointestinal infections such as appendicitis. That both intestinal infections and nonperforating appendicitis appear to have increased in incidence for the past decade mitigates against the hygiene hypothesis.

Our observation that intestinal infections are on the rise is interesting. One could hypothesize that increased use of potent antibiotics has changed the intestinal flora or that increased use of potent inhibitors of gastric acid secretion has reduced the pH barrier to intestinal infection. The intestinal infections resulting in hospitalization might be due to resistant strains of bacteria or from increased susceptibility to unidentified organisms that have become more pathogenic.

Viral illness has been implicated by some researchers as the cause for appendicitis. Viral infection of the appendix could cause mucosal ulceration followed by secondary bacterial infection of the appendix. Alternatively, viral disease could result in lymphoid hyperplasia of the appendix with resultant obstruction and mucosal injury followed by bacterial infection. Several viral agents have been hypothesized to cause appendicitis. Coxsackievirus has been associated with cecal inflammation and periappendiceal lymphoid hyperplasia. Animal studies have shown that coxsackievirus infection can result in an appendicitis-like syndrome. Lymph nodes and sera obtained from patients with appendicitis have shown evidence for simultaneous adenovirus infection. Measles virus and cytomegalovirus have also been associated with appendicitis. Bacterial infection with pathogens, such as Yersinia enterocolitica, has been implicated.
Figure 5. Quarterly rates of appendicitis and rotavirus infection. Data are reported in terms of the number of hospital admissions per 3-month quarter per 10,000 US population. No correlation was observed between rotavirus infections and appendicitis rates.

Figure 6. Monthly rates of intestinal infections. Intestinal infections have been increasing in frequency over the years with substantial increases in peak incidence occurring after 1989.
in appendicitis pathogenesis. One viral illness that we could investigate was rotavirus since the NHDS database had sufficient numbers of these cases, allowing for a comparison between rotavirus and appendicitis admissions. We found no correlation for these disease entities, suggesting that rotavirus is not a cause of appendicitis.

Most theories regarding the underlying causes of appendicitis rely on the notion that the appendix becomes obstructed. This line of thinking dates back to Reginald Fitz’s first description of appendicitis wherein he had observed fecaliths on autopsies and assumed that they contributed to the pathogenesis of this disease. Animal studies have shown that artificially elevated appendiceal luminal pressure can result in appendicitis. Although an attractive hypothesis, experimental evidence suggests that the role of fecaliths as a cause for appendicitis is limited. Intraoperative intraluminal pressure measurements revealed that pressures were normal in acute appendicitis and only became elevated in late-stage disease, suggesting that obstruction occurs as inflammation progresses. Although fecaliths can be seen in appendicitis specimens, they only occur rarely. Factors more complex than simple obstruction must contribute to appendicitis pathogenesis.

In conclusion, although influenza and nonperforating appendicitis have dissimilar seasonal peak incidences, parallel year-to-year peak incidence trends suggest a viral etiology for appendicitis. No association was found between the intestinal infections, rotavirus, and appendicitis. Further work more precisely identifying infectious agents in cases of appendicitis is necessary to identify potential causative agents.

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Dr Alder and colleagues have attempted to clarify the causative agents for appendicitis by analyzing the NHDS for associations between rates of appendicitis and several infectious diseases. They concluded there was no association between intestinal infections and rotavirus with appendicitis but did see a parallel year-to-year peak incidence with nonperforated appendicitis and influenza.

While this is an interesting concept, it does not appear to implicate influenza virus as a causative agent for appendicitis. Certainly concerning is that the peak of influenza is in the winter months, which is not replicated in appendicitis. Also, appendicitis is more often a disease of the young and influenza a disease of the older population, which goes against influenza as a proximate agent. Additionally, the study relies on hospital discharge data, which are likely much more complete for appendicitis as this is a disease necessitating hospitalization. The vast majority of patients with a viral illness are not hospitalized, and many likely do not even seek medical attention. Certainly this makes comparison onerous.

What is perhaps most significant in this analysis is that the rates of perforated and nonperforated appendicitis show no similarity in pattern, implying that they are perhaps separate entities. Certainly this goes against the thought that perforated appendicitis is the result of delaying definitive treatment. Further investigation of this concept is definitely warranted, as it could have a significant impact on management.

The causative agent for appendicitis remains unknown and is likely multifactorial. With the majority of viral illnesses treated without hospitalization or even a visit to the physician, identifying the viral agent responsible will remain elusive. While perhaps influenza plays a role in the development of appendicitis by sensitizing the immune system to another viral agent, there remains no clear evidence that it is a causative agent for appendicitis.

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