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[About this Journal](#)

[Find Citing Articles](#)

[Table of Contents](#)

[Browse TOC](#)

[Email Jumpstart](#)

[Save Article Text](#)

[Email Article Text](#)

[Print Preview](#)

Links

[Abstract](#)
[Complete Reference](#)
[Catalogo Biblioteca ISS](#)

Outline

- [Abstract](#)
- [IMMUNOLOGIC TESTS](#)
- [FOOD PROTEIN-INDUCED MUCOSAL LESIONS](#)
 - [Esophagus](#)
 - [Stomach](#)
 - [Small Intestine](#)
 - [Animal Data](#)
 - [Intestinal Biopsy Findings](#)
 - [Colon](#)
 - [Eosinophils](#)
- [FUNCTIONAL MUCOSAL ALTERATIONS](#)
- [INTESTINAL PERMEABILITY](#)
 - [Intestinal Permeability to Macromolecules](#)
 - [Intestinal Permeability to Inert Molecules](#)
- [FOOD PROTEIN-INDUCED MOTOR DISORDERS](#)
- [SYSTEMIC CONSEQUENCES OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME](#)
 - [Cytokine Secretion](#)
 - [Circulating Immune Cells](#)
- [MEASUREMENT OF MUCOSAL PRODUCTION IN FECES](#)
- [TESTING ALLERGENICITY OF COW'S MILK SUBSTITUTES](#)
- [REFERENCES](#)

Recent History



[Previous Page](#)

Food Protein-Induced Enterocolitis Syndrome: Laboratory Perspectives

[Supplement Contents]

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Abstract

ABSTRACT: The expression of food protein allergy in man is very heterogeneous, varies with the age of the subject and is to a certain extent genetically determined. Skin prick tests with standardized food extracts are a sensitive method for detection of immunoglobulin E bound to reactive cells such as mast cells. Various tests on cellular immunity have been developed, especially because T-cell mediated reactions are considered to play a role in mainly delayed gastrointestinal reactions to cow's milk proteins. Food allergy may involve the entire gut, from mouth to rectum, including the esophagus. Abnormalities in intestinal permeability are the hallmarks of the inflamed gut, and may contribute to diagnosis of food induced enteropathy. What determines the characteristics of the intestinal inflammatory response is largely the cytokine responses triggered by the pathologic mechanism, whatever its origin, in the stomach, the small intestine, and the colon. A so-called T-helper type 2 response is characteristic of the allergic subject. A secretion of tumor necrosis factor-[alpha] alpha by blood cells of children allergic to milk was shown. All means of investigation may help in analyzing food substitutes for allergic infants.

The gastrointestinal tract has a limited number of responses to pathogens and entirely different mechanisms may lead to similar histopathologic responses. The expression of food protein allergy in humans is heterogeneous, varies with the age of the subject, and is, to a certain extent, genetically determined. Food allergy is more frequent in childhood than in adulthood. The intestinal mucosa in the child with cow's milk allergy may appear flat, such as that observed in gluten-sensitive enteropathy or celiac disease, whereas subjects with other forms of food allergy may have a morphologically normal small intestinal mucosa, occasionally with increased immunoglobulin (Ig)E plasma cells and often only characterized by an increased intestinal permeability.

Abnormalities in intestinal permeability are the hallmarks of an inflamed gut, occurring in subjects with celiac disease as well as in those with Crohn's disease. It has become clear that the characteristics of the intestinal inflammatory response are largely determined by the cytokine responses triggered by the pathologic mechanism, whatever its origin, in the stomach, the small intestine, and the colon. A so-called T-helper (Th) type 2 response is characteristic of the allergic subject and may be a predominant response in subjects with ulcerative colitis. The Th1 response, with an increased production of interferon (IFN)-[gamma], tumor necrosis factor (TNF)-[alpha], and other proinflammatory cytokines may be more associated with a delayed gut response during food allergy and thus may resemble that observed in the

stomach when infected by *Helicobacter pylori*, in the small intestine when a subject with celiac disease consumes normal bread, and during the active phases of Crohn's disease (1).

All these aspects of gut function may be analyzed in the search for appropriate laboratory explorations of the gut during food allergy. Their specificity always emanates from the fact that changes are elicited by food or disappear in the absence of the offending food.

IMMUNOLOGIC TESTS

Skin-prick tests with standardized food extracts are a sensitive method for detection of IgE bound to reactive cells, such as mast cells. They are considered to be superior to measuring circulating IgE antibodies (2). It is commonly acknowledged that because most food-allergic reactions with slow onset are not caused by IgE antibodies, the diagnostic value of skin-prick tests is confined to patients with immediate-onset reactions (3–5). The potential help of patch testing, which has been reported to be useful in atopic dermatitis, (6) is still to be established.

Various tests on cellular immunity have been developed, especially because T-cell–mediated reactions are considered to play a role mainly in delayed gastrointestinal reactions to cow's milk proteins. They include the in vitro lymphoblast transformation test (7), lymphoblastic stimulation test (8), and leukocyte migration inhibition test (9).

Taino and Savilahti (8) used a [beta]-lactoglobulin lymphocyte stimulation test and found among young infants (<8 months of age) with immediate reactions to cow's milk proteins that most did not have specific IgE to cow's milk proteins but had positive results in a [beta]-lactoglobulin lymphocyte stimulation test. Overall, however, recent results indicate that lymphocyte proliferation assays are neither diagnostic nor predictive of clinical reactivity in individual patients with milk allergy, because lymphocytes of many control subjects are highly responsive to milk antigens, whereas lymphocytes of many patients with milk allergy are not (10).

FOOD PROTEIN–INDUCED MUCOSAL LESIONS

Esophagus

Esophagitis, whatever its endoscopic appearance, is the most frequent feature of gastroesophageal reflux. The presence of eosinophils in the mucosa of the esophagus has been considered a highly specific marker for damage from gastric acid reflux and since the study by Kelly et al. (11), has been associated,

at least in part, with food allergy, as was demonstrated by a significant decrease of the eosinophil count as a result of an amino acid–based trial diet in 10 children with intractable gastroesophageal reflux disease. A close relationship seems to exist between the esophageal eosinophil and the mucosal mast cell, as has been shown by a significant increase in patients with eosinophilic esophagitis compared with control subjects and with children with acid-induced peptic esophagitis (12). However, the exact meaning of eosinophils in the esophageal mucosa still remains to be clarified.

Stomach

The eosinophilic invasion of the stomach may occur during allergic eosinophilic gastroenteritis and is readily observed during pathologic examination of biopsy specimens obtained during endoscopic procedures (13,14).

Small Intestine

Animal Data

In rats sensitized to and challenged with ovalbumin followed by orally administered [beta]-lactoglobulin as an intestinal permeability marker, histopathologic examinations of the intestine show mast cell infiltration of the intestinal mucosa at 1 hour, marked edema of villi at 3 hours, eosinophil infiltration at 6 hours, an increase of goblet cells at 12 hours, and villous atrophy and lymphocyte infiltration at 24 hours. The appearance of three [beta]-lactoglobulin peaks of comparable heights in the serum suggest that the intestinal absorption of [beta]-lactoglobulin may be related to a late and delayed phase as well as to the immediate IgE-dependent phase response (15).

Intestinal Biopsy Findings

Food hypersensitivity may induce chronic malabsorption due to immunologic hypersensitivity within the intestinal mucosa (16). Villous atrophy may occur, as has been reported in earlier studies (17), although in contrast with celiac disease, it is now recognized that food enteropathy may occur in the absence of obvious microscopic alterations of the gut mucosa (18,19).

In one of the first reports concerning duodenal biopsies during cow's milk protein intolerance, 31 infants constantly exhibited mucosal damage, with partial villous atrophy being the most usual finding (17). These changes were reported as nonspecific, and recovery of normal mucosal appearance was achieved with a milk-free diet for 3 to 13 months. In contrast, in 12 infants with suspected cow's milk protein intolerance challenged with cow's milk after at least 1 month of a cow's milk–free diet, the morphology of the mucosa

varied from normal to slight damage at the same biopsy sampling, with no difference found in morphology judged by light microscopy between pre-and postchallenge specimens (20).

Discrepancies may occur between clinical reactions and biopsy findings (17). Of four infants with suspected cow's milk protein intolerance who were placed on an elimination diet and then challenged with cow's milk, none reacted clinically, yet in two of the four, jejunal biopsy revealed clear histologic, ultrastructural, and immunologic changes (21). IgE plasmacytes in small intestinal biopsy tissue have been reported seldom in children and were found in 3 of 15 children with intractable gastroesophageal reflux, which responded dramatically to cow's milk elimination (22).

Analysis of specific cellular subsets, such as increased tumor-infiltrating antigen 1 (TIA1)-expressing intraepithelial lymphocytes (19) is still at its early stages, and we still do not know the fine-tuning of the cellular interactions in the lamina propria. Recently, it has become clear that the intestinal mucosa has a unique subset of CD4+ T cells that secrete TGF- β (Th3 cells) that provide help for IgA production (23). These cells have downregulatory properties for Th1 cells and therefore play an important role in the active suppression of oral tolerance and IgE response. What information can be taken from this finding in clinical practice remains speculative.

Colon

Allergic colitis is a condition characterized by inflammatory changes in the rectum and colon as a result of immune-mediated reactions to ingested foreign proteins, usually derived from proprietary formulas or found in human milk as a result of the maternal diet (24). Many foods have been associated with the development of allergic colitis, including wheat, eggs, corn, fish, seafood, and nuts (25). The most common antigens implicated in allergic colitis, however, are present in cow's milk and soy formulas. Pathologic features of allergic colitis are provided by endoscopy and the evaluation of mucosal biopsy specimens in any segment of the colon (24,26,27). Endoscopic features are focal erythema, a friable-appearing mucosa, and increased hyperplasia and, in severe cases, multiple erosions mimicking infectious colitis (28–31). Microscopically, the overall architecture of the mucosa in allergic colitis is well maintained (26,32,33) together with, as the most striking and characteristic histologic feature, focal infiltrates of eosinophils in all mucosal compartments. This infiltrate is particularly prominent in the lamina propria (32) and is absent in infectious colitis (32–34). Nodular lymphoid hyperplasia is a possible endoscopic finding in children with rectal bleeding associated with food allergy (35).

Eosinophils

Eosinophils appear as a potential common feature of mucosal lesions induced by food allergy, even though their exact prevalence and role still remain debatable. Eosinophils are developed and differentiate in the bone marrow under the influence of at least three cytokines, granulocyte-monocyte colony-stimulating factor, interleukin (IL)-3, and IL-5 (36,37), with the latter more specific for eosinophils (38). The degranulation of eosinophils results in the release of granule-associated mediators and the generation among others of major basic protein and eosinophil cationic protein (36,37). In addition, eosinophils can produce other mediators, such as platelet activating factor (PAF), shown to induce bowel injury in experimental animals (39).

FUNCTIONAL MUCOSAL ALTERATIONS

Malabsorption may occur as a result of small intestinal insult (40,41). A particular feature is the occurrence of protein-losing enteropathy (42), a condition more frequently associated with gastric mucosal hyperplasia during Ménétrier disease or with intestinal lymphangiectasia during childhood.

INTESTINAL PERMEABILITY

Despite major improvements in intestinal mucosa sampling, such as the reduction of its duration through the use of endoscopy, intestinal biopsy remains an invasive test that has to be carefully programmed and cannot be repeated. In addition, it has become evident that most children with proven food allergy are free from any epithelial lesion, at least when evaluated through light microscopy.

The intestinal epithelium is not an absolute physical barrier between the intestinal lumen and the milieu intérieur. First, enterocytes prove capable of absorbing intact proteins, a phenomenon appearing to be physiological, albeit enhanced during food allergy. Second, the lateral cell membrane exhibits three different types of junctions. Among them, the tight junctions, close to the apical pole of the cell, appear as fused regions of adjacent lateral cell membranes and variably occlude the intercellular space, therefore playing a major role in determining transepithelial permeability. The tight junction may thus be thought of as a sentry with highly selective entrance criteria (43).

Intestinal Permeability to Macromolecules

Intestinal absorption of intact antigens occurs in the intestine as a normal event. The rate appears to decrease a few months after birth, according to a phenomenon called closure (44). This absorption may

increase during pathologic events, such as diarrhea (45), cow's milk-sensitive enteropathy (46), and atopic dermatitis (47).

It is likely that dietary antigens evoke a local immunoinflammatory response that alters the barrier function of the mucosa, resulting in the aberrant increased absorption of luminal antigens. These modifications may be the result of a local increased secretion of different cytokines such as IFN-[gamma] (48,49) and TNF-[alpha] (50), a cytokine for which local secretion seems highly probable during cow's milk allergy (51).

However, the measurement of intact proteins in the serum of food-allergic patients is of no practical value in the assessment of the clinical reactivity to food, especially because it has been shown that no correlation exists between the intensity of symptoms and the plasma levels of food antigens (52).

Intestinal Permeability to Inert Molecules

Taking advantage of discrete modifications of the small intestine's epithelial integrity, intestinal permeability studies provide a potentially useful means of investigating children whose troubles lie in the offending effect of some food and for whom repeat procedures during challenges is the sole way to establish a diagnosis.

The intestinal permeability test (IPT) is noninvasive and is designed not to replace mucosal sampling but to allow an appropriate evaluation of the intestinal epithelium's integrity. Intestinal permeability may be defined as the ability of the intestinal mucosa to be crossed during a given period by compounds that diffuse across the mucosa and are not actively transported. To reach the blood stream before elimination in the urine, markers have to cross the epithelial intestinal monolayer (i.e., the membranous wall of enterocytes and/or the different spaces between enterocytes) which depend on the mutual array of epithelial cells and confers the epithelium with its functional properties.

Measuring intestinal permeability in humans requires a probe molecule that should be inert, water soluble, nontoxic, and undegraded by intestinal bacteria and should remain nonmetabolized after absorption. Its transport through intestinal mucosa should decrease with increased molecular size and follow first-order kinetics. The probe should be measurable with sensitivity, accuracy, and ease in biologic fluids such as urine (53). The different probe molecules used to measure intestinal permeability are xylose, lactulose, lactitol, erythritol, mannitol, inulin, raffinose, cellobiose, polyethylene glycols of

different molecular weights (MW), urea, uric acid, creatinine, and ^{51}Cr EDTA (53). Nonabsorbable monosaccharides include rhamnose (MW 164) and mannitol (MW 182). The first disaccharide suggested as a permeability marker was lactulose (MW 342), now with cellobiose (MW 342) the most frequently used (54,55).

Differential absorption works on the simultaneous use of two or more probe molecules, assuming that they behave similarly in all respects except in their permeation across the mucosa (18). Therefore, expressing the urinary excretion of the markers as a ratio may overcome the effects of the many nonrelevant variables that can influence the individual markers, such as the adequacy of the oral load ingested, the gastric emptying time, the intestinal transit time, the dilution of the marker by intestinal secretions, the renal clearance, and the completeness of the urine collection. The monosaccharides rhamnose and mannitol are thought to pass through aqueous pores in the enterocyte membrane, with a radius of 0.4-nm diameter for mannitol (56). In contrast, the larger sugars, lactulose and cellobiose, permeate the intestinal mucosa either through larger pores, with a 0.52-nm diameter or more predominantly through the intercellular spaces and at extrusion zones at the villus tips. In patients with villous atrophy related to untreated celiac disease, reduction in mannitol recovery should result from a reduced surface area and the number of pores available for diffusion, whereas the increased recovery of larger molecules may be through epithelial discontinuities such as altered tight junctions and cell extrusion zones (57). The increase in passage of mannitol through paracellular pathways may remain quantitatively limited in comparison with the decrease related to the modifications of surface area (58) so that during villous atrophy the overall result is a decrease of the mannitol urine recovery.

In children with cow's milk allergy with a normal diet, the lactulose:mannitol (L:M) ratio is increased (59), in relation with mucosal intestinal abnormalities, which, according to data from analyses of biopsy samples, vary from mild inflammation to various grades of villous atrophy.

In a previous work (60), we identified a group of 25 children with cow's milk allergy in whom the L:M ratio was $7.02 \pm 2.65\%$ mean $\pm$ SD (vs. $2.13 \pm 0.77\%$ in control subjects). This increase was due both to an increased passage of lactulose ($0.69 \pm 0.51\%$ vs. $0.36 \pm 0.17\%$; $P < 0.05$) and a reduced passage of mannitol ($9.62 \pm 6.02\%$ vs. $17.03 \pm 5.44\%$; $P < 0.05$). An increased permeability to ^{51}Cr -EDTA was reported in similar conditions (61). These abnormalities are not restricted to symptoms observed during cow's milk allergy and may appear during respiratory or skin diseases (61).

It is noteworthy that intestinal permeability abnormalities were also described in atopic dermatitis by several investigators using different markers such as polyethylene glycol 600 or 4000 (62), ⁵¹Cr-EDTA (63), lactulose, and rhamnose (64). The L-M test indicates that in approximately half the children with atopic dermatitis, hyperpermeability to lactulose, that is reflected in urinary elimination, is tripled (65). This results in an increase of the L:M ratio, although permeation to mannitol remains unchanged, indicating the absence of surface area reduction in the intestinal mucosa (65), which in accordance with previous reports, indicates the absence of major intestinal changes during atopic dermatitis (66).

Briefly, IPTs measure the differential elimination of two ingested, nonmetabolizable markers of different molecular weight, such as lactulose and mannitol. They are noninvasive, nonirradiating, and repeatable, thus allowing the clinician to monitor the inflammatory state of the mucosa after administration of food allergens without requiring biopsies. Moreover, they have proved to be more sensitive than biopsies in the detection of minimal pathologic mucosal abnormalities (57,67) and can be used as follows:

- before any intestinal biopsy to detect mucosal abnormalities and suggest the need for a mucosal sample, such as during cow's milk-sensitive enteropathy;
- after institution of an elimination diet to monitor the restoration of a normal value, indicating the disappearance of the inflammatory state of the mucosa;
- during a provocation procedure, in reference to tests performed during an exclusion regimen, to detect intestinal permeability abnormalities and therefore mucosal damage induced by ingestion of the offending food (68,69).

However, IPT changes reported up to now have not shown consistent differences between the different manifestations of food allergy (70), a problem that could probably be overcome if a correct analysis of the kinetics of permeability changes were performed, a prospect limited by the tediousness of the procedure.

FOOD PROTEIN-INDUCED MOTOR DISORDERS 🚩

Little is known about motor disorders induced by food allergy, although the issue seems to have gained considerable interest, especially after the recent evidence of an association between cow's milk allergy and gastroesophageal reflux (71) and constipation (72,73).

In children with cow's milk allergy manifested by vomiting, gastroesophageal reflux, and retching, an oral challenge with cow's milk is responsible for the disruption of normal gastric motor activity, as

demonstrated by electrogastrography (74).

SYSTEMIC CONSEQUENCES OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

Growth is delayed in young atopic infants with food allergy, possibly because of sustained allergic inflammation (75). Iron deficiency is a classic symptom of cow's milk protein allergy and probably results both from occult blood losses and from minimal malabsorption.

Cytokine Secretion

The abnormal immune response in the human gut may involve predominantly a Th2- or a Th1-like inflammatory response, with the latter more likely in delayed reactions. These reactions can be elicited by bacteria, peptides, possibly the bacterial flora, and some viruses. One interesting means of analysis is the deciphering of the cytokine response in comparison with the clinical observations.

Circulating Immune Cells

Hill et al. (9) demonstrated an increased production of leukocyte migration inhibitor factor in response to cow's milk proteins in clinically well-defined late reactors, but not in immediate reactors and control subjects. The same group reported an increased in vitro IFN- γ production in response to β -lactoglobulin stimulation of blood mononuclear cells from patients with late reactions to cow's milk proteins (76).

We have shown that peripheral blood mononuclear cells from infants with cow's milk allergy manifested by intestinal symptoms, but not those of infants who had recovered from cow's milk allergy, secreted high amounts of TNF- α , when cultured during 5 days in the presence of a mixture of intact cow's milk proteins (50). Moreover, the threshold of mononuclear cell reactivity was substantially decreased in infants with active cow's milk allergy compared with infants cured of the disease (77).

In addition, we have recently reported that a peak of TNF- α secretion may be observed when incubating mononuclear cells in the presence of cow's milk proteins for only 24 hours, indicating the occurrence of two peaks of TNF- α secretion (78). The differences appeared related to the presence of predominantly skin or intestinal symptoms: in the former, TNF- α secretion is exclusively observed after 24 hours of mononuclear cells culture, whereas in the latter, two peaks of secretion are observed, one peak after 24 hours of culture and another peak after 5 days (Dupont et al., unpublished

data, 1999).

MEASUREMENT OF MUCOSAL PRODUCTION IN FECES

The mucosal secretion of mediators may be demonstrated by the measurement of their fecal content. A positive cow's milk challenge in infants with atopic dermatitis is associated with increased TNF- α , eosinophil cationic protein and α_1 -antitrypsin in feces (79). An elevated concentration of eosinophil cationic protein in feces seems to be associated with immediate-type reactions, whereas TNF- α release was associated with delayed-type reactions (79) or the occurrence of digestive symptoms (80). These modifications seem to occur regardless of the concentration of IgE in the stools.

TESTING ALLERGENICITY OF COW'S MILK SUBSTITUTES

To preserve normal growth, cow's milk-allergic infants are fed hypoallergenic formulae, often based on extensively hydrolyzed casein or whey proteins. The quantitative evaluation of the immunogenicity of infant formulae, and their clinical tolerance, are problems the food industry and clinicians have respectively to deal with. More precisely, although these formulae are extensively hydrolyzed, they may contain tiny amounts of immunoreactive proteins or fragments (in the nanogram/milliliter range) that have been shown to trigger a clinical reaction in some extremely reactive children. In these cases, as well as in multiple food allergy, such hydrolyzed formulas are replaced by amino acid-based formulas (81).

Animal models of food allergy most often rely on the guinea pig (82–84), used to analyze the residual allergenicity of milk formulae. A rat model of milk sensitization has also been developed, using the mast cell-triggering capacity of various hydrolyzed milk proteins (85).

In human models, residual allergenicity has also been tested by measuring the remaining milk protein epitopes still capable of reacting with serum IgE antibodies or IgG antibodies of allergic infants (radioallergosorbent test [RAST] and RAST inhibition). However, these tests are not relevant to delayed-type hypersensitivity, which is most often described in patients with cow's milk-sensitive enteropathy (18). IgE-binding capacity to a casein hydrolysate was described by a dot immunobinding assay, in sera from children with allergy to cow's milk (86). Other immunologic parameters have been proposed to evaluate immunologic reactions to foods in humans and are based on the measurement of immune mediators (histamine, tryptase, eosinophil cationic protein) and of cellular immune reactions (87).

The 24-hour TNF- α test was used to screen the immunogenicity of extensively hydrolyzed infant

formulae or amino acid–based formula, by using mononuclear cells from infants with allergic to intact milk proteins or to milk protein hydrolysates, who had development of intestinal or skin symptoms (88). The results confirmed that TNF-[alpha] secretion by mononuclear cells from infants with active cow's milk allergy is specifically increased in the presence of cow's milk proteins and further indicate that the TNF-[alpha] test could be used to identify potentially active peptides still present in extensively hydrolyzed formulas.

In conclusion, laboratory procedures intended to assess further the relevance of food allergy in the analysis of clinical conditions are still not available, and, especially, studies allowing quantitation of their clinical relevance have not been undertaken. The literature indicates that several directions for research may be envisioned. Microscopic analysis of biopsy samples shows that the significance of eosinophils in the esophagus may indicate allergy where only acid reflux was considered. Intestinal permeability tests are noninvasive and may be repeated, but the time courses of food-induced changes are still unknown, and this impairs their more general use. It is likely that the analysis of cytokine secretion, especially in response to food, whatever the medium or the cellular type analyzed, is the more promising field. However, transfer to clinical practice needs thorough clinical assessment to measure their precise clinical relevance.

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