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Non-enteric Infections, Antibiotic Use, and Risk of Development of Functional Gastrointestinal Disorders

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Abstract

Background—Gastrointestinal infections are risk factors for irritable bowel syndrome (IBS) and functional dyspepsia (FD). We investigated whether non-enteric infections and antibiotic exposure are also associated with the development of functional gastrointestinal disorders (FGIDs).

Methods—In a nested case-control study, random samples of Olmsted County, MN, were mailed valid self-report questionnaires from 1988 through 1994, and then follow-up questionnaires from 1995 through 2003. Survey responders who did not report any FGID symptoms at baseline, but then reported such symptoms in at least 1 subsequent survey, were classified as new-onset cases. Age-matched controls were individuals that did not have symptoms at either the initial or subsequent surveys.

Key Results—The overall response rate was 78% to the initial survey and 52% to the follow-up survey. Based on the responses, 316 participants had a new onset of an FGID (43 IBS constipation, 95 IBS diarrhea, 25 IBS mixed, and 153 other FGIDs, including FD) and 250 did not

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The authors have no competing interests.

(controls). 76% (241/316) of cases reported a non-enteric infection vs 66% (166/250) of the controls. The frequency of enteric infections was similar between the two groups. Of the new FGID cases, 83% had a non-enteric infection that was treated with antibiotic. In a logistic regression model, treatment with antibiotics for a non-gastrointestinal infection was associated with development of an FGID (odds ratio=1.90; 95% CI, 1.21–2.98; *P*=.005), after adjusting for age and sex.

Conclusions & Inference—Based on a case-control study, treatment of a non-gastrointestinal infection with antibiotics appears to be a risk factor for development of an FGID.

Keywords

irritable bowel syndrome; functional GI disorders; antibiotics; non-enteric infections

INTRODUCTION

The functional gastrointestinal disorders (FGIDs) are defined by a constellation of chronic or recurring gastrointestinal (GI) symptoms in the absence of a known underlying structural or biochemical cause (1). These symptoms include abdominal pain, episodes of either constipation or diarrhea, or sometimes both, and dyspepsia (2-4). Of the two most widely recognized FGIDs are the irritable bowel syndrome (IBS) and functional dyspepsia (FD) (1, 5).

A subset of individuals with IBS and FD report a previous GI infection as the triggering event (4, 6-10). Studies have shown that 4%-36% of patients suffering from an episode of acute gastroenteritis can develop IBS (11) and the symptoms may persist for up-to 8 years after the acute infection is over (12). The pathogens have included not only bacterial (Campylobacter jejuni, Salmonella enterica, Escherichia coli O157:H7) but also viral (Norovirus) and parasitic (*Giardia*) organisms (4, 6, 8-10, 13-16). Similarly, new onset of FD has also been reported after acute bacterial (*Salmonella enterica*) (17), parasitic (*Giardia*) (18), and viral (Norovirus) gastroenteritis (19). Little data are available, however, on the impact of non-gastrointestinal infections or subsequent treatment with antibiotics and the development of IBS or FD. One UK study observed an association between antibiotics and IBS symptoms but the sample size was relatively small and the study was not population-based (20). Antibiotic use may have an influence in altering gut flora and changes in cytokine production that could alter the risk of IBS (21). Prophylactic use of antibiotics is increasing (20), which may impact on the incidence of FGIDs in the future.

We postulated that antibiotic treatment of non-gastrointestinal infections may be an important factor in the development of IBS symptoms. This study prospectively investigated, in a population free of IBS or FD symptoms, the association of GI and non-GI infection with symptom onset of FGIDs. In addition, the association between antibiotic use and subsequent development of IBS and FD was examined.

MATERIALS AND METHODS

This was a nested case-control study using chart review and survey data from a prospective cohort studies conducted over 11 years (22, 23). Age- and sex-stratified random samples of Olmsted County, MN, residents from age 20 years were mailed valid, self-report symptom questionnaires from November 1988 to June 1994. All subjects were mailed an additional survey on at least one other occasion between 1995 and 2003. Since these surveys were conducted for various research questions, participants were unaware of our intention to study relationship between infections, antibiotic use, and development of FGIDs. The Mayo Bowel Disease Questionnaire was used to ascertain presence of GI symptoms (24, 25).

From the responders to the surveys, cases were identified (using modified Rome II criteria) (26) as those who developed new onset symptoms of FGID symptoms. These were subjects who did not report symptoms consistent with an FGID on the baseline or initial survey, but did report symptoms on at least one subsequent survey. Subjects who did not report the symptoms meeting modified Rome II criteria on either the initial or subsequent surveys were considered as possible controls. The age (20-34, 35-42, 43-48, 49-62, and ≥63) specific distribution of cases was generated and 250 controls were randomly selected following frequency matching to the corresponding age specific totals for cases. Gender was not matched to allow studying effects of gender in development of FGIDs. The following definitions were applied to the questionnaire to identify each of the symptom groups:

IBS

Rome criteria (modified) for IBS were used (27). In this modified criteria, IBS was defined as a combination of frequent abdominal pain and an altered bowel habit linked to the pain, with two of the following three characteristics: 1) relieved by defecation, 2) associated with a change in stool frequency (greater than >3 bowel movements per day or <3 bowel movements per week), or 3) associated with a change in stool form (lumpy/hard or loose/watery stool). The questionnaire asked subjects if they had frequent abdominal pain but did not measure the frequency.

IBS-constipation predominant (IBS-C) fulfills the definition of IBS and includes 2 or more of the following symptoms: 1) less than 3 bowel movements per week, 2) straining to have a bowel movement, 3) often passing hard stools, and 4) incomplete evacuation.

IBS-diarrhea predominant (IBS-D) fulfills the definition of IBS and includes greater than 3 bowel movements per day or often passage of loose or watery stools.

IBS-both meets the definition for both IBS-C and IBS-D.

Functional dyspepsia

Two or more of the following criteria had to be fulfilled: Frequent upper pain (>6 times per year), nausea (at least weekly), vomiting (at least weekly), early satiety, or loss of appetite.

Frequent abdominal pain

Persons who reported having had more than 6 episodes of abdominal pain in the prior year were considered to have frequent abdominal pain.

All cases and controls had Mayo Clinic registration numbers and had not denied use of their medical records for research (per Minnesota law).

Chart review—A chart review of Mayo Clinic medical records of all identified cases and controls was carried out using a standard data extraction form to extract information on infections and antibiotic usage. Chart reviews were not used to identify cases or controls which was determined solely on the basis of survey responses. The data extractor was blind to the case-control status of the subjects. A subset of the charts (n=10) were re-reviewed to verify accuracy.

For each case, the first survey where FGID symptoms were noted represented their 'positive' survey. The date this positive survey was sent was taken as the 'symptom onset' date for cases. The last survey date was considered the 'symptom onset' date for chart review in the controls. Information was collected on a history of any infection-like episodes up to the 'symptom onset' date in both cases and controls. These included any bacterial GI infection such as Salmonella enterica, Campylobacter jejuni, Clostridium difficile, Shigella and *E. coli* infections. In addition, information was collected on any chest, eye, skin, joint or urinary infections, otitis media, conjunctivitis, sinusitis or dental sepsis. Infection was defined by a clinician's documentation of an infection episode in the chart. Culture was not required to define the episode. For each episode, it was noted if a hospital admission was required, number of days in hospital, whether antibiotics were used to treat the infection, whether microbiological samples were submitted and their analysis results, any complications such as renal failure, and if antibiotics were then used for prophylaxis. The chart reviews (including data on antibiotic use) were restricted to the duration between the baseline or initial survey and the subsequent survey when absence or presence of new FGID was determined.

Data analysis and calculations—The odds for new onset FGID (cases) compared to those with symptoms that do not meet Rome II criteria for new onset of FGID (controls) on any survey were estimated in those with infections (relative to those without) using a logistic regression analysis, adjusting for age and gender. Similarly, the odds for cases (versus controls) were estimated in those using antibiotics (relative to those not using them). With 316 cases and 250 controls, there was approximately 80% power to detect differences in proportions (e.g. proportion with GI infection) of 8% to 12%. The logistic regression analysis would have provided similar power for corresponding odds ratios adjusting for age and gender.

RESULTS

The average response rate to the initial questionnaires was 78% and 52% for the followup surveys. The mean period between the two surveys was 11.5 years (range 8 to 16 years) for the cases and 12 years (range 8 to 16 years) for the controls. Data has been analyzed for

response bias using this survey strategy and none was detected (28). Only those individuals who responded to at least one follow survey were included in the analysis. The mean age of participants in this study was 47 years (range 20-73 years) and 52% were female. Of the 566 subjects who responded to at least one follow up survey, 316 were classified as having an FGID (43 IBS-C, 95 IBS-D, 25 mixed IBS, and 153 other FGIDs) and 250 were classified as controls (Table 1). The other FGID category consisted of FD, undefined IBS subtype and frequent abdominal pain.

In Table 2, the results show that both cases and controls had a similar frequency of GI infections: 9.2% for controls and 8.9% for cases (OR 1.48; CI=0.75-2.93; p=0.26). The rate of non-GI infections was higher in cases (76.3%) than controls (66.4%) (OR 1.74; CI=1.12-2.69; p=0.01). Table 2 also summarizes the rate of subjects treated with antibiotics for their infections. A total of 83% of cases with a non-GI infection were at least treated once with antibiotics. The controls were significantly more likely to have not used any antibiotics and the FGID cases more likely to have used ≥3 antibiotic courses. Table 3 splits the rates of infection and antibiotic use according to case status and gender. Eight people (4 cases and 4 controls) had only GI infections and none of them received antibiotics. Forty-three people (19 controls and 24 cases) had a GI infection plus a non-GI infection. Of these, 16 (84%) controls had been given antibiotics, compared to 23 (96%) of cases.

Table 4 presents the results of the logistic regression model which included GI infection, non-GI infection (with and without antibiotic treatment) as possible predictors of FGID development. Female gender was an independent predictor for FGID development (OR 2.1; CI=1.5-2.9, P<0.001). In addition, only non-GI infections treated with antibiotics was an independent predictor for FGID development (OR 1.90; CI=1.21-2.98; p=0.005). Female gender (OR 2.54; CI=1.61-3.99; p<0.001) and non-GI infections treated with antibiotics (OR 2.30; CI=1.22-4.33; p=0.01) were also independent predictors when IBS development was studied alone (Table 5). Table 6 lists episodes of hospitalization, availability of microbiological samples, antibiotic use and types of non-GI infections among FGID cases and controls.

DISCUSSION

In this population-based study, IBS development was independently associated with nonenteric infections treated with antibiotics. It is generally accepted that the onset of IBS can occur after post-infectious gastroenteritis (4). An estimated 4% to 36% of people can develop IBS following a gastroenterological infection (6-9). However, what proportion of these IBS cases is incident cases is unclear as pre-existing history of IBS is either not available or is subjected to recall bias. In this population sample from a semi-rural U.S. community, we observed that the proportion of cases with a documented GI infection (8.9%) was not different from that observed in the controls (9.2%). This finding may reflect the stringent definitions used in this study to be considered a case, or the relative isolation of this community which may have less exposure to enteric infections (~8-9% reporting an enteric infection in a mean 11-12 year period as compared to CDC estimates of 15% U.S. population having a reported episode of gastroenteritis every year (29)). A subset of post-enteritis FGID patients' improves and loses their FGID phenotype over time (12, 30, 31). It

is unknown if FGID related to other infections or repeated antibiotic use have a similar long-term prognosis. Also, previous cohort studies have looked at the prevalence of IBS post-infection (4, 6, 8-10, 14-16) whereas we looked at the converse, i.e., the rates of GI infection reported prior to the onset of IBS and other FGIDs in a case-control design.

Our data indicate that antibiotic treated non-GI infections may also be a trigger for IBS and other FGIDs. The findings might be explained by extra-intestinal infection inducing changes in a primed GI tract (e.g. via altered cytokine production), or use of antibiotics modifying the intestinal flora, in turn triggering symptoms, or both. Another study has investigated the possible link between non-GI tract infections and functional bowel disease. In this prospective cohort study, McKeown *et al* (32) established the incidence after non-GI infection, GI infection and no infection, using valid questionnaires distributed at baseline, 3 and 6 months. IBS was more frequent in people with non-GI infections than in controls at 3 months, but this failed to reach statistical significance at 6 months. Our data agree with these findings; overall, 76% of cases had exposure to non-enteric infections versus 66% of controls, with a significantly increased risk of IBS in those treated with antibiotics. A recent study showed that antibiotic treatment in girls between the ages of 0-2 years was associated with development of abdominal pain at the age of 12 years. However, antibiotic treatment between the ages of 9-12 years was not associated with the same outcome (33). This suggests that a complex interplay of host related-factors such as gender, immune dysregulation, and microbiota resiliency may play a role in development of FGIDs following infections or antibiotic treatment.

The fecal flora is likely to be abnormal in a subset with IBS, but whether the flora contributes to the pathogenesis of IBS remains unclear (34, 35). Some studies have observed that antibiotics do reduce symptoms of IBS and the treatment is superior to placebo, although only a subset of patients responds (36, 37). However, these studies evaluated antibiotics that act locally in the gut and cannot be directly compared to those which have a systemic effect. Probiotics may also reduce IBS symptoms based on randomized trials (38). In a British case-control study by Maxwell *et al.* (20), 42 IBS study subjects were given antibiotics; they were compared with 49 IBS controls who had not been given antibiotics in over a year. At follow-up 4 months later, 48% of cases reported additional functional bowel symptoms, versus 22% of controls and subjects who were treated with antibiotics were at a threefold increased risk of developing more IBS symptoms 4 months later. Gwee *et al.* (39) also observed that more IBS subjects (82%) had been treated with antibiotics in contrast to non-IBS subjects (68%), but these results failed to reach statistical significance.

The strengths of the present study lie in the fact that the cohorts were recruited prospectively, that people with preexisting IBS and FD were excluded carefully, and we used validated standardized questionnaires (modified Rome II) to determine the outcome. The sample size of 566 study subjects represents an adequate number based on the power calculations. There are also limitations in this work. It was not possible to determine which type of IBS (IBS-C, IBS-D, IBS-mixed) was more likely to result from previous non-enteric infection, since the numbers studied were too small. Similarly, the number of cases with dyspepsia was too small to sub-analyze. Additionally, we assume that the dyspepsia is functional dyspepsia but that cannot be totally confirmed in the absence of diagnostic

workup to exclude organic causes. A potential source of bias was the visit propensity of the subjects. Not every single infection during the study interval may have been reported, and not everyone would have gone to the doctor when they were feeling ill. Also, it is reasonable to assume that some subjects may have taken antibiotics themselves without a doctor's orders to do so (perhaps from left-over prescriptions), although this was probably very uncommon. The Rochester Epidemiology Project allows medical record analysis of >95% surveyed population catered by the two major medical centers (Mayo Clinic and Olmsted Medical Center) reducing chances of missing information on infection episodes and antibiotic use. Topical antibiotics were not taken into account in this study, although plausibly these should not alter gut flora. Another limitation is that the onset of the FGID could be anywhere in that time interval between the two surveys. This makes it difficult to determine precise temporal relationship between antibiotic exposure or non-GI infections and development of an FGID. However, biological plausibility favors these to be risk-factors and precede onset of FGIDs. Additional bias could have been introduced from responders vs. non responders to the survey. However, when this was evaluated, none was found (28). Cause and effect needs further attention; it is possible, for example, individuals who are more susceptible to infections may also be more prone to IBS since these might share common underlying susceptibility factors (e.g., altered/vulnerable microflora, disrupted barrier or predisposition for immune dysregulation).

In conclusion, antibiotics for non-enteric infection may play a role in the etiology of gastrointestinal symptoms. Further investigation is needed to confirm these observations.

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KEY MESSAGES

- Acute gastrointestinal infections are associated with development of IBS and other FGIDs.

- It is uncertain if non-gastrointestinal infections and antibiotic exposure are associated with the development of FGIDs.

- A nearly 2-fold increased risk of an FGID was observed with antibiotic exposure for a non-gastrointestinal infection.

- The risk of an FGID was two-fold higher in women than men but was not increased by non-gastrointestinal infection alone.

Table 1

Demographic characteristics of the study population.

	Cases n=316	**IBS Constipation n=43**	**IBS Diarrhea n=95**	**IBS Mixed n=25**	**Dyspepsia/Other n=153**	**Controls n=250**
Gender Female: n (%)	190 (60.1%)	29 (67.4%)	55 (57.9%)	14 (56.0%)	92 (60.1%)	101 (40.4%)
Age (years) (Mean ± SD)	47 ± 13	50 ± 14	45 ± 12	49 ± 15	46±13	47 ± 13
Number of antibiotics* (Mean ± SD Median [Range])	2.8 (3.4) 2.0 [0,23]	2.9 (3.9) 2.0 [0,23]	2.7 (3.1) 2.0 [0,16]	2.8 (2.3) 3.0 [0,8]	2.9 (3.5) 2.0 [0,18]	2.1 (2.7) 1.0 [0,18]

*Number of antibiotics defined as antibiotic courses received before onset of GI symptoms

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Table 2

Infections preceding onset of irritable bowel syndrome and other functional GI disorders including dyspepsia.

	Cases n=316	IBS Constipation n=43	IBS Diarrhea n=95	IBS Mixed n=25	Dyspepsia/Other† n=153	Controls n=250
No infection (n=108)	47 (14.9%)	4 (9.3%)	20 (21.1%)	0	23 (15.0%)	61 (24.4%)
Any GI infection (n=51)*	28 (8.9%)	4 (9.3%)	7 (7.4%)	4 (16.0%)	13 (8.5%)	23 (9.2%)
Any antibiotic for GI infection	8 (28.6%)	0	3 (42.9%)	1 (25.0%)	4 (30.8%)	7 (30.4%)
Any non-GI infection (n=407)	241 (76.3%)	35 (81.4%)	68 (71.6%)	21 (84.0%)	117 (76.5%)	166 (66.4%)
Any antibiotic	199 (82.6%)	31 (88.6%)	57 (83.8%)	14 (66.7%)	97 (82.9%)	124 (74.7%)
1-2 infections	122 (50.4%)	18 (51.4%)	34 (50.0%)	15 (71.4%)	55 (47.0%)	91 (54.8%)
>= 3 infections	119 (49.4%)	17 (48.6%)	34 (50.0%)	6 (28.6%)	62 (53.0%)	75 (45.2%)
Overall antibiotic use						
0	78 (24.7%)	8 (18.6%)	26 (27.4%)	5 (20.0%)	39 (25.5%)	88 (35.2%)
1-2	111 (35.1%)	18 (41.9%)	32 (33.7%)	7 (28.0%)	54 (35.3%)	85 (34.0%)
>= 3	127 (40.2%)	17 (39.5%)	37 (39.0%)	13 (52.0%)	60 (39.2%)	77 (30.8%)

*43 of the 51 patients with a GI infection also had at least one non-GI infection

†13 patients had dyspepsia only; 75 patients with IBS (undefined subtype); 65 patients with frequent abdominal pain only.

Table 3

Infections preceding the onset of irritable bowel syndrome and other functional GI disorders, by case control status and gender

	Cases n=316		Controls n=250	
	Males (n=126)	**Females (n=190)**	**Males (n=149)**	**Females (n=101)**
No infection (n=108)	25	22	39	22
Any GI infection (n=51) *	12	16	13	10
Any antibiotic	1	7	5	2
Any non-GI infection (n=407)	89	152	97	69
Any antibiotic	69	130	72	52
1-2 infections	52	70	57	34
≥ 3 infections	37	82	40	35

* 43 of the 51 patients with a GI infection also had at least one non-GI infection

Table 4

Logistic regression model: Estimated Odds Ratios (95% Confidence Interval) for new onset FGID (case).

	OR & 95% CI	**p-value**
Age*	1.0 (0.99, 1.01)	0.88
Male	1.0 (ref)	
Female	**2.1 (1.5 ,2.9)**	**<0.001**
No infection	1.0 (ref)	
GI infection – no antibiotics	1.57 (0.73,3.40)	0.25
GI infection – antibiotics	1.30 (0.43,3.91)	0.64
Non GI infection – no antibiotics	1.25 (0.70,2.24)	0.45
Non GI infection - antibiotics	**1.90 (1.21,2.98)**	**0.005**

* per year of age

Table 5

Logistic regression model: Estimated Odds Ratios (95% Confidence Interval) for new onset IBS (case).

	OR & 95% CI	p-value
Age*	0.99 (0.97,1.00)	0.13
Male	1.0 (ref)	
Female	**2.54 (1.61,3.99)**	**<0.001**
No infection	1.0 (ref)	
GI infection – no antibiotics	1.67 (0.57,4.88)	0.34
GI infection – antibiotics	1.07 (0.20,5.83)	0.94
Non GI infection – no antibiotics	1.52 (0.68,3.39)	0.31
Non GI infection - antibiotics	**2.30 (1.22,4.33)**	**0.01**

* per year of age

Table 6

Comparison of hospitalization, availability of microbiological samples, antibiotic use and types of non-GI infections among cases and controls

	Cases n=316	Controls n=250
Hospitalization		
Number hospitalized	35	20
Total days of hospitalization	146	175
Microbiological samples		
Number with available samples	178	112
Total number of positive samples	436	225
Antibiotics used *Prescriptions used (number used antibiotic)*		
Penicillin	298 (137)	172 (83)
Ciprofloxan	0 (0)	0 (0)
Aminoglycosides	15 (13)	5 (4)
Cephalaosporins	93 (68)	62 (44)
Macrolides	189 (112)	116 (67)
Tetracyclines	45 (22)	15 (8)
Sulfamethoxazole/Trimethoprim	141 (84)	92 (54)
Flouroquinolones	90 (55)	30 (24)
Antifungal	15 (12)	8 (8)
Other	25 (23)	11 (10)
Non-GI infection episodes *Infection episodes (number infected)*		
Respiratory	687 (230)	363 (143)
Eye	114 (72)	50 (38)
Skin	184 (109)	136 (87)
Joint	2 (2)	3 (1)
Urinary	151 (66)	62 (38)
Dental	43 (12)	8 (6)
ENT	338 (142)	188 (83)
Appendicitis	12 (12)	5 (5)
Other	74 (51)	42 (34)