

ORIGINAL ARTICLE

Food patch testing for irritable bowel syndrome

Michael B. Stierstorfer, MD,^{a,b} Christopher T. Sha, BS,^b and Marvin Sasson, MD^a
North Wales and Philadelphia, Pennsylvania

Background: The traditional classification of irritable bowel syndrome (IBS) as a functional disorder has been challenged in recent years by evidence of ongoing low-grade gastrointestinal tract inflammation. Inflammation may alter gastrointestinal motility and thus be central to the pathogenesis of IBS. Many foods and food additives are known to cause allergic contact dermatitis. We hypothesize that allergenic foods and food additives may elicit a similar allergic reaction in the gastrointestinal tract, giving rise to symptoms suggestive of IBS.

Objective: We sought to determine whether skin patch testing to a panel of foods and food additives may identify food allergens that may be responsible for symptoms of IBS.

Methods: We performed skin patch testing to common allergenic foods and food additives on individuals with a history of or symptoms suggestive of IBS. We used patch test–guided avoidance diets to determine whether avoidance alleviates IBS symptoms.

Results: Thirty of the 51 study participants showed at least 1 doubtful or positive patch test result. Fourteen of the participants reported symptomatic improvement, ranging from slight to great, upon avoidance of the foods/food additives to which they reacted.

Limitations: Double-blind study design, inclusion of only patients with active IBS, larger sample size, more balanced gender distribution, testing of more foods/food additives, and longer duration of and more precise quantification of response to dietary avoidance are suggested for future studies.

Conclusion: Allergic contact enteritis to ingested foods, food additives, or both may contribute to IBS symptoms. Patch testing may be useful in identifying the causative foods. (J Am Acad Dermatol 10.1016/j.jaad.2012.09.010.)

Key words: allergic contact dermatitis; allergic contact enteritis; food patch testing; functional bowel disorder; gastrointestinal dysmotility; irritable bowel syndrome; type-4 hypersensitivity.

Approximately 10% of the population in Western countries carries a diagnosis of irritable bowel syndrome (IBS),¹ characterized by unexplained abdominal discomfort or pain associated with changes in bowel habits.² The origin of IBS is unknown but traditionally has been classified as a functional gastrointestinal disorder with visceral hypersensitivity, gastrointestinal motor disturbances, and significant psychologic overlay.^{1,3}

This classification has been challenged in recent years by evidence of ongoing low-grade gastrointestinal tract inflammation in IBS.^{4,5} A

change in peripheral cytokine profiles in IBS has been observed, with an abnormal interleukin 10/12 ratio suggesting a proinflammatory state.⁶ Whether inflammation can alter gastrointestinal motility is an area of active research. Studies have demonstrated that a large array of inflammatory mediators is able to alter neuromuscular function and that inflammation is able to induce persistent neuromuscular dysfunction in the gastrointestinal tract.^{7,8}

These observations suggest the label “functional” is perhaps inappropriate and instead point to inflammation as central to the pathogenesis of IBS, and raise

From East Penn Dermatology PC, North Wales,^a and University of Pennsylvania School of Medicine, Philadelphia.^b

Funding sources: None.

Disclosure: Dr Stierstorfer has submitted a patent application to the US Patent and Trademark Office for food and food additive skin patch testing for irritable bowel syndrome and undifferentiated gastrointestinal disease. Mr Sha and Dr Sasson have no conflicts of interest to declare.

Accepted for publication September 3, 2012.

Reprint requests: Michael B. Stierstorfer, MD, East Penn Dermatology PC, 311 N Sumneytown Pike, Suite 1E, North Wales, PA 19454. E-mail: mstierstorfer@eastpennnderm.com.

Published online October 24, 2012.

0190-9622/\$36.00

© 2012 by the American Academy of Dermatology, Inc.

<http://dx.doi.org/10.1016/j.jaad.2012.09.010>

the question as to the source of the inflammation. About 50% of individuals with IBS report that foods aggravate their symptoms,⁹ bringing into question the role of foods in this process.

Many foods and food additives are known to cause allergic contact dermatitis (type-4 hypersensitivity).¹⁰ Many of these are ubiquitous in the average American diet. We speculate that allergenic foods and food additives may elicit a similar allergic reaction in the gastrointestinal tract in some individuals, resulting in allergic contact enteritis, and giving rise to symptoms suggestive of IBS.

We performed skin patch testing to common foods and food additives known to cause allergic contact dermatitis (Table 1) on individuals with physician-diagnosed IBS or symptoms suggestive of IBS. Participants who demonstrated 1 or more doubtful or positive patch test results were placed on an avoidance diet for 1 week, avoiding the food(s)/food additive(s) to which they reacted, to determine whether avoidance of the suspect allergen(s) alleviated their gastrointestinal symptoms.

METHODS

Inclusion criteria

Criteria for participation in the study included individuals with physician-diagnosed IBS (32 individuals) and others with gastrointestinal symptoms of unknown origin (19 individuals) (Fig 1) adapted from the Rome II IBS diagnostic criteria.¹

Exclusion criteria

Study participants were at least 18 years of age. Other exclusion criteria were: pregnancy, severe rash, active treatment with immunosuppressive drugs including oral corticosteroids, known allergy to adhesive tape or to any of the food allergens used in the study, or other known cause for the symptoms.

Study design

The methodology and informed consent for this study were formally reviewed and approved by an accredited institutional review board. Study participants were recruited from a private dermatology practice during routine visits via a voluntary questionnaire. Informed consent was obtained. Participants were paid \$75 upon successful

completion of the patch testing. Allergens consisted of raw vegetables and commercially available food allergens (manufactured by Chemotechnique Diagnostics, Vellinge, Sweden, and distributed by Dormer Laboratories, Rexdale, Ontario, Canada).

Testing involved 3 visits to the office on day 1, day 3, and either day 4 or 5. The tests were conducted as follows.

Day 1: Using standard skin patch test procedure,¹⁰ small slices of raw vegetables, carefully prepared to avoid cross-contamination, and commercially prepared common food flavoring and preservative allergens in petrolatum were placed in inert polyethylene plastic chambers and secured with hypoallergenic adhesive tape to the upper aspect of the back.

Day 3: The tape and chambers containing the food and food additive allergens were removed and the patch test sites were outlined

with a nonpermanent marking pen. The first patch test readings were recorded immediately. Two board-certified dermatologist investigators performed the patch test readings. The grading system used was that advocated by the North American Contact Dermatitis Group.¹⁰

Day 4 or 5: The investigators read the patch test sites for the final time. Photographic documentation was recorded for some cases.

Results were tabulated using the day-4 (72-hour) or day-5 (96-hour) patch test readings. Participants who had 1 or more doubtful or positive patch test results were given information sheets for the allergens in question and instructed to avoid ingestion of these allergens for 1 full week. A brief follow-up outcome questionnaire was distributed (see below). Participants were instructed to complete and return the questionnaire after completion of the 1-week avoidance diet.

Questionnaire

Dear Food Patch Test Study Participant,

As you know, you had 1 or more allergic skin reactions to foods and/or food additives in the patch test study you recently completed. As such, you were given information how to avoid the foods/food additives to which you demonstrated an allergic reaction and asked to voluntarily restrict your diet to avoid these foods/additives for 1 week.

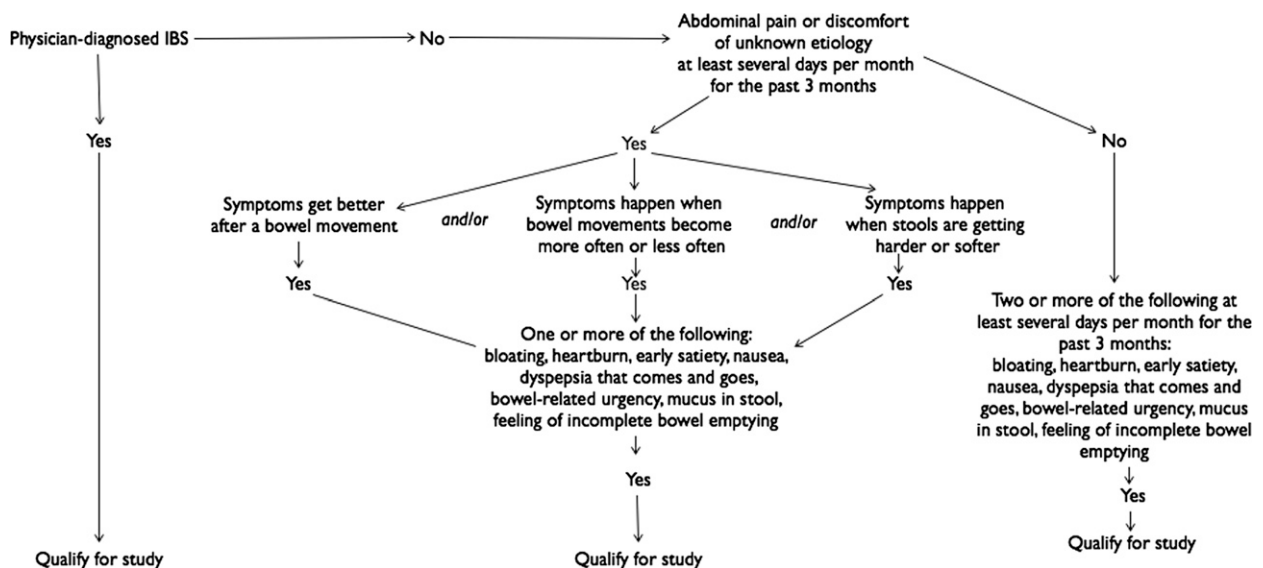
CAPSULE SUMMARY

- Irritable bowel syndrome (IBS) is a common gastrointestinal condition of uncertain origin, characterized by abdominal discomfort or pain associated with changes in bowel habits.
- Food-related type-4 hypersensitivity reactions in the gut may contribute to the pathogenesis of IBS and IBS-like symptoms in some individuals.
- Food and food additive skin patch testing may be a useful diagnostic tool to identify allergens that, with dietary avoidance, may alleviate IBS symptoms.

Table I. Patch test allergens

Raw vegetables	Flavorings/natural food components	Additives/preservatives
Garlic	Vanillin 10%	Sodium benzoate 5%
Onion	Eugenol 2%	2,6-Di-tert-4-cresol (BHT) 2%
Artichoke	Isoeugenol 2%	2-Tert-butyl-4-methoxyphenol (BHA) 2%
Asparagus	Menthol 2%	Sorbic acid 2%
Carrot	Cinnamic alcohol 2%	Benzoic acid 5%
Celery	Cinnamic aldehyde 1%	Propionic acid 3%
Chicory	Anethole 5%	Octyl gallate 0.25%
Chives	Dipentene (limonene) 1%	Benzoyl peroxide 1%
Corn	Nickel sulfate hexahydrate 2.5%	Propyl gallate 1%
Cucumber	Balsam of Peru 25%	Dodecyl gallate 0.25%
Endive	Sesquiterpene lactone mix 0.1%	Propylene glycol 5%
Horseradish	Diallyl disulfide 1%	Paraben mix 16%
Leek		DL-alpha-tocopherol acetate 10%
Lettuce		Wool alcohol 30%

First 18 participants were tested to 28 allergens (garlic, onion, and all allergens listed in columns 2 and 3). Last 33 participants were tested to all allergens listed. All raw vegetables were tested as is. All other allergens were commercially prepared, and were tested in petrolatum vehicle in concentrations listed.

**Fig 1.** Inclusion criteria for study participation. IBS, Irritable bowel syndrome.

As follow-up to the study, it would be helpful if you could answer a few other questions: (Circle the correct answer.)

1. Were you able to follow the avoidance diet for a week? Yes No
2. If you answered "yes" to question 1, which foods/food additives did you avoid? (Please list.)
3. If you answered "yes" to question 1, did you notice improvement in your gastrointestinal symptoms? Yes No
4. Was your improvement slight, moderate, or much? (Circle one.)

RESULTS

In all, 51 symptomatic (46 female, 5 male; age 18-88 years) participants completed the patch testing.

For the purposes of this study, where there was discordance in the patch test interpretation between the 2 investigators, the more positive interpretation was used for purposes of the 1-week allergen avoidance diet. There was discordance in the interpretation in 29 patches of a total of 1824 individual patch interpretations (1.6% of the readings).

Results of the patch testing and dietary avoidance are summarized in Table II. Of 51 participants, 19 (37.3%) had no reactions; 30 (58.8%) had at least 1 doubtful or positive reaction; and 2 (3.9%) had an irritant reaction. Overall, there were 21 doubtful

Table II. Patch test and dietary avoidance results

Participant	Age, y	Sex	Physician-diagnosed IBS	No. of allergens tested	Allergen(s)/patch test results	Response to allergen dietary avoidance
1	63	Female	Yes	40	Isoeugenol ++	N
2	42	Female	Yes	40	Nickel ++	G
3	50	Female	No	28	Limonene ++	G
4	61	Female	No	28	Garlic +	G
5	36	Female	Yes	28	Benzoyl peroxide + Onion ? Octyl gallate ?	N
6	33	Female	Yes	28	Nickel ++	M
7	53	Female	Yes	28	Dodecyl gallate ++	S
8	63	Female	Yes	40	Balsam of Peru ?	DNF
9	67	Male	Yes	40	Garlic IR	NA
10	66	Male	No	40	Garlic + Artichoke + Asparagus +	S
11	82	Female	Yes	40	Sodium benzoate ? 2,6-Di-tert-butyl-4-cresol (BHT) ? Menthol ?	DNF
12	67	Female	No	28	Garlic ?	N
13	59	Female	No	28	Garlic ?	DNF
14	72	Female	No	40	Paraben mix +	N
15	47	Female	Yes	40	Benzoyl peroxide + Celery ? Dodecyl gallate + Asparagus +	DNF
16	67	Female	Yes	40	Sodium benzoate +	N
17	88	Female	No	40	Octyl gallate +	S
18	69	Female	No	40	Balsam of Peru + Artichoke ? Asparagus + Garlic +	N
19	51	Female	Yes	40	Isoeugenol ? Cinnamic alcohol ? Octyl gallate ? Benzoyl peroxide +	M
20	63	Female	Yes	40	NR	NA
21	74	Female	No	40	Garlic ++ Benzoyl peroxide + Diallyl disulfide + Asparagus + Horseradish + Chives +	N
22	64	Female	Yes	40	Sodium benzoate ?	M
23*	28	Female	Yes	40	Nickel + Artichoke + Garlic ?	N M M
24	36	Female	Yes	40	Nickel ++	N
25*	59	Female	Yes	40	Garlic ? Asparagus + Garlic ?	M N M
26	58	Female	Yes	40	Octyl gallate ? Nickel +	M
27	20	Female	Yes	40	NR	M
28	46	Female	Yes		NR	NA
29	63	Female	Yes		NR	NA
30	68	Female	Yes	40	Garlic + Balsam of Peru ?	M

Continued

Table II. Cont'd

Participant	Age, y	Sex	Physician-diagnosed IBS	No. of allergens tested	Allergen(s)/patch test results	Response to allergen dietary avoidance
31	38	Female	Yes	28	NR	NA
32	56	Male	Yes	28	NR	NA
33	47	Female	Yes	40	NR	NA
34	46	Female	No	40	NR	NA
35	80	Male	Yes	28	NR	NA
36	84	Female	Yes	28	NR	NA
37	55	Female	Yes	40	NR	NA
38	58	Female	No	40	NR	NA
39	72	Female	Yes	40	NR	NA
40	53	Female	Yes	28	NR	NA
41	71	Female	Yes	28	NR	NA
42	59	Female	No	40	Balsam of Peru ?	DNF
43	65	Female	No	28	NR	NA
44	57	Female	No	40	2-Tert-butyl-4-methoxyphenol (BHA) ?	N
45	52	Female	No	40	NR	NA
46	75	Female	Yes	40	Nickel IR	NA
47	68	Female	No	28	Garlic + Onion +	DNF DNF
48	37	Female	Yes	28	NR	NA
49	18	Female	No	28	NR	NA
50	55	Male	No	40	Sodium benzoate +	DNF
51	52	Female	No	28	NR	NA

DNF, Did not finish dietary avoidance; G, great improvement; IBS, irritable bowel syndrome; IR, irritant reaction; M, moderate improvement; N, no improvement; NA, not applicable; NR, no reaction; S, slight improvement; ?, doubtful reaction; +, weak reaction; ++, strong reaction. *Participants 23 and 25 avoided allergenic foods individually rather than simultaneously and reported moderate improvement as noted. They are included in moderate improvement group of responders.

patch test results (21/1824 total patch tests = 1.2%) and 35 positive patch test results (35/1824 total patch tests = 1.9%). Twelve participants had more than 1 doubtful or positive test result.

Of the 30 participants who had at least 1 doubtful or positive patch test result, 9 reported no improvement, 3 slight improvement, 8 moderate improvement, and 3 great improvement with dietary avoidance. Seven did not finish the dietary avoidance phase and are included with the nonresponders. Except where noted in the table, participants with more than 1 doubtful or positive reaction avoided all suspect foods simultaneously.

DISCUSSION

IBS is a chronic gastrointestinal condition affecting about 10% of people in the United States and many more worldwide.¹ Age of onset typically is adolescence or early adulthood. Females are affected more often than males. Its socioeconomic burden is high because of absenteeism from work and school, lost productivity, and decreased quality of life, affecting many normal daily activities.¹¹ Medical costs are estimated to be \$1.7 to \$10 billion annually in the United States, with indirect costs such as loss of worker productivity estimated at \$20 billion.¹² Most

treatments (eg, laxatives, antidepressants, antispasmodics, and bulking agents) remain largely based on symptomatic rather than disease-modifying therapy and generally have low efficacy and tolerability.¹²

The diagnosis of IBS may be made on clinical grounds alone. Often, however, consultation and diagnostic testing (endoscopic, radiologic, laboratory) are overused when evaluating these patients.¹³ “Red flags” such as weight loss, gastrointestinal bleeding, anemia, fever, frequent nocturnal symptoms, or age of onset older than 50 years should prompt a search for organic causes.

The underlying causes of IBS remain unknown. Current considerations include postinfectious, serotonin dysregulation, bacterial overgrowth, central dysregulation, and a genetic predisposition.¹⁴ Consideration of the role of foods in IBS generally has been given low priority. There has been intense scrutiny of food allergies in recent consensus guidelines issued by the National Institute of Allergy and Infectious Diseases (NIAID) but the focus largely has been directed at immediate hypersensitivity (type-1) reactions.¹⁵ IgE-mediated food allergy has been suggested in a subset of patients with diarrhea-predominant IBS and a history of atopy.¹⁶ In another study, comparing elimination diets guided by IgG

food antibody levels versus random control elimination diets, significantly better symptom relief was demonstrated in the former group despite the fact that IgG antibodies to foods are commonly observed and traditionally thought to be physiologic.¹⁷ These observations notwithstanding, there has been insufficient evidence that food allergy testing or exclusion diets are efficacious and they are not routinely recommended for IBS.^{16,18}

There is a well-described entity in the pediatric population, food protein–induced enterocolitis syndrome. It is a disease of infants and young children, characterized by emesis, diarrhea, and failure to thrive, and thought to be caused by a non-IgE-mediated food allergy. Researchers claim food patch testing useful and, other than oral food challenge, the only testing available for this syndrome.¹⁹ Infants typically outgrow this condition at an early age.

Eosinophilic esophagitis is a chronic condition occurring at any age, characterized histologically by eosinophilic infiltration, and suspected to be of mixed IgE- and non-IgE-mediated mechanisms. Food allergens may play a role in its pathogenesis and serum IgE testing, skin prick testing, and food patch testing may be helpful in identifying a potential cause. The usefulness of these tests in other rarer chronic eosinophilic gastrointestinal diseases has not been established.¹⁵

To our knowledge, allergic contact enteritis (type-4 hypersensitivity) has not been addressed formally in the pathogenesis of IBS. The recent guidelines for the diagnosis and management of food allergy issued by NIAID advised against the use of food patch testing to diagnose food allergy with the exception of contact dermatitis because of insufficient evidence to support its use.¹⁵ Contrarily, patch testing in our study suggests a possible significant role for food/food additives and type-4 hypersensitivity in the pathogenesis of at least some individuals with IBS or IBS-like symptoms. Thirty of 51 (58.8%) participants had at least 1 doubtful or positive patch test result. Of these 30, 14 benefited (3 slight improvement, 8 moderate improvement, 3 great improvement) when avoiding the food(s)/food additive(s) in question. Overall, 14 of the 51 (27.5%) study participants experienced slight, moderate, or great symptomatic relief by identification of food and/or food additive type-4 allergy by patch testing with subsequent dietary avoidance (Fig 2).

We hypothesize the same type-4 reaction being demonstrated on the skin is occurring in the gut; ie, a type-4 allergic contact enteritis, resulting in chronic inflammation as observed in recent studies^{4,5} with consequent altered gut motility and gastrointestinal symptoms that may mimic IBS.

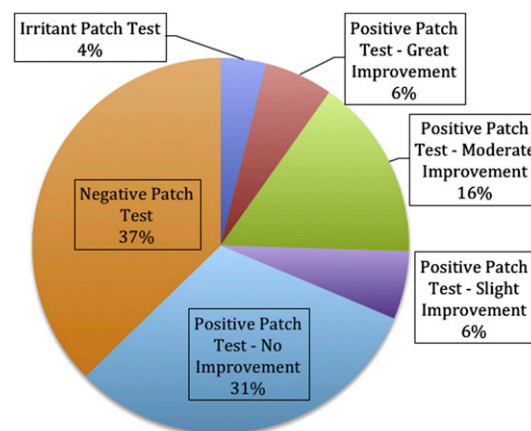


Fig 2. Impact of food patch testing and dietary avoidance on gastrointestinal symptoms in all study participants. Doubtful patch test (macular erythema) results are included with positive patch test results. Group with positive patch test result and no improvement includes participants who did not complete dietary avoidance phase.

A recent study demonstrated some efficacy of the antibiotic rifaximin for diarrhea-predominant IBS.²⁰ This study supports previous observations that bacterial overgrowth¹⁴ contributes to IBS, with rifaximin offering relief by reducing bacterial counts. The authors question the conditions that allow for bacterial overgrowth. We submit that allergic contact enteritis is 1 condition that alters gut motility and thus may allow for bacterial overgrowth in some patients with IBS.

In our study, there did not seem to be a strong correlation between the degree of patch test result positivity and the degree of symptomatic improvement with dietary avoidance. A variety of confounding variables including but not limited to concomitant hypersensitivity to foods not tested in this study, variable discordance between skin and gut hypersensitivity, variable thresholds for inflammation in the gut to affect motility, variable degrees of motility disturbance to cause symptoms, and/or other pathophysiologic mechanisms, may account for this observation.

The food showing the highest prevalence of patch test result positivity was garlic (5 doubtful reactions, 5 weak reactions, 1 strong reaction) (Table III). Garlic also is known to be a skin irritant but, of the reactions observed by both experienced clinicians reading the patch tests, only 1 reading was deemed irritant with the remaining 11 thought to be of an allergic contact nature. Other foods of the Alliaceae family that were tested (chives, onion, and leeks) showed very few reactions (Table III), and there was just 1 case of cross-reactivity between garlic and onion, despite both sharing the allergen diallyl disulfide.¹⁰ In addition, only 1 participant showed a positive skin test result to both garlic and diallyl

Table III. Patch test allergens with corresponding numbers of patch test reactions

Allergen	NR	?	+	++	Irritant
Garlic	39	5	5	1	1
Onion	49	1	1	0	0
Vanillin	51	0	0	0	0
Eugenol 2%	51	0	0	0	0
Isoeugenol 2%	49	1	0	1	0
Sodium benzoate 5%	47	2	2	0	0
2,6-Di-tert-butyl-4-cresol (BHT) 2%	50	1	0	0	0
Menthol 2%	50	1	0	0	0
Cinnamic alcohol 2%	50	1	0	0	0
Cinnamic aldehyde (Cinnamyl) 1%	51	0	0	0	0
2-Tert-butyl-4-methoxyphenol (BHA) 2%	51	0	0	0	0
Anethole 5%	51	0	0	0	0
Sorbic acid 2%	51	0	0	0	0
Benzoic acid 5%	50	1	0	0	0
Propionic acid 3%	51	0	0	0	0
Octyl gallate 0.25%	47	3	1	0	0
Dipentene (limonene) 1%	50	0	1	0	0
Benzoyl peroxide 1%	45	1	5	0	0
Propyl gallate 1%	51	0	0	0	0
Dodecyl gallate 0.25%	49	0	1	1	0
Nickel sulfate hexahydrate 2.5%	45	0	2	3	1
Propylene glycol 5%	51	0	0	0	0
Paraben mix 16%	50	0	1	0	0
Balsam of Peru 25%	48	2	1	0	0
Sesquiterpene lactone mix 0.1%	51	0	0	0	0
DL-alpha-tocopherol acetate 10%	51	0	0	0	0
Wool alcohol 30%	51	0	0	0	0
Diallyl disulfide 1%	50	0	1	0	0
Artichoke	29	1	3	0	0
Asparagus	29	0	4	0	0
Carrot	33	0	0	0	0
Celery	31	2	0	0	0
Chicory	33	0	0	0	0
Chives	31	1	1	0	0
Corn	33	0	0	0	0
Cucumber	33	0	0	0	0
Endive	33	0	0	0	0
Horseradish	32	0	1	0	0
Leek	33	0	0	0	0
Lettuce	33	0	0	0	0

NR, No reaction; ?, doubtful reaction; +, weak reaction; ++, strong reaction.

disulfide despite the latter being viewed as the usual garlic allergen.¹⁰ These observations suggest other garlic allergens such as allyl propyl disulfide and allicin also may play prominent roles in its allergenicity. Two subjects with doubtful and positive garlic patch test results, respectively, incidentally reported only raw garlic ingestion was problematic, whereas cooked or other forms of garlic were not, suggesting 1 or more garlic allergens may be denatured, thus losing allergenicity, by cooking or other processing.

Given its ubiquity in American and many international cuisines, we suggest garlic may be responsible for many cases of so-called irritable bowel syndrome around the world. Moreover, any food or food additive capable of eliciting type-4 hypersensitivity should be viewed as a potential cause of IBS in an appropriately sensitized individual. This study demonstrates 10 distinct foods and food additives that showed doubtful or positive patch test results (Table II) and that, when excluded from the diet, resulted in varying and at times substantial improvement in IBS-like symptoms.

Thus, in this proof-of-concept case series, we provide evidence that food-related type-4 hypersensitivity should be considered in the pathogenesis of IBS and chronic undifferentiated IBS-like symptoms. Furthermore, we demonstrate a diagnostic tool, skin patch testing, to detect the allergens responsible. If our observations are supported by further study, food/food additive patch testing may provide a valuable addition to the evaluation and treatment of patients with symptoms of IBS. In essence, once again, the skin may be providing a window for the diagnostician to peer “inside.” Indeed, a diagnosis of allergic contact enteritis may be more appropriate for some individuals with IBS-like symptoms. With refinement, such testing may reduce the use of more costly, more invasive endoscopic, radiologic, and laboratory testing and establish dietary avoidance as a viable treatment modality for these individuals.

The authors thank Katherine S. Fields, MD, Bruce Brod, MD, and Joel Gelfand, MD, for their invaluable review of and suggestions for the manuscript.

REFERENCES

1. Talley N, Spiller RC. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002;360:555-64.
2. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. In: Drossman DA, Corazziari E, Delvaux M, Spiller RC, Talley NJ, Thompson WG, et al, editors. *Rome III: The functional gastrointestinal disorders*. McLean, Virginia: Degnon Associates; 2006. pp. 487-509.
3. Thompson WG, Longstreth GL, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999;45(Suppl II):II43-7.
4. Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, Wilson I. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002;122:1778-83.
5. Tornblom H, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. *Gastroenterology* 2002;123:1972-9.
6. O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005;128:541-51.
7. Collins SM. Is the irritable gut an inflamed gut? *Scand J Gastroenterol* 1992;192(Suppl):102-5.

8. Vergnolle N. Modulation of visceral pain and inflammation by protease-activated receptors. *Br J Pharmacol* 2004;141:1264-74.
9. Ragnarsson G, Bodemar G. Pain is temporally related to eating but not to defecation in the irritable bowel syndrome (IBS): patients' description of diarrhea, constipation and symptom variation during a prospective 6-week study. *Eur J Gastroenterol Hepatol* 1998;10:415-21.
10. Rietschel RL, Fowler JF Jr. Fisher's contact dermatitis. Hamilton, Ontario (Canada): BCDecker; 2008. pp. 11-28, 324-8, 566-75.
11. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion* 1999;60:77-81.
12. Hulisz D. The burden of illness of irritable bowel syndrome: current challenges and hope for the future. *J Manag Care Pharm* 2004;10:299-309.
13. Holten KB, Wetherington A, Bankston L. Diagnosing the patient with abdominal pain and altered bowel habits: is it irritable bowel syndrome? *Am Fam Physician* 2003;67:2157-62.
14. Talley NJ. Irritable bowel syndrome. *Intern Med J* 2006;36:724-8.
15. Boyce JA, Arshad SA, Assa'ad A, Bahna SL, Beck LA, Burks AW, et al. Guidelines for the diagnosis and management of food allergy. *J Allergy Clin Immunol* 2010;126:S1-58.
16. Petitpierre M, Gumowski P, Girard JP. Irritable bowel syndrome and hypersensitivity to food. *Ann Allergy* 1985;54:538-40.
17. Atkinson W, Sheldon T, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut* 2004;53:1459-64.
18. Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, et al. An evidence-based systematic review on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;104(Suppl):S1-35.
19. Fogg MI, Brown-Whitehorn TA, Pawlowki NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. *Pediatr Allergy Immunol* 2006;17:351-5.
20. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011;364:22-32.