Use of Broad-Spectrum Antibiotics and the Development of Irritable Bowel Syndrome

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is a functional bowel disorder with an estimated prevalence of 9% to 22% in the United States. It is responsible for 28% of gastroenterology visits, with associated health care costs of $8 billion annually. Yet, IBS etiology is the subject of much debate.

Objectives: Our study examines a possible relationship between IBS and exposure to broad-spectrum antibiotics. It is known that antibiotics alter the colonic flora; we hypothesize that this can create the manifestations seen in IBS patients.

Methods: Following approval by the Gundersen Clinic, Ltd Human Subjects Committee/IRB, the medical records of adults who were started on a broad-spectrum antibiotic at Gundersen Lutheran Health System between January 1, 2008, and December 31, 2008, were reviewed retrospectively. From this population, we identified those who developed IBS within 12 months and compared their demographic and clinical characteristics with the characteristics of those who did not.

Results: Of the 26,107 adult patients exposed to broad-spectrum antibiotics during the study period, 115 received an IBS diagnosis within 12 months. Most were women (84%; n=97), and they had a higher prevalence of associated comorbidities than those who did not develop IBS. Patients indicated for macrolide or tetracycline use had a higher proportion of IBS development within 12 months; indication for tetracycline use maintained significance even after controlling for sex and comorbid conditions (odds ratio; 1.48; *P*=.046).

Conclusion: Use of broad-spectrum antibiotics—particularly macrolides or tetracyclines—may be associated with IBS development. To date, we know of no other study that has associated these antibiotics with IBS development. Further studies are necessary.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional bowel disorder estimated to have a prevalence of 9% to 22% in the United States.[1] It is responsible for 28% of gastroenterology visits, with associated health care costs of $8 billion annually.[2] Features of IBS are abdominal discomfort or pain associated with defecation or a change in bowel habits and disordered defecation.[3] Traditionally, functional bowel disorders were identified only by symptoms. In 1984, a working team of international experts was set up to produce guidelines for the management and study of IBS. In 1988, the first Rome criteria were presented; the guidelines were published the following year.[4] Over the years, these classifications became known as Rome I, II, and III.

The Rome III criteria for the diagnosis of IBS established that the patients must have had "recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months with symptom onset at least 6 months prior to diagnosis associated with 2 or more of the following: (1) relief with defecation, and/or (2) onset associated with change in frequency of stool, and/or (3) onset associated with change in form (appearance) of stool." The Rome III criteria go on to describe several different types of IBS: constipation-predominant (IBS-C); diarrhea-predominant (IBS-D); mixed (IBS-M), and unsubtyped (because of the lack of definite consistency of the stools).[3] IBS has many comorbid conditions, such as fatigue, depression, fibromyalgia, and chronic pelvic pain. According to Cole et al, those suffering from IBS have a 40% to 80% higher prevalence for 1 of the 3 aforementioned conditions.[5] It is possible that all will have the same underlying biological mechanism.

A number of hypotheses as to the etiology of this condition have been advanced—among them, bacterial overgrowth. In a recent article, Quigley[6] suggested that the likelihood of this hypothesis being a major factor in IBS is remote, based on recent findings of "dysfunctional interaction between the

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indigenous flora and the intestinal mucosa which, in turn, leads to immune activation in the colonic mucosa." Adding to the controversy, there is currently no explanation for why this condition is more common in women than men (women are 3 to 4 times more likely than men to be diagnosed with IBS[3]) and why in individuals there is a high correlation of IBS occurring with symptoms not necessarily related to the gastrointestinal tract, such as fatigue, depression, and fibromyalgia.

In the same article, Quigley[6] makes reference to a survey of 421 subjects performed in the United Kingdom that showed strong association between antibiotic use and an increased risk of IBS. We know that the use of broad-spectrum antibiotics, such as beta-lactam, cephalosporins, and macrolides are associated with alteration of the colonic flora.[7-11] In 2001, Acar[12] demonstrated that "Ampicillin-clavulanic acid and Ampicillin administration were associated with colonization with resistant strains of Enterobacteriacae as well as *Candida* spp. Ceftriaxone selected resistant strains of *Clostridium difficile* and *Candida* spp." While previous studies had indicated the "transient effect" of these drugs in the microflora, more recent ones are beginning to show a long-term effect[7,13]; moreover, we are unaware of any studies evaluating the effects that these drugs could have if they were used frequently on the same group of individuals. Our study provides a preliminary assessment of the relationship between exposure to these drugs and the development of IBS.

METHODS

Patients

Following approval by the Gundersen Clinic, Ltd Human Subjects Committee/IRB, the medical records of adults who were started on a broad-spectrum antibiotic (inpatient or outpatient) at Gundersen Lutheran Health System between January 1, 2008, and December 31, 2008, were reviewed retrospectively. Broad-spectrum categories included penicillins, macrolides, cephalosporins, tetracyclines, and betalactams; topical antibiotics were not included. We then used ICD-9 diagnosis code 564.1 to identify those patients with a subsequent IBS diagnosis within 12 months. We excluded (1) patients who were pregnant during antibiotic use; (2) patients with inflammatory bowel disease (IBD), Crohn disease, ulcerative colitis, gastrointestinal cancer, diverticulitis, celiac disease, or peptic ulcer prior to the start of antibiotics in 2008; (3) patients with diagnosis of gastroenteritis prior to the start of antibiotics in 2008; and (4) patients with a diagnosis of IBS prior to the start of antibiotics in 2008.

For those who developed IBS within 12 months, antibiotic use was assessed during the 1-year period prior to the IBS diagnosis. For those who did not develop IBS, antibiotic use was assessed over a random 1-year interval ending between the 2008 antibiotic start date and 1 year later. This provided an equal-length study period for each individual and study periods that reflected a variety of start/end dates, as did the cohort who developed IBS (an attempt to reduce antibiotic administration bias that may occur over time). For this study, we studied only indication for antibiotic use rather than duration and more refined measures.

Statistical Methods

Simple statistics such as means, standard deviations, frequencies, and percentages were calculated. For the primary analysis, the association of broad-spectrum antibiotic use (indication of use rather than verified use) between those who developed IBS within 1 year of the patient's 2008 antibiotic start date and those who did not was assessed via χ^2 tests for penicillin use, macrolide use, cephalosporin use, and tetracycline use—and via Fisher exact test for betalactam use due to low frequency of indication. As secondary measures, we compared the 2 study groups on demographic measures and comorbid conditions (identified by ICD codes) that existed prior to the start of the antibiotic time interval (fibromyalgia, anxiety, depression, pelvic pain, diabetes mellitus, chronic fatigue), and number of comorbid conditions existing prior to the start of the antibiotic time interval (excluding diabetes mellitus and chronic fatigue); continuous variables were assessed via *t* tests. Categorical (and ordinal) variables were assessed via χ^2 tests; if at least 25% of expected cell counts were less than 5, the Fisher exact test was used instead. In addition, a multivariate logistic regression model was built using significant univariate variables; a stepwise selection method was used with entry at the 0.05 level. A *P* value <.05 was considered significant. We report a C statistic (area under the receiver operating characteristic curve) for the multivariate model; the C statistic is a value from 0.5 to 1 in which values closer to 1 indicate a model that better differentiates between those who developed IBS within 1 year and those who did not than do models with a lower C statistic value.

RESULTS

After applying exclusionary criteria, 26,107 patients remained in the study. However, 4743 did not have at least 1 year of follow-up to be included in analysis. Of the remaining 21,364, 115 (.54%) developed IBS in the year after they began the antibiotic. Of these, 38 (33%) had a gastroenterology visit, and the remaining 77 (67%) did not. In addition, a retrospective review of the medical records of the 115 patients with an IBS diagnosis showed that 9 (8%) fulfilled Rome III criteria, while the medical records of the remaining 106 (92%) did not contain enough information to determine whether the criteria were met. The mean time to IBS was 5.9 ± 3.3 months.

Primary analysis showed that those who took a macrolide had a higher rate of IBS development than those who did

not take the antibiotic (0.71% [40 of 5595] vs 0.48% [75 of 15,769]; $P = .036$); likewise for those on a tetracycline (0.73% [40 of 5479] vs 0.47% [75 of 15,885]; $P < .025$). Those on a betalactam (0% [0 of 17] vs 0.54% [115 of 21,347]; $P > .999$), a cephalosporin (0.58% [27 of 4669] vs 0.53% [88 of 16,695]; $P = .673$), or a penicillin (0.58% [55 of 9387] vs 0.5% [60 of 11,922]; $P = .432$) did not exhibit the same pattern.

Secondary analyses revealed there were differences in sex, age, body mass index (BMI) class, and comorbid conditions between those who developed IBS and those who did not (Table 1). After including the significant univariate predictors of sex, age, or indications of fibromyalgia, anxiety, depression, pelvic pain, macrolide, and tetracycline into a multivariate model, the following were simultaneous significant predictors for IBS development: sex, fibromyalgia, anxiety, pelvic pain, and tetracycline (Table 2).

DISCUSSION

Irritable bowel syndrome is a functional bowel disorder of unknown etiology; several hypotheses have been formulated—among them, bacterial overgrowth has been extensively debated. We assume that in a healthy individual, antibiotics are responsible for the alteration of the intestinal microbiota. Whether that leads to bacterial or yeast overgrowth, the end results could be responsible in part for the development of IBS.

As mentioned previously, Quigley and others believe that bacterial overgrowth is less likely to contribute to the development of IBS, but the authors made no mention of yeast overgrowth. However, data regarding the efficacy of rifaximin in IBS would tend to support a bacterial overgrowth type of process. Santelmann et al[14] suggest that *Candida* overgrowth could be responsible in part for the development of IBS.

Candida is a genus of fungus that thrives in the abundance of sugar and can be cultured from 80% of human feces.[15] *Candida* is known to proliferate rapidly in the colon after antibacterial therapy.[16] *Candida* releases alcohol and glycoproteins that stimulate mast cells to release histamine and prostaglandins. Both of these aforementioned substances cause inflammation, which can cause the symptoms associated with IBS.[17]

Unfortunately, we do not have a test that distinguishes between yeast sensitivity and yeast overgrowth in the gut,[14] which makes diagnosis of this condition more challenging. We do know, however, that antibiotics that inhibit obligate anaerobes in the intestinal tract (ie, amoxicillin, erythromycin, and several cephalosporins[7,9,10,12]) may be more likely to promote overgrowth of *Candida* than those that do not.[11]

While the mechanisms, including causality, are beyond the scope of the study, and while the number of patients who received betalactams was too small to draw any real conclusion, some of the antibiotics seem to be associated with the development of IBS. Thus, further studies that investigate the IBS relationship between yeast sensitivity and overgrowth are recommended.

There are limitations to our study. For example, we were unable to confirm the diagnosis of IBS because in many of the medical records reviewed, the scientific criteria required for the diagnosis (ie, Rome III criteria) are not documented. This

Table 1. Demographic and Clinical Data for Patients Treated with Broad-Spectrum Antibiotics by Irritable Bowel Syndrome Status[a]

Characteristic	IBS (n=115)	No IBS (n=21,249)	*P* value
Age, mean years ± SD	46.2 ± 18.6	49.8 ± 18.6	.036
Women	97(84)	12,739 (60)	<.001
BMI class, kg/m2			<.001
Normal	22(19)	3027 (14)	
Overweight	26(23)	3888 (18)	
Obese	52(45)	6134 (29)	
Not available	15(13)	8200 (39)	
Comorbid condition			
Fibromyalgia	29 (25)	2269 (11)	<.001
Anxiety	33 (29)	2779 (13)	<.001
Depression	38 (33)	4493 (21)	<.001
Pelvic pain	26 (23)	1396 (7)	<.001
Diabetes mellitus	14 (12)	2524 (12)	.922
Chronic fatigue	0 (0)	20 (<1)	>.999
Number of comorbid conditions[b]			**<.001**
0	50 (44)	13,919 (66)	
1	25 (22)	4514 (21)	
2	23 (20)	2118 (10)	
3	13 (11)	605 (3)	
4	4 (3)	93 (<1)	
Antibiotic prescribed			
Betalactam	0 (0)	17 (<1)	>.999
Cephalosporin	27 (24)	4642 (22)	.673
Macrolide	40 (35)	5555 (26)	.036
Penicillin	55 (48)	9387 (44)	.432
Tetracycline	40 (35)	5439 (26)	.025

[a]Values are presented as number of patients (%) unless otherwise indicated.
[b]Comorbidities included were fibromyalgia, anxiety, depression, and pelvic pain.
Abbreviations: IBS = irritable bowel syndrome; SD = standard deviation; BMI = body mass index.

Table 2. Multivariate Logistic Regression

Variable	Odds Ratio	95% CI	*P* value
Sex (women vs men)	2.74	1.63-4.60	<.001
Fibromyalgia	2.03	1.31-3.14	.002
Anxiety	1.87	1.23-2.85	.003
Pelvic pain	2.49	1.57-3.95	<.001
Tetracycline	1.48	1.01-2.18	.046
Model C statistic	.71		

Abbreviation: CI = confidence interval.

does not mean that the attending did not make an effort to use scientific criteria.

Another limitation was the retrospective nature of the study, a circumstance in which we lack control over the assignment of patients to an antibiotic category. Moreover, we were not able to determine exactly how long (duration) patients were scheduled to be on the particular antibiotic(s), patient compliance during the scheduled period(s), or what specific antibiotic(s) patients were using; thus, we measured indication for use rather than confirmed use. In order to accurately capture duration and compliance data, a prospective study is needed. In addition, many patients were lost to follow-up (about 5000). This latter issue could have been related to the fact that we identified only 115 patients who developed IBS within a year of their 2008 antibiotic start date. Another confounding variable is that patients with IBS tend to seek healthcare more frequently, thereby increasing the likelihood that they will be exposed to antibiotics; however, we attempted to factor out pre-existing IBS and related diagnoses.

Even with the above-mentioned limitations, the study does show some interesting relationships. First, our results were consistent with findings from other studies regarding the associations of IBS with sex, age, BMI (although BMI was unavailable in a substantial number of records, the percentage of which differs between cohorts), and comorbid conditions. Further, we found an association between IBS development and antibiotic use in both univariate and multivariate models; however, with the apparently low overall IBS rate, it is also not known if the antibiotics relationships found in this study indicate that they increase the chance of IBS development or simply that they do not decrease it as much as other antibiotics. Further studies are needed, particularly those with a prospective, randomized, controlled format or those using a prospectively designed database geared toward a more elaborate matched case-control study.

CONCLUSION

The use of broad-spectrum antibiotics may have a relationship with the development of IBS, particularly when tetracyclines and macrolides are used. To date, we know of no other study that has associated use of these antibiotics with the development of this condition. Further studies are necessary.

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