

FEATURED ARTICLE

Utility of Food Patch Testing in the Evaluation and Management of Irritable Bowel Syndrome

Grace H. Shin MD^a, Michael S. Smith MD MBA^b, Butros Toro MD^c, Adam C. Ehrlich MD MPH^a, Sanjana Luther MD^c, Deena Midani MD^a, Inki Hong MD^c, Michael Stierstorfer MD^{d,e,f}

^aSection of Gastroenterology, Department of Medicine, Lewis Katz School of Medicine at Temple University

^bSection of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai

^cLewis Katz School of Medicine at Temple University

^dEast Penn Dermatology, PC

^eUniversity of Pennsylvania School of Medicine

^fIBS Centers for Advanced Dermatology Food Allergy Testing, LLC

ABSTRACT

Background. Irritable Bowel Syndrome (IBS) is a functional gastrointestinal (GI) disorder of unknown etiology.

Objective. We sought to investigate whether specific type 4 food allergens identified by skin patch testing, when eliminated from the diet, alleviate symptoms of IBS.

Methods. In this case series, skin patch testing was performed on 60 IBS patients using an extensive panel of type 4 food allergens after which food avoidance diets directed by the patch test results were implemented. Questionnaires assessing abdominal pain/discomfort and global improvement in IBS symptoms were used to assess one month and three or more month outcomes.

Results. There were statistically significant improvements in abdominal pain/discomfort and in global IBS symptoms after one month and again at an average of 7.6 months of patch test-guided food avoidance.

Conclusions. Sustained improvement with avoidance of type 4 food allergens identified by skin patch testing suggests a role for delayed-type food hypersensitivities in the pathogenesis of some cases of IBS. A subset of patients whose IBS symptoms resolve completely may be better characterized as having a newly proposed disease, allergic contact enteritis (ACE).

INTRODUCTION

Irritable Bowel Syndrome (IBS) is the most common gastrointestinal (GI) disorder presenting to a primary care office, accounting for up to 50% of visits associated with a GI problem¹. It is characterized by abdominal pain coinciding with altered stool form or frequency, with a complex microbiome-brain-gut axis². Despite the high prevalence of IBS, its pathophysiology is not fully understood and patients often undergo a variety of tests to rule out other diseases prior to being diagnosed with IBS.

Recent observations of the pathophysiology of IBS suggest various causes for the symptoms³. Mounting evidence points to the presence of inflammation in the intestinal lining and proinflammatory mediators in the bloodstream in many individuals with IBS symptoms^{4,5,6}. An association of IBS in some individuals with quiescent inflammatory bowel disease or post-infectious gastroenteritis⁷ also supports a role for inflammation, but most IBS sufferers have had neither. Furthermore, there has been increased interest in looking at the potential inflammatory effects of food in the GI tract^{8,9,10}, as up to 50% of IBS sufferers report that foods aggravate their symptoms¹¹. The preponderance of investigation of food allergy in IBS has focused on the antibody-mediated humoral (type 1, 2 and 3 allergy) arm of the immune system. Both a landmark consensus report considering all aspects of food allergy¹² issued by the National Institutes of Allergy and Infectious Disease and a comprehensive position statement on IBS management¹³ by an American College of Gastroenterology task force fail to invoke an immunologic mechanism for the pathogenesis of IBS, by default suggesting a

poorly understood non-immunologic mechanism for food intolerance.

In contradistinction to skin prick and scratch tests, antibody assays and other serologic tests used to investigate humoral immunity, skin patch testing is a common dermatologic procedure used to investigate the cell-mediated (type 4 allergy) arm of the immune system. Patch testing is routinely employed to detect causes of allergic contact dermatitis, a T lymphocyte-mediated type 4 eczematous allergic reaction in the skin. Many foods have the potential to cause allergic contact dermatitis¹⁴. A proof-of-concept case series in 2013 used food patch testing to investigate a role for a cell-mediated immune mechanism in IBS¹⁵. In that study, 27% of the 51 individuals with IBS symptoms benefited from limited type 4 food allergen patch testing and subsequent dietary avoidance of the foods identified by the testing.

By performing skin patch testing with an expanded panel of type 4 food allergens on patients with physician-diagnosed IBS and/or who fulfill the Rome III criteria¹⁶, followed by assessment of their IBS symptoms one month and again three or more months after implementation of an elimination diet guided by the patch test results, our study further probes the question whether food-related type 4 hypersensitivities may cause IBS symptoms.

METHODS

This prospective case series was conducted in a secondary care community-based setting. All participants were self-referred over a 36 month period, had physician-

diagnosed IBS and/or met the Rome III criteria for IBS and presented expressly for the food patch testing on a fee-for-service basis. IBS subtype was determined upon presentation by self-reported historically predominant symptom. Duration of IBS symptoms was self-reported and was rounded to the nearest year for purposes of data collection. If duration was reported as a range of years, the average between the shorter and longer estimate was used and if reported as “at least X” years, “X” was the duration used for data collection. Patients who were pregnant; were known to have an allergy to adhesive tape or any of the food allergens used in the study; had a severe skin rash; had symptoms that had a known cause other than IBS; or were on active

treatment with any systemic immunosuppressive medications were excluded from the study.

Skin patch testing was initiated using an extensive non-FDA-approved panel of 117 to 121 type 4 food allergens (Table 1) identified in the literature¹⁴, most utilizing standard formulations¹⁷ or available from reputable patch test manufacturers (Brial Allergen GmbH, Greven, Germany; Chemotechnique Diagnostics, Vellinge, Sweden). The freeze-dried vegetable formulations were derived from unpublished data. Standard skin patch test procedure protocols¹⁴ were used affixing the patches to the upper aspect of the back.

Table 1. Type 4 food allergens used in the patch testing and the total number of questionable or positive reactions for each allergen at 72 or 96 hours.

Allergen	# of positive results	Allergen	# of positive results
1-Malic acid	1	Formic acid	1
2-tert-Butyl-4-methoxyphenol (BHA)	1	Garlic	0
Acetoin	0	Garlic powder	1
Aconitic acid	0	Geraniol	0
Almond oil	0	Geranyl acetate	1
Amaranth (Red #2)	5	Ginger oil	1
Anethole	0	Glyceryl tributyrates	0
Anise seed oil	0	Green food color (Yellow #5, Blue #1)	2
Arabic gum	0	Guar gum	0
Artichoke	0	Horseradish	28
Asparagus	2	Hydroxycitronellal	0
Aspartame	1	Isoeugenol	2
Azorubine	3	Karaya gum	1
Balsam of Peru	6	Leeks	1
Bay leaf oil	3	Lettuce	1
Beeswax	0	Linalyl acetate	0
Benzaldehyde	1	Menthol	1
Benzoic acid	7	Methyl anthranilate	0
Benzoin gum	0	Mushroom	4
Benzoyl peroxide	25	Nickel sulfate hexahydrate	8
Benzyl benzoate	0	Octyl gallate	11
Blue food color	0	Oil of bergamot	0

Table 1 (Continued)

(Blue #1)			
Brilliant black	0	Oil of chamomile	1
Calcium disodium EDTA	0	Oil of cinnamon	1
Capsicum	1	Oil of clove	1
Caraway oil	0	Oil of eucalyptus	0
Carmine	29	Oil of rose	0
Carnauba wax	1	Oil of rosemary	0
Carrot	0	Onion	1
Carrot seed oil	0	Paraben mix	2
Carvone	1	Patent blue	1
Acetaldehyde	0	Pectin	0
Celery	1	Pinene alpha	2
Chicory	0	Polysorbate 80	2
Chives	0	Potassium bromate	3
Chlorophyll	0	Potassium sorbate	2
Allyl isothiocyanate	0	Propionic acid	0
Cinnamic aldehyde	1	Propyl gallate	1
Cinnamon bark oil	36	Quinolone yellow	0
Citral	1	Red food color (Red #3, Red #40)	7
Citric acid	1	Saccharin	1
Citronellal	0	Salicylaldehyde	0
Aluminum sulfate	0	Sesame oil	0
Corn	1	Sesquiterpene lactone mix	1
Coumarin	1	Sodium benzoate	1
Cucumber	1	Sodium bisulfate	8
D Limonene	1	Sodium bisulfite	27
DL-alpha-Tocopherol	0	Sodium diphosphate	0
Dodecyl gallate	6	Sodium glutamate	1
Endive	2	Sodium nitrite	2
Erythrosin (Red #3)	2	Sorbic acid	2
Ethyl acetate	0	Strawberry aldehyde	2
Ethyl butyrate	1	Tartrazine	0
Ethyl vanillin	1	Tomato	2
Vanilla extract	1	Vanillin	0
Eucalyptol	0	Wool alcohol	2
Eugenol	0	Yellow food color (Yellow #5)	0
2,6-di-tert-Butyl-4-cresol (BHT)	1	Polysorbate 60	1
Butyric acid	0	Propylene glycol	0
Diallyl disulfide	0	Terpineol alpha	0
Nutmeg	0		

of Positive Results, all patch test results that were questionable or positive by standard patch test reading convention.¹⁸

Following patch test application on Day 1, two follow up visits occurred on Day 3 and either Day 4 or 5. On Day 3, patches were removed and the initial results were read by one board-certified dermatologist according to a standard grading system¹⁸.

Interpretation of patch tests included no reaction; questionable reaction consisting of macular erythema; weak reaction consisting of erythema and slight edema; or strong reaction consisting of erythema and marked edema. On Day 4 or 5, the final patch test reading was performed to account for delayed reactions up to 96 hours. Patients were informed of the results and advised to avoid ingestion of all foods that elicited a questionable or positive patch test response, with information about the foods distributed and reviewed.

Those with questionable or positive patch tests at 72 or 96 hours were invited to participate in an Investigational Review Board (IRB)-approved study by completing a questionnaire (Chart 1) that assessed both compliance with dietary avoidance and response of gastrointestinal symptoms to these changes. Abdominal pain/discomfort was assessed at baseline and at one month with the difference at these two junctures used to measure effect of dietary avoidance on these symptoms. Global IBS symptom improvement at one month was assessed by a single 0 to 10 self-rated scale. The questionnaire was to be completed and returned by each patient along with the questionnaire informed consent after avoidance of the identified allergens for one month. Patients received \$20 compensation for completion and return of both.

A second IRB-approved long term follow-up questionnaire assessing compliance with the dietary avoidance, abdominal pain/discomfort and global improvement

(Chart 2) was mailed to individuals with IBS who reported symptom improvement at the one month interval. It was accompanied by an IRB-approved follow-up study invitation, informed consent, \$10 non-binding cash payment and a stamped, addressed return envelope. These materials were mailed three or more months after implementation of the avoidance diet. Each participant's responses after one month from the first questionnaire were provided on the follow-up questionnaire as a frame of reference for the long term follow-up answers. Data from the follow-up questionnaire was subsequently compared to those same endpoints from the initial one month questionnaire. Total duration from initiation of the avoidance diet also was recorded for each completed long term follow-up questionnaire.

Statistical analysis of data collected from the study questionnaires was performed with Microsoft Excel. Mean abdominal pain/discomfort and mean global improvement scores were reported with one standard deviation. For comparison of mean abdominal pain/discomfort and improvement in global IBS symptoms after 1 month and after 3 months of identified allergen avoidance, a paired sample t-test was used as the data followed a normal distribution, with a value of $p < 0.05$ being considered statistically significant. All authors had access to the study data and had reviewed and approved the final manuscript.

IBS Food Avoidance Questionnaire

INSTRUCTIONS: Please read the accompanying Informed Consent. If you choose to complete this questionnaire, sign and date the Informed Consent, sign and date this completed questionnaire, and mail them back to us in the enclosed stamped, addressed envelope. Please do so within 2 weeks after avoiding the foods in question for 1 month. We will send you a check for \$20 within 4 weeks after receiving your completed Informed Consent and questionnaire.

Your full name: _____ Age: ____

Sex: Female Male

Race: Caucasian African-American Hispanic Asian Mixed
Other _____
Prefer Not To Answer

Have you or any blood-related family members ever had eczema, asthma, hay fever, other seasonal allergies or allergies to dogs, cats, pollen, mold, grass or other environmental allergens? (circle one)

Yes No Not sure

Dermatologist who performed your food patch testing:

Foods/food additives to which you had a positive skin test (list all):

1. _____
2. _____
3. _____
4. _____

In the past month, how well were you able to avoid the foods/food additives listed above?

Completely Partially Not at all Not sure

Please explain, if necessary: _____

On a scale of 0 to 10, before you had the food patch testing done, how severe, on average, was your belly pain/discomfort? (0 = no symptoms and 10 = very severe) (circle your answer)

0 1 2 3 4 5 6 7 8 9 10

On a scale of 0 to 10, after you avoided the food(s) to which you reacted with the patch tests for one month, how severe, on average, was your belly pain/discomfort? (0 being no symptoms and 10 being very severe) (circle your answer)

0 1 2 3 4 5 6 7 8 9 10

By the end of the one month food avoidance period, how much improvement in your overall IBS symptoms did you have? (0 = no improvement, 10 = great improvement) (circle your answer)

0 1 2 3 4 5 6 7 8 9 10

Which of your IBS symptoms, of the following, have you mostly had problems with? (circle one)

constipation diarrhea neither both, at various times

On average, about how many times a day did you have bowel movements before you underwent the patch testing and avoided the foods in question? (circle one)

0 to 1 1 to 2 2 to 3 3 or more

or: very variable, can't choose any of the above choices

After avoiding the foods in question for one month, about how many times a day do you have bowel movements? (circle your answer)

0 to 1 1 to 2 2 to 3 3 or more

or: very variable, can't choose any of the above choices

If you did experience improvement in your IBS symptoms, about how long after starting to avoid the foods did you notice the improvement? (circle your answer)

Within a few days, or less Within a week or two

Not until the end of the month

Please write any comments about the testing or your experience that you feel are relevant:

Chart 1. Questionnaire to assess IBS symptoms one month after starting the patch test-guided food avoidance diet.

IBS Food Avoidance Follow-up Questionnaire

INSTRUCTIONS: Please read the accompanying Informed Consent. If you choose to complete this questionnaire, sign and date the Informed Consent, complete the questionnaire (where appropriate, circle your answers), and mail them *both* back to us in the enclosed stamped, addressed envelope at your earliest convenience. Enclosed please find \$10 for your efforts.

Your full name: _____ Age: _____

Foods/food additives to which you had a positive skin test:

5. _____
6. _____
7. _____
8. _____
9. _____

As a reminder, on a scale of 0 to 10, before you had the food patch testing done, you reported to us that the severity, on average, of your belly pain/discomfort was (0 = no symptoms and 10 = very severe):

0 1 2 3 4 5 6 7 8 9 10

You also previously had reported to us that after one month, the success you had with avoiding the foods in question was:

Completely Partially Not at all Not sure

1. Now, at this point in time, how well have you been able to avoid the foods/food additives listed above?

Completely Partially Not at all Not sure

Please explain, if necessary: _____

2. Now that it has been at least several months since you underwent the food patch testing, on a scale of 0 to 10, how severe, on average, has your belly pain/discomfort been? (0 being no symptoms and 10 being very severe)

0 1 2 3 4 5 6 7 8 9 10

As a reminder, on a scale of 0 to 10, after one month of avoidance of the food(s) in question, you reported to us that the improvement in your overall IBS symptoms was (0 = no improvement and 10 = great improvement):

0 1 2 3 4 5 6 7 8 9 10

3. Now that it has been at least several months since you underwent the food patch testing, on a scale of 0 to 10, how much improvement in your overall IBS symptoms have you had? (0 = no improvement, 10 = great improvement)

0 1 2 3 4 5 6 7 8 9 10

Please write any comments about the food patch testing or your experience that you feel are relevant:

Chart 2. Follow-up questions to assess IBS symptoms and dietary compliance 3 or more months after start of the patch test-guided avoidance diet, for patients who reported improvement one month after starting the same diet.

RESULTS

Eighty-five consecutive patients underwent the patch testing and were eligible for participation in the study. One patient had no patch test reactions and 24 did not return the initial one month questionnaire. Sixty patients were included for this study by virtue of having at least one questionable or positive patch test reaction and subsequently completing and returning their initial questionnaire informed consent and study questionnaire. Fifty-six of the patients (93.3%) were Caucasian, two (3.3%) were African-American and one (1.7%) each were Hispanic and Asian. Subcategories of IBS included 46.7% diarrhea-predominant, 20.0% constipation-predominant, and 33.3% mixed. Table 2 summarizes the raw data and overall results for all 60 study participants as well as results for the subgroups of 40 patients reporting improvement at one month and at three or more months (Subgroup A), 10 patients reporting improvement at one month but not returning their long term follow-up questionnaire (Subgroup B), and 10 patients reporting no improvement at one month (Subgroup C).

Fifty (83.3%) patients reported at least slight to marked improvement in their abdominal pain/discomfort and in their global IBS symptoms after one month of patch test-directed food avoidance. Accounting for all 60 patients including those who reported no improvement, there was a mean decrease in the severity of abdominal pain/discomfort of 4.1 ± 2.6 points ($p < 0.001$) and a mean improvement in global IBS symptoms vs. baseline of 6.0 ± 3.2 points ($p < 0.001$) at one month of food avoidance. There were no

statistically significant differences in improvement of abdominal pain/discomfort or global improvement among the IBS subtypes.

Of the 50 patients who reported improvement one month after start of the patch test-directed avoidance diet, 40 (80.0%) completed and returned the long term follow-up questionnaire and accompanying informed consent (Table 2, Subgroup A). 92.5% were Caucasian, 5.0% African American, and 2.5% Hispanic. Mean duration of food avoidance was 7.6 ± 3.9 months. The improvement in abdominal pain/discomfort at baseline vs. at three or more months was 4.7 ($p < 0.001$). Mean global IBS symptom improvement at three or more months was 7.3 ± 2.8 ($p < 0.001$).

Table 3 and Table 4 provide an overview of global IBS symptom improvement and abdominal pain/discomfort scores at one month and at three or more months of patch test-guided dietary avoidance, respectively.

Table 2. Raw data and overall results for all study participants.

Subgroup A	Sex	Age	IBS duration (years)/ IBS type	Total # of ? or 1+ or > patches	Total # of 1+ or > patches	Abdominal pain/discomfort			Dietary compliance		Global symptom improvement		Time to improvement
						Base -line	At 1 month	At 3 or more months	At 1 month	At 3 or more months	At 1 month	At 3 or more months	
Patients who reported improvement with avoidance diet at one month and at three or more months	F	35	18/D	3	1	9	1	7	P	P	8	7	D
	M	30	3/D	1	1	7	3	3	P	P	7	7	W
	F	42	20/D	2	2	7	2	2	P	P	9	9	W
	M	64	1/D	4	2	7	2	2	C	C	7	9	W
	F	76	31/D	4	2	10	3	0	C	C	10	10	W
	M	35	20/C	7	1	10	4.5	3.5	C	P	6	8	W
	F	46	20/D	3	1	10	1	0	C	C	10	10	D
	F	43	12/M	10	6	8	1	3	P	P	9	10	W
	F	40	2/C	4	3	8	5	4	P	P	8	10	W
	F	11	2/D	6	4	10	0	0	P	P	10	10	D
	M	31	1/M	6	1	5	1	2	C	C	8	8	M
	F	47	15/D	8	4	6	2	1	C	C	8	9	D
	F	59	20/D	6	1	7	2	2	P	P	7	9	W
	M	45	7/D	7	3	6	1	3	P	P	10	9	D
	F	75	12/M	6	2	2	1	2	P	P	4	4	W
	M	35	14/D	5	4	4	2	3	P	P	5	7	W
	F	57	1/D	4	1	10	6	5	P	P	6	7	W
	F	21	5/M	1	1	7	1	2	C	C	10	8	D
	F	55	3/C	4	2	7	2	7	C	P	2	5	D
	F	65	47/D	8	1	8	3	2	P	P	7	8	D
	F	42	25/C	4	1	6	3	5	P	P	5	0	D
	F	13	2/M	3	3	8	1	3	P	P	10	9	D
	F	52	13/C	7	2	8	0	3	C	P	10	8	W
	F	48	8/M	6	2	7	1	1	P	P	9	10	W
	F	46	10/M	4	3	4	1	1.5	P	P	2	9	W
	F	48	3/M	4	3	7	3	2.5	P	P	8	2.5	M
	F	57	10/M	5	0	10	6	1	C	P	6	10	M
	F	13	9/C	6	2	8.5	7	1.5	P	C	3.5	7	W
	F	45	2/D	3	2	8	3	5	C	P	8	7	W
	F	29	6/D	7	2	8	5	2	P	P	4	9	M
	F	42	20/M	2	0	8	4	2	C	C	7	8	W
	F	20	5/D	7	1	8	1	1	P	P	8	9	W
	F	41	20/D	6	3	8	6	4	P	P	5	2	M
	F	52	7/C	2	1	8.5	1	0	C	C	10	10	D
F	37	6/M	2	1	7	5	5	C	P	5	6	W	
F	31	7/D	3	1	10	1	2	C	P	10	10	W	
F	59	1/D	8	6	10	2	7	P	P	7	7	D	
F*	30	2/M	4	1	8	2	8*	P	N	9	0*	D	
F	65	13/D	5	2	3	0	1	P	P	3	3	D	
F	27	22/M	3	1	8	6	3	P	P	3	3	M	
Subgroup A Totals/averages	34 F 6 M	42.7 ± 16.0	11.1 ± 9.8	4.8 ± 2.1	2.1 ± 1.4	7.5 ± 1.9	2.5 ± 1.9	2.8 ± 2.0	15 C 25 P	9 C 30 P 1 N	7.1 ± 2.5	7.3 ± 2.8	14 D 20 W 6 M

Table 2 (Continued)

Subgroup B Patients who reported improve- ment at one month but did not return follow-up question- naire	F	24	15/M	3	0	8	5	P	5	M
	F	16	4/D	4	0	7	5	P	9	W
	F	41	15/C	3	1	8	4	C	8	M
	F	42	20/M	6	1	5.5	0	P	8	D
	F	33	10/D	2	1	6	1	C	10	D
	M	59	15/D	9	4	6	1	P	10	D
	F	37	2/M	4	3	9	4	P	7	W
	F	27	10/M	5	1	7	3	C	6	D
	F	45	15/M	9	2	10	5	C	5	M
	M	61	35/M	5	5	6	5	P	3	W
Subgroup B Totals/ averages	8 F 2 M	38.5 ± 14.4	14.1 ± 9.2	5.0 ± 2.4	1.8 ± 1.7	7.3 ± 1.5	3.3 ± 2.0	4 C 6 P	7.1 ± 2.3	4 D 3 W 3 M
Subgroup C Patients who reported no improve- ment with avoidance diet at one month	F	52	35/D	1	0	8	8	C	0	
	M	64	10/D	4	0	3	3	P	0	
	M	64	2/D	7	1	4	4	C	0	
	F	24	2/C	7	2	8	8	C	0	
	F	59	5/M	1	1	1	0	C	0	
	F	28	10/C	5	1	4	1	C	1	
	F	22	3/D	2	1	4	4	C	0	
	M	44	10/C	2	2	7	7	C	0	
	F	24	2/C	3	1	8	8	P	0	
	F	56	40/D	4	1	10	10	P	0	
Subgroup C Totals/ averages	7 F 3 M	43.7 ± 17.6	11.9 ± 14.0	3.6 ± 2.2	1.0 ± 0.6	5.7 ± 2.7	5.3 ± 3.4	7 C 3 P	0.1 ± 0.3	
Complete study group totals/ averages	49 F 11 M	42.2 ± 15.9	11.7 ± 10.4/ 28 D 12 C 20 M	4.6 ± 2.2	1.8 ± 1.4	7.2 ± 2.1	3.1 ± 2.4	26 C 34 P	6.0 ± 3.2	

F, female; M, male; IBS type: C, constipation-type; D, diarrhea-type; M, mixed-type; ?, questionable; >, greater than; Dietary compliance: P, partial; C, complete; N, Not at all; Time to improvement: D, days; W, 1 to 2 weeks; M, end of month.

* This patient reported pain/discomfort and overall improvement at one month of patch test-directed food avoidance. At some time after the first month her IBS symptoms reverted to baseline, prompting self-abandonment of this diet and start of a low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet¹⁹ which resulted in sustained improvement. For data collection purposes for this study, her baseline and one month follow-up data were used as she reported. Since her long term follow-up self-assessment scores were attributable to the low FODMAP diet, they were discarded for purposes of this study in favor of her baseline pain/discomfort score (8) and assignment of a score of 0 for her long term overall improvement score, to more accurately reflect the patch test-guided avoidance diet outcome.

Table 3. Global IBS symptom improvement scores with patch test-guided food avoidance diet.

Reported improvement in global IBS symptoms vs. baseline	Number of patients / Percentage	
	At one month N=60	At three or more months *N=40
None (0 to <2)	10/16.7%	1 / 2.5%
Slight (2 to <5)	8 / 13.3%	5 / 12.5%
Moderate (5 to <8)	17 / 28.3%	9/ 22.5%
Marked (8 to 10)	25 / 41.7%	25 / 62.5%

N, Number of patients

*Includes all patients who reported improvement at one month and returned their three or more month follow-up questionnaire.

Table 4. Abdominal pain/discomfort scores with patch test-guided avoidance diet.

Abdominal pain/discomfort	Number of patients / Percentage		
	Baseline N=60	At one month N=60	At three or more months *N=40
0 to <2	1 / 1.7%	19 / 31.7%	11 / 27.5%
2 to <5	8 / 13.3%	19 / 31.7%	22 / 55.0%
5 to <8	20 / 33.3%	12 / 20.0%	7 / 17.5%
8 to 10	31 / 51.7%	10 / 16.7%	0

Based on a 0 to 10 self-reported rating scale with 0=no abdominal pain/discomfort and 10=very severe abdominal pain/discomfort.

N, Number of patients

*Includes all patients who reported improvement at one month and returned their three or more month follow-up questionnaire.

DISCUSSION

Approximately 50% of patients with IBS report that foods aggravate their symptoms¹¹, spawning great interest in the role of food allergies in its pathogenesis. Until recently, attention has focused on IgE-mediated immediate-type (type 1) hypersensitivity and IgG antibody-mediated mechanisms but there has been insufficient evidence to support the routine recommendation of such diagnostic testing¹².

In contrast, the aforementioned 2013 proof-of-concept study¹⁵ and our study investigate a role for cell-mediated (type 4) immunity in IBS pathogenesis. The 2013 study was, to our knowledge, the first to investigate the utility of patch testing a panel of type 4 food allergens for IBS. Food allergens generating a type 4 allergic reaction mostly are different substances than type 1 food allergens (i.e. peanuts, shellfish, milk proteins, etc.). The 2013 study showed partial or complete overall improvement after one week of patch test-directed food avoidance in 27.5% of participants tested to 28 to 40 foods. Stierstorfer, et al posit that the same or a similar allergic contact response as elicited in the skin by contact with the allergenic foods during patch testing likely occurs in the intestinal lining when the same foods are ingested, resulting in inflammation that triggers IBS symptoms, and newly described as allergic contact enteritis (ACE).

Limitations of that study include short duration of the avoidance diet and follow-up, non-blinded participation, and absence of a control group. Additionally, placebo effect is most prevalent for conditions such as IBS where primarily subjective outcome measures are available²⁰, with a prevalence

of up to 40% in IBS²¹. In a 1999 report²², Spiller analyzed 25 randomized, placebo-controlled IBS clinical trials, observing that placebo effect begins to diminish after about 12 weeks. He concluded that the optimum length of an IBS trial be greater than three months.

In the absence of blinding and of a control group in our study, its extended follow-up of over seven months vs. the 2013 study allows for better assessment of durability of response and validity of its results. Forty (80.0%) of the 50 patients who benefited after one month of food avoidance returned their long term follow-up questionnaires. The average follow-up of 7.6 ± 3.9 months in these 40 patients surpasses Spiller's minimum IBS study duration recommendation of at least 3 months. The decrease in abdominal pain/discomfort and improvement in overall IBS symptom scores were largely sustained over this time period, thus supporting a role for delayed-type food hypersensitivities in the pathogenesis of IBS symptoms, independent of placebo effect.

The retrospective manner in which the self-assessments were reported in this study introduces the potential for recall bias, another variable that could affect results. The presence and direction of bias by any given individual cannot be known, making it difficult to determine any effect it may have had.

Mechanistically, our findings support the hypothesis that in some patients who fulfill the diagnostic criteria for IBS, a very similar inflammatory response as elicited in the skin (allergic contact dermatitis) by the patch tests likely occurs in the intestinal mucosa

when culprit foods are ingested, thereby disrupting motility and causing IBS-like symptoms. In the subset of IBS sufferers whose symptoms have remitted completely over a sustained period with patch test-guided food avoidance, these results further support the existence of the newly proposed disease, allergic contact enteritis (ACE), its symptoms mimicking those of IBS.

Many of the type 4 food allergens used in this study are commonly encountered in the average American diet. Some of the most reactive allergens are also some of the most ubiquitous, including cinnamon bark oil; carmine, a red food dye; sodium bisulfite, a preservative; and benzoyl peroxide, used to bleach flour and cheese. Examples of food components that less often elicited patch test skin reactions are pinene alpha, naturally occurring in parsley, carrots, parsnips and celery, and d-limonene, present in citrus. Dietary avoidance of the foods identified by patch testing proved to be challenging. Thirty (75.0%) of the 40 participants with sustained improvement at 3 or more months reported partial avoidance. Twenty-seven elected to comment, reporting as reasons for partial rather than complete avoidance: difficulty avoiding the multiple or ubiquitous allergens to which they reacted; uncertainty when their food was not self-prepared; and/or difficulty when processed food labels did not specifically identify each ingredient; i.e., “artificial flavors”, “natural flavors”, “spices”. Many of these same participants correlated minor or major flares of their IBS symptoms when straying from their avoidance diet.

In summary, the findings of this expanded proof-of-concept study suggest the possible pathophysiology for some cases of IBS. Dietary avoidance of trigger foods identified by patch testing may offer a cost effective, non-pharmacologic approach to treat

patients who carry this diagnosis. Further study is needed to investigate the hypothesis that delayed-type food hypersensitivities may contribute to or mimic IBS. Randomized trials in which IBS patient cohorts are blinded to their patch test results and assigned blinded diets with food allergen(s) avoided or not avoided for a period of time, then crossed over, would further mitigate the role of placebo in future validation studies. Small bowel biopsy in patients who benefit from patch test-guided food avoidance while on the avoidance diet and after food rechallenge could definitively investigate the hypothesized correlation between skin inflammation elicited by food patch testing and intestinal mucosal inflammation elicited by ingestion of the same food(s). Strategically timed cytokine profile assays in search of a proinflammatory state may be similarly informative in a less invasive manner. It will also be of interest to compare efficacy of patch test-guided type 4 food allergen elimination diets with that of a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs), another dietary intervention recently demonstrated to improve IBS symptoms¹⁹.

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Conflict of Interest Disclosures: Michael B. Stierstorfer, MD is the director of the IBS Centers for Advanced Food Allergy Testing, LLC; has a Canadian patent: Food Patch Testing for Irritable Bowel Syndrome and Undifferentiated Gastrointestinal Disorders; and has submitted patent applications to United States Patent and Trademark Office and the equivalent agency in Europe for the same. For the remaining authors, there are no conflicts of interest.

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Corresponding Author:

Michael B. Stierstorfer, MD
 2101 Market Street, Suite 2802
 Philadelphia, PA 19103
 215-557-7430 (Office)
 215-661-0302 (Fax)
 mstierstorfer@eastpennderm.com

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