Postinfectious Irritable Bowel Syndrome: Clinical Aspects, Pathophysiology, and Treatment

by Herbert L. DuPont

Although acute diarrhea is usually a self-limiting illness, postinfection complications may persist long after the initial infection resolves. Postinfectious irritable bowel syndrome (PI-IBS), which is defined as new onset of irritable bowel syndrome after an acute episode of infectious diarrhea, has been reported in 4%–31% of patients within 6 months to 3 years after an initial enteric infection. Chronic mucosal inflammation, immunologic changes, and biochemical alterations triggered by microbial infection may be involved in mechanisms leading to persistent intestinal symptoms. Patients with PI-IBS may have heightened mucosal inflammatory response during an acute infection that leads to a persistent pathophysiologic response and serotonin release long after the acute infection has resolved. Treatment for PI-IBS often focuses on symptom relief, but prevention and early treatment of acute bacterial illness with antimicrobial drugs may be important potential strategies for reducing the risk of PI-IBS development.

KEY WORDS: postinfectious irritable bowel syndrome, antibiotics, acute bacterial diarrhea

INTRODUCTION

Bacterial diarrhea is considered a self-limiting illness lasting 3–5 days, but its complications can persist for weeks, months, and even years in some patients (1–3). One such complication is postinfectious irritable bowel syndrome (PI-IBS), defined as the development of new enteric symptoms meeting objective criteria of irritable bowel syndrome (IBS) in patients who had normal bowel function prior to an enteric infection (1,4). Factors such as duration of initial episode of diarrheal illness may increase a patient's risk of developing PI-IBS (5,6). Most current treatments target the symptoms of PI-IBS, but therapies aimed at preventing or reducing the duration of acute infection

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Table 1
Incidence of IBS Development After Acute Enteric Infection

Study	*Follow-up*	*Patients (N)*	*Incidence (%)*
Borgaonkar, et al, 2006 (9)	3 mo	191	4
Dunlop, et al, 2003 (7)	3 mo	747	14
Gwee, et al, 1996 (10)	12 mo	75	22
Gwee, et al, 1999 (11)	12 mo	94	23
Ilnyckyj, et al, 2003 (12)	3 mo	109	4
Ji, et al, 2005 (6)	12 mo	101	15
Marshall, et al, 2006 (8)	2–3 y	1,368	30
McKendrick and Read, 1994 (13)	12 mo	38	32
Mearin, et al, 2005 (14)	12 mo	467	12
Neal, et al, 1997 (5)	6 mo	386	6
Neal, et al, 2002 (2)	6 y	192	4
Okhuysen, et al, 2004 (3)	6 mo	97	7
Parry, et al, 2003 (15)	6 mo	128	14
Rodríguez and Ruigómez, 1999 (16)	12 mo	318	4
Thornley, et al, 2001 (17)	6 mo	188	9

IBS = irritable bowel syndrome.

are under investigation. This article reviews the clinical aspects, pathophysiology, and management of PI-IBS.

CLINICAL ASPECTS OF POSTINFECTIOUS IRRITABLE BOWEL SYNDROME

Postinfectious irritable bowel syndrome is characterized by chronic gastrointestinal (GI) symptoms meeting objective criteria for IBS that persist following an episode of enteric infection in patients with previously normal bowel function (1). Although PI-IBS most frequently occurs after acute infection with a bacterial pathogen, it has also been observed following viral or protozoal enteric infection (1). Common symptoms, which include diarrhea, abdominal pain, urgency, and bloating, are similar to those associated with diarrhea-predominant IBS (IBS-D) (3,5,7). In a 2003 study of 747 patients who experienced acute bacterial enterocolitis, 63% of 103 patients who developed GI symptoms within 3 months postinfection met Rome I criteria for IBS-D (7).

For patients with PI-IBS, abnormal stool patterns and abdominal symptoms may persist for months to years following the initial acute infectious episode (2,3). Although symptoms may fluctuate or diminish in severity compared with the initial enteric illness, bowel function for patients who develop PI-IBS does not usually return to normal (1). A 2002 prospective study of 97 adults with no history of travelers' diarrhea reported that 10% of the 61 subjects who developed diarrhea while traveling to Mexico still met Rome II criteria for IBS 6 months after travel (3). In a longer-term follow-up study of patients who experienced food poisoning, 57% of 14 patients who developed PI-IBS after the initial illness remained symptomatic for up to 6 years (2).

Incidence

Most studies reporting the incidence of PI-IBS assessed the number of PI-IBS cases as a fraction of the total cases of acute diarrhea, with a 4%–32%

reported incidence of PI-IBS (Table 1) (2,3,5–17). When the number of cases was reported as a fraction of total IBS cases, the proportion of patients with PI-IBS who could attribute the onset of illness to an acute episode of diarrhea was similar and ranged from 6%–35% (4,18). The most reliable data on the risk of PI-IBS following acute enteric illness are from studies that compared the frequency of PI-IBS among individuals with diarrheal illness with a matched control group of patients without the condition (6,8,12,14–16). These studies indicated that patients who experienced acute diarrhea were 3–12 times more likely to develop IBS during follow-up periods of up to 3 years compared with those in the control group who had not had an episode (6,8,12,14–16).

Variations in IBS definition and follow-up duration among these studies may have contributed to the wide range in reported incidence. Furthermore, many studies depended on patient recollection of symptoms, sometimes over a period of years, in relation to an acute episode of diarrhea. The estimated frequency of PI-IBS may have been underestimated because patients may have failed to remember or perceive a link between acute GI infection and persistent intestinal abnormalities. Despite these limitations, these findings suggest that PI-IBS may be relatively common among patients who have had a bacterial enteric infection resulting in diarrhea (1).

Risk Factors

Duration of acute infectious illness has been shown to be a strong risk factor for the development of PI-IBS (5,6). In a study of 101 patients, the relative risk for development of PI-IBS within 12 months following acute bacterial enterocolitis was 5.5 (confidence interval [CI]: 1.1–26.3) for patients with symptoms of diarrhea that lasted longer than 4 days compared with those who experienced diarrheal symptoms for fewer than 2 days (6). Similarly, in a survey of patients diagnosed with acute diarrheal illness due to a confirmed bacterial pathogen (N = 300), the relative risk of developing PI-IBS within 6 months of infection increased as the duration of diarrheal symptoms during the acute episode increased (Table 2) (5). Because longer duration of acute bacterial diarrhea may reflect more severe illness, it is possible that severity of illness may confer increased risk of developing PI-IBS (1,5).

Table 2
Effect of Duration of Diarrheal Symptoms on Risk of PI-IBS (5)

Duration of diarrhea, d	*Adjusted relative risk (95% CI)*
0–7	1.0
8–14	2.94 (0.6–15)
15–21	6.46 (1.3–34)
≥22	11.37 (2.2–58)

CI = confidence interval; PI-IBS = postinfectious irritable bowel syndrome.

The severity and/or duration of illness may be influenced by the pathogen responsible for the acute infection (1). Pathogens such as *Campylobacter* and *Shigella* may cause more severe mucosal injury and longer duration of acute illness than *Salmonella* (1). In a study of 231 patients who were followed for 3 months, a greater percentage of patients (4.2% of 119) developed PI-IBS following infection with *Campylobacter* than infection with *Salmonella* (2.6% of 38 patients), but this difference was not significant (9). Although some researchers have suggested an increased risk of development of PI-IBS based on the infecting pathogen, other researchers have observed no association among specific bacterial species and the development of PI-IBS (3,5).

In addition to factors associated with the acute illness and pathogens responsible for that illness, several patient-related factors, including sex, age, and psychologic factors, may also impact the risk of development of PI-IBS (2,5,10,11,13). Being female has been identified as a risk factor for PI-IBS in several studies (2,5,11,13), with a reported relative risk for females three times higher than for males (5). Older individuals have a lower risk of developing PI-IBS compared with younger individuals, with a relative risk of 0.4 (CI: 0.1–0.9) for those older than 60 years of age compared with 1.0 for those 19–29 years of age (5).

Table 3
Differential Diagnosis of PI-IBS (1,4,19)

Diagnosis	*Considerations*
Colon cancer	Should be considered in individuals ≥40 y and in those with family history of colon cancer
Diverticular disease	Should be considered in elderly
Celiac disease	May be diagnosed with IgA endomysial antibody test
Crohn's disease	Should be suspected in individuals with anemia, increased erythrocyte sedimentation rate, or nocturnal diarrhea and pain
Ulcerative colitis	Diagnosis established by endoscopy and biopsy
Drug-induced diarrhea	May be caused by antibiotics, antacids containing magnesium, proton pump inhibitors, angiotensin-converting enzyme inhibitors, or statins
Microscopic colitis	May be excluded by flexible sigmoidoscopy and biopsy
Small bowel bacterial overgrowth	Should be considered in individuals who have had small bowel resections or received radiation therapy
Brainerd diarrhea	Diagnosis of exclusion involves biopsy, which often shows focal lymphocyte inflammation

IgA = immunoglobulin A; PI-IBS = postinfectious irritable bowel syndrome.

Additionally, in two prospective studies of patients hospitalized with acute gastroenteritis, patients who subsequently developed PI-IBS (n = 22 of 75 patients [10] and n = 22 of 94 patients [11]) scored higher on measures of anxiety ($p = 0.0002$) and depression ($p = 0.02$) at the time of the acute episode (10), as well as on posthospitalization measures of anxiety ($p = 0.01$) and disruptive life events (e.g., minor illness, bereavement, end of a relationship; $p = 0.001$) (11) compared with patients whose bowel habits returned to normal. Although these findings suggest a relationship between psychologic factors and the development of PI-IBS, the degree to which these psychologic factors may be causally related to the development of PI-IBS is unknown.

Diagnosis

A diagnosis of PI-IBS should generally be considered for patients with persistent symptoms of diarrhea following acute onset of symptoms within a single day and in patients with a change in bowel habits after confirmed or presumed exposure to enteric pathogens (4). In PI-IBS, symptoms usually persist following the initial diarrheal episode. Although symptoms of diarrhea may decrease, bowel habits usually do not return to normal, and symptoms such as urgency with loose stools and abdominal cramps may persist (4). Patients who develop PI-IBS may lose weight during the initial infection or may experience minor bleeding with defecation. However, persistent weight loss or rectal bleeding are not generally associated with PI-IBS and may indicate an alternative diagnosis (1,4,19).

Differential diagnosis of PI-IBS involves ruling out other conditions that may cause prolonged diarrheal symptoms, including persistent enteric infection, coinfection, and malabsorption or food intolerance (1,19). Various GI conditions known to cause changes in bowel function resembling those associated with PI-IBS may be unmasked by an acute enteric infection (Table 3) (1,4,19). In addition, medications such as antibiotics, proton pump inhibitors, and antacids containing magnesium can mask persistent diarrheal illness with symptoms similar to PI-IBS and should also be considered as potential factors during differential diagnosis (1,4,19).

PATHOPHYSIOLOGY

Research concerning the pathophysiology of PI-IBS suggests that inflammation of intestinal mucosa may play a role in the persistence of bowel dysfunction following acute enteric infection (1). One line of support is derived from observations of increased concentrations of inflammatory mediators in patients with PI-IBS. Patients who developed PI-IBS within 3 months following acute diarrheal illness (n = 8) were reported to have higher rectal mucosal concentrations of the inflammatory cytokine interleukin-1β during the acute illness and 3 months after the illness compared with the seven patients whose bowel habits returned to normal following the episode ($p < 0.005$ and $p < 0.001$, respectively) (20). Patients who developed PI-IBS also had higher interleukin-1β concentrations compared with the 18 participants who had not had an episode of acute diarrhea ($p < 0.001$) (20). A second line of evidence for chronic inflammation in PI-IBS involves increased concentrations of immune and enterochromaffin cells. T lymphocyte and enterochromaffin cell levels in intestinal mucosa were significantly elevated 6 and 12 weeks after acute diarrheal illness for 21 patients with PI-IBS compared with 12 patients in the control group ($p < 0.001$ for each timepoint); similar increases were observed for 10 patients who had persistent IBS symptoms up to 48 months after an enteric infection ($p < 0.001$) (21). Similarly, T lymphocyte and enterochromaffin cell counts in rectal biopsy specimens obtained approximately 4 months after initial bacterial infection were higher in 28 patients with newly diagnosed PI-IBS compared with 28 patients who were asymptomatic after bacterial infection ($p = 0.02$ for enterochromaffin cell counts) or 34 healthy volunteers ($p = 0.006$ for each cell type) (7).

The increase in enterochromaffin cell concentrations associated with PI-IBS may contribute to GI symptoms through serotonin-mediated mechanisms (1). Because enterochromaffin cells are the primary source of intestinal serotonin, a neurotransmitter that stimulates enterocyte secretions and peristalsis, it is conceivable that increased cell numbers could lead to increased serotonin levels and subsequent diarrheal symptoms (4). Indeed, patients with PI-IBS have been shown to have elevated postprandial plasma levels of serotonin compared with patients with constipation-predominant IBS or healthy volunteers (22).

In addition to increased concentrations of inflammatory mediators and cells, increased small bowel permeability may also be involved in the pathogenesis of PI-IBS. Intestinal permeability, determined by the ratio of lactulose to mannitol excreted in the urine, was significantly higher 12 weeks after acute diarrheal illness for 16 patients with PI-IBS compared with 12 controls with normal bowel habits ($p = 0.0001$); similar increases were observed for 10 patients who had persistent IBS symptoms 8–48 months after an acute episode of diarrhea ($p = 0.005$) (21). These results are consistent with a 2004 report of increased intestinal permeability in 132 patients with IBS following an episode of acute diarrhea compared with 86 patients in the control group without IBS ($p = 0.007$) (23). Several authors have suggested that increased intestinal permeability may allow bacterial and luminal antigens access to the submucosa, which could perpetuate chronic inflammation and disrupt enteric sensation and motility, which have been implicated in the pathogenesis of IBS (23–26).

TREATMENT AND MANAGEMENT

Currently, there is no widely accepted management strategy for PI-IBS. Treatment is frequently symptom directed rather than curative and includes agents prescribed for the treatment of IBS-D (1,27). Antispasmodics, such as the anticholinergic agent hyoscyamine, reduce intestinal smooth muscle activity, and antidiarrheal agents, such as the opioid agonist loperamide, increase stool consistency. Tricyclic antidepressants, which promote constipation, and serotonin-3 receptor antagonists, which delay colonic transit, have been shown to reduce symptoms in patients with IBS-D and may be beneficial for patients with PI-IBS (1,27,28).

Prophylaxis aimed at prevention or early treatment of acute bacterial diarrhea may reduce the risk of PI-IBS development by reducing the occurrence, duration, and severity of the chronic inflammation and mucosal alterations believed to play a role in disease persistence (1). Several agents, including bismuth subsalicylate and antibiotics (e.g., fluoroquinolones and rifaximin), have been evaluated for prevention of travelers' diarrhea (29). Bismuth subsalicylate is not as effective as antibiotics in preventing diarrheal illness, and concerns about bacterial resistance may limit the prophylactic use

Table 4
Frequency of Diarrhea in US Travelers to Mexico Who Received Rifaximin Versus Placebo for Disease Prevention

	Patients (n/n)				
	Rifaximin 200 mg/d (%)	*Rifaximin 400 mg/d (%)*	*Rifaximin 600 mg/d (%)*	*Placebo (%)*	*p value**
Week 1	1/50 (2)	7/52 (14)	2/54 (4)	17/54 (31)	< 0.001
Week 2	5/49 (10)	3/45 (7)	5/52 (10)	12/37 (32)	0.003

*Rifaximin 200 mg/d vs 400 mg/d vs 600 mg/d vs placebo by study week.
From DuPont et al (31). With permission.

of fluoroquinolones (29). Rifaximin is a nonabsorbed (<0.4%) oral antibiotic currently approved in the United States for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* (30). The efficacy of rifaximin as prophylaxis has been suggested by two randomized, double-blind, placebo-controlled studies (31,32). In a study of 210 adults from the United States visiting Mexico, travelers' diarrhea occurred in significantly fewer participants who received rifaximin 200–600 mg/day for 2 weeks compared with those who received placebo ($p < 0.005$ for each rifaximin dose group), with rifaximin providing protective benefit during both weeks of treatment (Table 4) (31). In a study of 25 healthy volunteers who were challenged with *Shigella flexneri,* none of the 15 participants who received rifaximin 600 mg/day for 3 days developed diarrhea or exhibited microbiologic evidence of *S. flexneri* colonization compared with 60% and 50%, respectively, of the 10 patients who received placebo ($p = 0.001$ and $p < 0.005$, respectively) (32). The possibility that preventing travelers' diarrhea with rifaximin reduces the risk of new-onset IBS during long-term follow-up is currently being assessed.

Although efficacy data for antibiotic prophylaxis in the prevention of acute bacterial diarrhea are limited, antibiotics have demonstrated efficacy for treating bacterial diarrheal illnesses and reducing the duration of illness by 1–2 days compared with placebo or no intervention (33). Although fluoroquinolones have become standard therapy for the treatment of travelers' diarrhea, rifaximin 600–1,800 mg/day for 3–5 days has also been shown in randomized, double-blind, placebo-controlled (34) and comparative studies (35,36) to be effective treatment.

The efficacy of antibiotics for the treatment of PI-IBS has not been specifically evaluated, but research suggests that antibiotics may be effective in treating a subset of patients with IBS (37–39). In a randomized, double-blind, placebo-controlled study of 111 patients with IBS, neomycin 500 mg/day for 10 days significantly reduced composite IBS symptom scores ($p < 0.05$) and increased the percentage of patients who reported bowel normalization ($p < 0.001$) compared with placebo (37). Similarly, in a randomized, double-blind, placebo-controlled study of 87 patients with IBS, rifaximin 1,200 mg/day administered for 10 days resulted in greater global improvement in IBS symptoms compared with placebo ($p < 0.02$) (39).

CONCLUSIONS

Postinfectious IBS appears to be a relatively common complication of acute diarrheal illnesses, especially those caused by bacterial enteropathogens. Chronic mucosal inflammation and associated alterations in host response triggered by enteric infection may underlie persistent bowel symptoms in patients who develop PI-IBS. Antimicrobials, such as rifaximin, have shown potential benefit in the prevention and treatment of acute bacterial illness in international travelers, as well as in the treatment of established IBS. Prevention and treatment of acute bacterial illness with antibiotics may constitute an important strategy for preventing PI-IBS and warrant further study. ■

References

1. Connor BA. Sequelae of traveler's diarrhea: focus on post-infectious irritable bowel syndrome. *Clin Infect Dis,* 2005;41(suppl 8):S577-S586.
2. Neal KR, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study. *Gut,* 2002;51:410-413.
3. Okhuysen PC, Jiang ZD, Carlin L, Forbes C, DuPont HL. Post-diarrhea chronic intestinal symptoms and irritable bowel syndrome in North American travelers to Mexico. *Am J Gastroenterol,* 2004;99:1774-1778.
4. Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology,* 2003;124:1662-1671.
5. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. *BMJ,* 1997;314:779-782.
6. Ji S, Park H, Lee D, Song YK, Choi JP, Lee SI. Post-infectious irritable bowel syndrome in patients with Shigella infection. *J Gastroenterol Hepatol,* 2005;20:381-386.
7. Dunlop S, Jenkins D, Neal K, Spiller R. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. *Gastroenterology*, 2003;125:1651-1659.
8. Marshall JK, Thabane M, Garg AX, Clark WF, Salvadori M, Collins SM. Incidence and epidemiology of irritable bowel syndrome after a large waterborne outbreak of bacterial dysentery. *Gastroenterology,* 2006;131:445-450; quiz 660.
9. Borgaonkar MR, Ford DC, Marshall JK, Churchill E, Collins SM. The incidence of irritable bowel syndrome among community subjects with previous acute enteric infection. *Dig Dis Sci,* 2006;51:1026-1032.
10. Gwee KA, Graham JC, McKendrick MW, et al. Psychometric scores and persistence of irritable bowel after infectious diarrhoea. *Lancet,* 1996;347:150-153.
11. Gwee KA, Leong YL, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut,* 1999;44:400-406.
12. Ilnyckyj A, Balachandra B, Elliott L, Choudhri S, Duerksen DR. Post-traveler's diarrhea irritable bowel syndrome: a prospective study. *Am J Gastroenterol,* 2003;98:596-599.
13. McKendrick MW, Read NW. Irritable bowel syndrome–post salmonella infection. *J Infect,* 1994;29:1-3.
14. Mearin F, Perez-Oliveras M, Perello A, et al. Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. *Gastroenterology,* 2005;129:98-104.
15. Parry SD, Stansfield R, Jelley D, et al. Does bacterial gastroenteritis predispose people to functional gastrointestinal disorders? A prospective, community-based, case-control study. *Am J Gastroenterol,* 2003;98:1970-1975.
16. Rodriguez LA, Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *BMJ,* 1999;318:565-566.
17. Thornley JP, Jenkins D, Neal K, Wright T, Brough J, Spiller RC. Relationship of Campylobacter toxigenicity in vitro to the development of postinfectious irritable bowel syndrome. *J Infect Dis,* 2001;184:606-609.
18. Boulton-Jones JR, Spiller RC. Significance of anxiety in IBS outpatients: relation to bowel symptoms and final diagnosis [abstract]. *Gut,* 2003;52(suppl 1):A86.
19. Spiller RC. Infection as a cause of irritable bowel syndrome. *Hosp Med,* 2003;64:270-274.
20. Gwee KA, Collins SM, Read NW, et al. Increased rectal mucosal expression of interleukin 1β, in recently acquired post-infectious irritable bowel syndrome. *Gut,* 2003;52:523-526.
21. Spiller RC, Jenkins D, Thornley JP, et al. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. *Gut,* 2000;47:804-811.
22. Dunlop SP, Coleman NS, Blackshaw E, et al. Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol,* 2005;3:349-357.
23. Marshall JK, Thabane M, Garg AX, Clark W, Meddings J, Collins SM. Intestinal permeability in patients with irritable bowel syndrome after a waterborne outbreak of acute gastroenteritis in Walkerton, Ontario. *Aliment Pharmacol Ther,* 2004;20:1317-1322.
24. Spiller R, Campbell E. Post-infectious irritable bowel syndrome. *Curr Opin Gastroenterol,* 2006;22:13-17.
25. Delvaux M. Role of visceral sensitivity in the pathophysiology of irritable bowel syndrome. *Gut,* 2002;51(suppl 1):i67-i71.
26. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA,* 2004;292:852-858.
27. Schoenfeld P. Efficacy of current drug therapies in irritable bowel syndrome: what works and does not work. *Gastroenterol Clin North Am,* 2005;34:319-335, viii.
28. Camilleri M, Mayer EA, Drossman DA, et al. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT3 receptor antagonist. *Aliment Pharmacol Ther,* 1999;13:1149-1159.
29. DuPont AW, DuPont HL. Travelers' diarrhea: modern concepts and new developments. *Curr Treat Options Gastroenterol,* 2006;9:13-21.
30. Baker DE. Rifaximin: a nonabsorbed oral antibiotic. *Rev Gastroenterol Disord,* 2005;5:19-30.
31. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med,* 2005;142:805-812.
32. Taylor DN, McKenzie R, Durbin A, et al. Rifaximin, a nonabsorbed oral antibiotic, prevents shigellosis after experimental challenge. *Clin Infect Dis,* 2006;42:1283-1288.
33. Ericsson C, DuPont H, Mathewson J, West M, Johnson P, Bitsura J. Treatment of traveler's diarrhea with sulfamethoxazole and trimethoprim and loperamide. *JAMA,* 1990;263:257-261.
34. Steffen R, Sack DA, Riopel L, et al. Therapy of travelers' diarrhea with rifaximin on various continents. *Am J Gastroenterol,* 2003;98:1073-1078.
35. DuPont HL, Ericsson CD, Mathewson JJ, et al. Rifaximin: a nonabsorbed antimicrobial in the therapy of travelers' diarrhea. *Digestion,* 1998;59:708-714.
36. DuPont HL, Jiang ZD, Ericsson CD, et al. Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect Dis,* 2001;33:1807-1815.
37. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol,* 2003;98:412-419.
38. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol*, 2000;95:3503-3506.
39. Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of irritable bowel syndrome: a randomized trial. *Ann Intern Med,* 2006;145:557-563.