Outpatient Antibiotic Use and the Incidence of Acute Appendicitis in Finland: A Nationwide Study from 1990–2008

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Abstract

Background: The incidence of acute appendicitis (AA) has decreased in Finland. We hypothesized that changing trends in outpatient antibiotic use might explain at least part of this declining incidence of AA.

Methods: The number of all patients with AA in Finland was extracted from the national data base from 1990 to 2008. For comparison, the incidence of acute diverticulitis of the colon (AD) was also recorded. All outpatient prescriptions of antibiotics belonging to the major groups of these drugs were also recorded. We used unit root and co-integration analyses for statistical analysis of the data in the study.

Results: The incidence of AA in Finland declined from 14.5 to 9.8 per 10,000 inhabitants (32%) and the incidence of AD increased by 47% between 1993 and 2007. The total outpatient use of antibiotics did not increase during this same period, but the use of antibiotics effective widely against colonic pathogens (macrolides, fluoroquinolones, and cephalosporins) increased significantly. No correlation was found between the incidence of AA, that of AD, and the use of different groups of antibiotics.

Conclusions: Our nationwide registry study indicated that changes in outpatient antibiotic use do not explain the decreasing trend in AA in Finland. Other factors, such as improved diagnosis of AA, may have some role in the decreasing incidence of AA.

BOTH ACUTE APPENDICITIS (AA) and acute diverticulitis (AD) are common infectious diseases of the colon [1,2]. The incidence of AA has decreased in Western society, but the incidence of AD has increased by contrast in many countries [3–7]. The reason for the declining trend in AA is partly unknown [4]. Changes in diet, increasing obesity, and the Western style of living may explain partly the increasing incidence of AD [6,7]. Acute appendicitis and AD share some epidemiologic similarities and may represent differing manifestations of the same underlying pathophysiologic process [8]. Non-perforated appendicitis is primarily a disease of young adults, and non-perforated diverticulitis affects older patients mainly. Despite differences in their frequencies, little is known about the pathogenesis of these diseases. There is even a lack of evidence-based studies to confirm the types of colonic bacteria that play a central role in the pathogenesis of AA.

Acute appendicitis has for years been one of the diseases diagnosed most commonly in surgical emergency units, and its treatment has mainly been surgical [9]. Aerobic infection is common in early appendicitis, but mixed aerobic and anaerobic infection is predominant in late cases of the disease [10]. It seems that in most cases, uncomplicated appendicitis may resolve with antibiotic treatment alone, although its non-surgical treatment has not been adopted as an accepted, evidence-based practice [11–13]. In contrast to that for AA, the primary treatment for AD is mainly non-operative in uncomplicated cases [14]. The clinical appearance of AA is sometimes not straightforward, and in some cases AA mimicking another infection may be treated with antibiotics rather than surgery [15]. For example, symptoms of AD or gynecologic infection may be similar to those of AA and their treatment may be with antibiotics alone. During the past 10 years,

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the pre-operative diagnosis of AA has been made more reliable by improved computed tomographic (CT) imaging [16]. In a previous study, we noticed a 32% decrease in the incidence of AA during a 21-year period in Finland [4]. The decreasing incidence of AA in most Western countries is difficult to explain. One reason for it may be the increased use of CT in the diagnosis of AA [16], but another may be the widespread outpatient use of antibiotics. Among various explanations for the declining incidence of AA may be the treatment with antibiotics of patients with mild lower abdominal pain who are never referred to surgery. It is also possible that increased overall use of antibiotics may change the microflora of the gut and consequently affect the pathophysiology of AA. To test this hypothesis, we investigated whether changes in outpatient antibiotic use could explain partly the decreased incidence of AA in Finland. As a reference, we also investigated the changes during the same time in the incidence of AD as another common infection of the colon.

Patients and Methods

Data on the discharge diagnoses of AA and AD for all of Finland were gathered from the National Institute for Health and Welfare (NIHW) registry, a research and development institute of the Finnish Ministry of Social Affairs and Health. Diagnoses were classified according to the World Health Organization (WHO) International Classification of Diseases versions 9 and 10 (ICD-9 and ICD-10). The use of ICD-10 in Finland began in 1996. The diagnostic accuracy of the ICD data was calculated as the proportion of cases of appendicitis to the total number of appendectomies performed. Our previous article [4] provides a detailed analysis of the collection of the data and calculation of the results for AA. Population data from 1990 to 2007 were retrieved from the Official Statistics of Finland. Data on the outpatient use of antibiotics from 1990 to 2008 were collected through the Finnish Medicines Agency (FMA). We obtained data for the use of oral outpatient antibiotics grouped according to the drugs' active constituents from the anatomic therapeutic chemical (ATC) classification with defined daily dose (DDD) measurement units (WHO, version 2003) [17]. To study more specifically the relationship of antibiotic use to the incidence of AA, we also

conducted a sub-analysis for geographic areas with high incidences of AA (Oulu University Hospital; North Finland) and low incidences of AA (Tampere University Hospital; South Finland) for the years 2005–2007. To compare the results of this with those for AD, we obtained data on the discharge diagnoses of colonic AD (uncomplicated) from the NIHW registry (ICD-9: 562.11 and ICD-10: K57.3).

Statistical methods

Co-integration of time series of the diseases investigated in the study (diverticulitis and appendicitis) and of antibiotic use were tested with the procedure described by Livingston et al. [8]. According to this, two non-stationary time series are co-integrated if there is a linear combination of the rates of the two series that is stationary over time. Non-stationarity of time series was tested with the augmented Dickey–Fuller (ADF) test, using the lag order that minimizes the Akaike information criterion. The Phillips–Ouliaris test was used for testing co-integration. The analysis was done with R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

The incidence of AA and appendectomies in Finland decreased by more than 30% between 1993 and 2007, and the corresponding incidence of AD increased by more than 40% (Fig. 1). The incidences of AA and appendectomy (AE) had linear-like downward trends, whereas the incidence of AD had a respective upward trend. Correlation of the incidences of AA and AD was strongly negative ($r = -0.938$, $p < 0.001$), that of the incidences of AA and AE was strongly positive ($r = 0.991$, $p < 0.001$), and that of the incidences of AD and AE was strongly negative ($r = -0.908$, $p < 0.001$). The means ($\pm$ SD) of the incidences of AA and AD during the study period were 12.3 ± 1.7 cases/10,000 inhabitants/year and 6.2 ± 1.4 cases/10,000 inhabitants/year ($p < 0.001$), respectively.

The figures for the incidences of AA, AD, and appendectomy, as well as for the accuracy of diagnosis of AA, are presented in Table 1. The incidence of AA declined from 14.6

FIG. 1. Antibacterial agents prescribed for systemic use, trends in antibiotic use, and incidences of acute appendicitis and acute diverticulitis in Finland from 1990 to 2007.

TABLE 1. INCIDENCES OF ACUTE APPENDICITIS, ACUTE DIVERTICULITIS, AND APPENDECTOMY, AND DIAGNOSTIC ACCURACY FOR ACUTE APPENDICITIS

Year	Acute appendicitis (/10,000/year)	Acute diverticulitis (/10,000/year)	Appendectomy (/10,000/year)	Diagnostic accuracy for acute appendicitis (%)
1993	14.6	3.5	19.1	76.8
1994	15.1	3.9	19.8	76.5
1995	14.8	4.2	19.0	77.9
1996	13.2	5.9	17.8	74.3
1997	13.2	5.8	17.5	75.4
1998	12.9	6.0	17.0	75.6
1999	12.7	6.1	16.4	77.5
2000	11.9	6.4	15.4	77.4
2001	12.2	7.1	16.0	76.2
2002	11.1	7.1	14.6	76.0
2003	11.2	7.1	14.3	78.2
2004	11.1	7.8	14.0	79.4
2005	10.7	7.4	13.1	81.1
2006	10.3	7.3	12.6	81.7
2007	9.8	7.4	12.0	81.7

to 9.8 per 10,000 persons (32%) and the incidence of AD increased from 3.5 to 7.4 per 10,000 inhabitants (47%) over the 15-year study period. The accuracy of diagnosis of AA increased from 77% to 82% (Table 1).

Total outpatient antibiotic use during the study period of 1990–2007 showed a slowly declining trend in Finland, varying from a defined daily dose (DDD) per 1,000 inhabitants per day of 19 in 1995 to a DDD per 1,000 inhabitants per day of 15 in 2004, respectively, with a mean value of 17 (Fig. 1). The incidence curves for AA and AD, were correlated positively and negatively, respectively, with the use of antibiotics. The trends in the outpatient use of various antibiotics in Finland from 1990 to 2008 are shown in Figure 2. Penicillins (J01C) and tetracyclines (J01A) were the two main groups of antibiotics prescribed for outpatient use in Finland during this period. The group of beta-lactam antibiotics other than penicillin (J01D) made up more than three-quarters of all outpatient antibiotics used. All but the J01D (other beta-lactams), J01F (macrolides), and J01M (fluoroquinolones) groups showed a declining trend during the 18-year monitoring period. The reduced consumption of antibiotics was more pro-

nounced for the J01A (tetracyclines) and J01E (sulfonamides, trimethoprim) groups than for other groups. The overall consumption of antibiotics in the J01E, J01F (macrolides, lincosamides, and streptogramins), and J01M groups remained at less than 4 DDD/1,000 inhabitants/day (Fig. 2). A statistically significant increase was noted only in the J01F (macrolides, $p < 0.039$, 1.7 to 1.9 DDD/10,000 inhabitants) and J01M (fluoroquinolones, $p < 0.001$, 0.6 to 1.3 DDD/10,000 inhabitants). According to the ADF test, the time series of both diverticulitis and the J01C, J01E, and J01M groups of antibiotics turned out to be non-stationary ($p > 0.3$ for each time series). In any case, the time series of appendicitis and diverticulitis seemed not to be co-integrated with those of the antibiotics examined ($p > 0.15$ for each co-integration). To investigate whether areas of Finland with different incidences of AA also had different trends in outpatient antibiotic use, we compared the Oulu and Tampere university hospital districts from 2005 to 2007. The incidence of AA was higher in Oulu (11 vs. 9 events/10,000 inhabitants/year). The respective usages of antibiotics in groups J01D, J01F, and J01M in Oulu and Tampere were 2.9 versus 2.8, 1.7 versus 1.5, and 1.0 versus 1.2

FIG. 2. Consumption of antibiotics in Finland from 1990 to 2007 in defined daily dose per 1,000 inhabitants/day.

DDD/10,000 inhabitants/day. The use of quinolones was greater in Tampere, whereas that of macrolides and other beta-lactam drugs than penicillin was greater in Oulu. We did not find any correlation of geographical differences in the incidence of AA with antibiotic use.

Discussion

Both appendicitis and diverticulitis are common diseases of the colon. They are responsible for numerous admissions to hospitals in the United States and Europe. In 2007, there were 320,000 hospital discharges for colonic diverticular disease and 295,000 discharges for AA, with the two diseases costing more than \$8.9 billion and \$7.4 billion, respectively, in hospital charges in the United States [8,18]. Our nationwide study in Finland indicates that the incidence of AA in that country is decreasing, but the increased use of outpatient antibiotics does not explain this decrease. Surprisingly, overall prescriptions of antibiotics showed a decreasing trend in Finland during the period of our study. It is possible that some patients with AA can be treated non-operatively with antibiotics and without the need for surgical intervention [12]. The incidence of AD in Finland has increased in the past several decades. The clinical pictures of AA and AD may in some cases be similar, which may also explain the decrease in emergency appendectomies for both diseases [19].

A decrease in non-perforated appendicitis and the recent decrease in appendectomies in Finland might also be due to more frequent use of CT imaging. For the past decade, abdominal CT has been able to establish the diagnosis of AA with better than 90% sensitivity and specificity [20–22], and laparoscopic appendectomy, which carries a low morbidity, further increases the diagnostic accuracy for AA [23,24]. These two respective imaging and therapeutic modalities might reduce the frequency of unnecessary appendectomy and therefore the incidence of AA. Computed tomography is also the imaging modality used most commonly for the diagnosis of sigmoid diverticulitis. In this respect, CT has replaced barium and gastrografin enemas in the routine evaluation of the sigmoid colon [14–16], and can also help establish a differential diagnosis with regard to other conditions that might produce similar symptoms, such as gynecologic or urinary tract infections. Further efforts should be directed at identifying pre-operative characteristics associated with non-perforated appendicitis that may eventually allow surgeons to defer surgery for those cases of the latter disease in which the risk of perforation is low.

The age-adjusted hospitalization rate for diverticulitis in Finland increased from 61.8 per 100,000 inhabitants in 1998 to 75.5 (22%) per 100,000 inhabitants in 2005, and increased similarly in both genders [6]. Appendicitis and diverticulitis may have epidemiologic similarities, but they are treated differently, possibly because the therapeutic strategies for these two disease entities evolved differently [8]. Secular trends for the non-perforating and perforating forms of the two diseases are strikingly different. Perforating disease, at least in the case of AA, may not be an inevitable outcome of the delayed treatment of non-perforating disease. If appendicitis represents the same pathophysiologic process as diverticulitis, it may be amenable to antibiotic rather than surgical treatment.

Resistance to antibiotics is a major public health problem, and antibiotic use is being recognized increasingly as the main selective pressure driving this resistance [25–27]. During the period of our study, the prescription of antibiotics in primary care practice in Europe varied greatly, with the highest rate being in France (32.2 DDD per 1,000 inhabitants/day) and the lowest rate being in the Netherlands (10.0 DDD per 1,000 inhabitants/day) [25]. Among the Scandinavian countries, as also in other European countries, we noted a shift in Finland from the use of old, narrow-spectrum antibiotics to the use of new, broad-spectrum antibiotics. The use of penicillins decreased and the use of amoxicillin-clavulanic acid increased. The increased use of fluoroquinolones in particular might prevent some admissions of patients with suspected AA for surgical treatment. Antibiotic use in Finland is within the same range as in other western European countries, but the situation with regard to antibiotic resistance is better [26]. It may also be possible that the diminished overall use of antibiotics in Finland protects innate immunity and saves patients from acute appendicitis. However, the decrease in incidence of AA was 30%, whereas the use of antibiotics declined only by 15%. Nevertheless, the role of immunity in the decline in incidence of AA is theoretical, and future studies of this issue will be needed. There is an escalating problem with antibiotic resistance among intestinal pathogens in patients with acute surgical infections [27]. A recent randomized study indicates that a policy with strict indications for antibiotic use might be adopted successfully for uncomplicated AD [28].

A weakness of our study was the finding of changing trends in the incidences of AD and AA and that of antibiotic use, but without the establishment of a causal relationship between one and the other. The recorded diagnoses of AA and AD are reliable in Finland, because all patient data come from hospitals and are recorded. The daily dose data for antibiotics are also reliable because the Finnish drug reimbursement registry has nearly 100% coverage. However, a weakness of a registry-based study such as ours is that there are no exact data on the reasons for outpatient antibiotic prescriptions.

In conclusion, our results indicate that the incidence of AA decreased significantly while that of AD increased in Finland during the past 20 years. The changes in outpatient use of antibiotics in Finland during the same period may not fully explain these findings.

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Author Disclosure Statement

No conflicting financial interests exist.

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