図2　親世代のエピジェネティックな変化の子世代への遺伝

明をすることはできるが，わずか1世代の時間に急増したアレルギー疾患の原因となる環境変化と親子連鎖による子の早期発症に関しては，親世代のエピジェネティックな変化が子世代に遺伝することを考えると，よりうまく説明できるかもしれない(図2)。ということは，子どもの出産前から親自身の食事や環境にも気をつけることが大切となる。再び妊娠中や授乳中の食事指導の重要性が見直される時代が到来するかもしれないが，抗原除去というセントラルドグマに戻るのではなく，今後はGenetic Epidemiologyの成果をとりいれたEvidence-Based Medicineの時代が到来するものと予想している。

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特集

アトピー性皮膚炎診療ガイドライン改訂のポイント
—薬剤評価・位置づけを中心に—

4. 他科からの提言
2）小児科から

Ohya Yukihiro
大矢　幸弘*

*国立成育医療センター第一専門診療部アレルギー科

はじめに

　日本皮膚科学会から発行されたアトピー性皮膚炎診療ガイドラインは，皮膚科診療を専門とする医師向けとされ，2000年の策定以来何度か改訂を繰り返し，2008年に続いて2009年にはさらなる充実が図られており，皮膚科専門医の矜恃を感じさせる内容である．かつて，皮膚科医と小児科医との間には本疾患の原因や治療を巡る激しい論争があり，特に食物に関する指導に相違があったように思う．しかし，厚生労働省アレルギー総合研究事業による「アトピー性皮膚炎診療ガイドライン」が10年前に策定されて以来，皮膚科，小児科，内科を含めた複数診療科によるコンセンサスが進み，いつしか皮膚科医と小児科医の論争は鎮静化した．この変化には，わが国の医学界にEBM（evidence-based medicine）の影響が浸透したことも大きく貢献していると思われる．

　しかしながら，臨床現場にEBMがしっかり根付いているかというと，皮膚科医の間にも小児科医の間にも未だ不十分との印象が強い．ステロイド外用薬やカルシニューリン抑制薬をはじめとする外用薬や，第2世代抗ヒスタミン薬に関するEBMは製薬メーカーの後押しもあり，比較的普及が進みつつあるが，かつて論争の的になった食物アレルギーとの関連となると，小児科医・皮膚科医の区別なくEBMはほとんど無視されているという印象である．現在は，アトピー性皮膚炎と食物アレルギーは別の疾患ととらえる医師が大半であり，そのため両者の関連に言及が少ないことも一因かも知れない．両疾患を別疾患として診断治療を行

うことには大きなメリットがあり，臨床現場での混乱を収拾するために非常に有効な方法だと思われるが，日本皮膚科学会，日本アレルギー学会のいずれのアトピー性皮膚炎診療ガイドラインにおいても，食物の取り扱いはわずかな記述にとどまっており，現場の医師の裁量で食物に関する指導は大いに異なっている．アトピー性皮膚炎と食物アレルギーの両者の診療に深く携わるものとして，臨床現場の混乱を鎮め，患者に最大の利益をもたらす治療が普及することを願って，タブー視されてきたきらいのある両者の関連について，あえて論争が再燃することも厭わず提言してみたい．

食物との関連に関する新しいパラダイム構築の必要性

　日本皮膚科学会の『アトピー性皮膚炎診療ガイドライン』には「乳児では，食物アレルゲンの関与が認められることがある．食物アレルギーに関しては「食物アレルギー診療の手引き」を参照する」という記述があるのみで，食物に関する詳細な記述はない．日本アレルギー学会の『アトピー性皮膚炎診療ガイドライン2009』には，「乳幼児期では食物は原因・悪化因子の一つとして認められている．その検索には①詳細な問診，②アレルゲン検査を行い，疑わしいアレルゲンが検出されたら，③除去試験，④誘発試験を統合して食物アレルゲンの確定を行う」という『食物アレルギー診療の手引き』の内容を簡略化した内容が記載されている．いずれのガイドラインも同じことを述べているに過ぎず，両者の相違はない．これらの記述の乏しさは，逆にか

つての論争のトラウマが両者に残っていることを感じさせるが，本稿は「提言」を述べてよいとのことであるので，あえて将来の改訂に向けて2つのポイントを提言させて頂こうと思う．

1つは，アトピー性皮膚炎の悪化因子としての食物は，必ずしも食物アレルゲンに限らないということ（すなわち，食物アレルギーとは異なる機序で生ずる機能性栄養成分による影響があり得るということ）．もう1つは，食物アレルギーがアトピー性皮膚炎の原因であるという従来の観点よりも，アトピー性皮膚炎が食物アレルギーの原因となる可能性があるという観点を検討すべきだということ．これらの視点は，どちらの『アトピー性皮膚炎診療ガイドライン』にも記述がないが，臨床上極めて重要な問題を含んでおり，今後の改訂に向けて検討が必要と思われる．

1. 食物アレルギーとは別の機序による食物の影響

痒みや紅斑に直接影響する，化学成分としての仮性アレルゲンを多く含む食品の摂りすぎによるアトピー性皮膚炎の悪化を時々経験する．子どもの場合，イチゴ狩りで食べ過ぎた時，チョコレートを食べ過ぎた時に悪化したというケースに何人か出会ったことがある．ヒスタミンやサリチル酸，あるいはカフェインを多く含む食品や薬品の摂取で悪化する者もいるので，詳細な問診をとることが大切である．これらは，特異的IgE抗体を検出する検査では同定できないので，原因不明の食物アレルギーとされることがあるが，そもそも食物アレルギーではない．

鮮度の落ちた魚の摂取によるscombroid syndromeなどの存在を，青身の魚はアレルギーが強いなどと誤解している患者もいるが，魚油に含まれるEPAやDHAは，むしろアラキドン酸カスケード由来のロイコトリエン4系列の産生を抑制し，抗炎症効果をもたらす．こうしたN3系列の脂肪酸摂取による湿疹の改善効果を認めたランダム化比較試験（RCT：randomized controlled trial）[1]があるほどで，むしろ鮮度管理のよい魚ならアトピー性皮膚炎やアレルギー疾患の対策に推奨すべきと思われる．

ヒトの腸内細菌叢は，生後数カ月で100種類以上の成人と同等の構成が完成するといわれているが，健常な腸内細菌叢は腸管におけるIgA抗体の産生と，経口免疫寛容の誘導に必要で，特に乳児においてはアレルギーの発症を抑制する働きがあり，腸内細菌叢に影響する食物のバランスは重要である．乳酸菌などのプロバイオティクスを妊娠後期から授乳期に投与して，ア

トピー性皮膚炎の発症を抑制したというRCTsはある[2]が，乳児早期の投与に関する発症予防に関しては確かではない[3]．アトピー性皮膚炎を発症した患者に対する効果に関しては，やや重症の小児患者に限定すれば多少の効果が期待できるかも知れないが[4]，現時点では，腸内細菌叢の正常化をもたらすオリゴ糖や食物繊維など，プレバイオティクスを含む伝統的な食事で得られるメリットを生かした指導にとどめておくのが，保険診療上は無難と思われる．いずれにしても，これらは食物アレルゲンの除去とは異なる機序による対策である．

食物アレルギーの治療のために，加水分解乳やアミノ酸乳を使用しているケースでは，ビオチンが不足するため，離乳食が進まないと関連する代謝酵素の働きが不十分となり，皮膚病変が出現することがある．よく観察するとアトピー性皮膚炎とは異なる分布と皮疹であることがわかるが，湿疹病変であるため，外来で一見しただけでは誤診を受ける場合もある．こうしたケースはビオチンの補充により皮膚状態が改善するが，なるべく早く除去を解除して，可能な限り離乳食のレパートリーを増やした方がよい．

極端な除去食療法を受けている患児は，低栄養のために代謝が低下して湿疹も抑制されている．そこで，除去食を解除して現代風の高タンパク高脂肪食を摂れば，一過性に紅斑や瘙痒が認められる．これらの現象を，除去食試験によって湿疹が改善し，負荷試験によって原因食品が同定できたと解釈し，長期に多種目の除去食を続けたために成長障害を来し，なかには脚気やくる病を合併した幼児もいる．こうした誤診による被害者は少なくないが，精査の結果，真の食物アレルギーとして除去を必要とする食品数は極めて少なく，また食物アレルギーの関与によりアトピー性皮膚炎が悪化していたことを証明できた症例はほとんどいなかった．

このほかにも，様々な機序によって食物がアトピー性皮膚炎の悪化に影響することが考えられるが，多くは食物アレルギーとは異なる機序によるものである．アトピー性皮膚炎の悪化因子に食物が含まれているのは確かであるが，食物アレルギーと混同すべきではない．この問題を整理するために，図1に提示した概念を提唱する．すなわち，食物アレルギーに関しては除去食が必要となるが，アトピー性皮膚炎の治療のためには，除去食ではなくバランスのよい食事を心がけることが大切である．
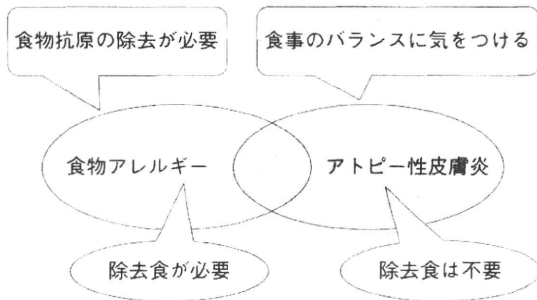
図1　食物アレルギーとアトピー性皮膚炎

2．皮膚感作による食物アレルギーの成立と経口免疫寛容

　昨今は，皮膚科医にも食物アレルギーが関与するアトピー性皮膚炎の存在が認知されたからであろうか，乳児期に発症した患者で食物除去を皮膚科医から指導されているケースが珍しくない．しかし，『食物アレルギーの診療の手引き』に記述された手順に従って診断されているケースはまれで，多くは血液検査や皮膚テストの結果を参考にして特異的IgE抗体が陽性と判定された食品の除去を指導されている．こうした検査の結果は，必ずしも当該食物に対するアレルギーがあることを意味しないため，過剰に食物除去を行うことになる．さらに問題だと思われるのは，授乳中の母親に対する食物除去指導である．これは小児科医，皮膚科医を問わず随分多いという印象を受ける（当科を受診した患者のアナムネ聴取の結果なので，重症患者というサンプルバイアスがある）．妊娠中および授乳中の母親の食物除去は，児の食物アレルギーやアトピー性皮膚炎の予防効果はないというRCTsが，Cochrane systematic reviewにメタアナリシスの結果として報告されている[5]．

　また，食物アレルギーがある患者本人に対する当該食物の除去は，正しい診断に基づくものであれば当然であるが，授乳中の母親に対しても行うべきとする根拠はない．むしろ，授乳中の母親の食物摂取により児の経口免疫寛容を誘導するという観点からすると，母親への除去指導は初期の軽度の食物アレルギーが自然治癒する機会を奪ってしまい，児の食物アレルギーを増加させる危険性すらある[6]．欧米では重篤なアナフィラキシーを呈するピーナツによる食物アレルギーの有病率が高く，米国小児科学会ではハイリスク妊婦と児に対するピーナツ摂取を，授乳中から3歳まで控えるようにというガイドラインを発行していたが，これは根拠がないとして2008年に取り下げとなった．こ

うした変化の背景には，多くの疫学研究による新たなエビデンスの発見や，動物実験によるメカニズム研究の進展がある．例えば，イスラエルと英国の子どものピーナツアレルギーの有病率は，後者が前者の10倍もあるが，説明変数の決定的な違いは，イスラエルの子どもは0歳からピーナツを摂取している率が高いのに対して，英国では除去している率が高いということである[7]．また，オランダの出生コホート研究では，児の乳製品の摂取開始時期が遅い方が2歳時点で湿疹を罹患している率が高くなること，その他の離乳食の開始時期が遅い（8カ月以降）児では2歳時のアトピー性皮膚炎の有病率が高いことが示された[8]．これらの研究の結果は，乳児期における経口免疫寛容の導入が，食物アレルギーの発症予防やアトピー性皮膚炎の悪化予防に効果がある可能性を示唆している．また，ピーナツ抗原の環境曝露が多い方が，ピーナツアレルギーの発症率が高くなるという報告もあり[9]，皮膚感作の可能性が示唆されている．これは動物実験の結果と矛盾しない．

　こうしたエビデンスをつなぎ合わせて考えると，食物アレルギーとアトピー性皮膚炎の新たな関係がみえてくる．すなわち，多くの乳児が離乳食開始前に顔面に湿疹を経験する．ハウスダストからはその国や家庭で多く消費される食物の抗原が検出されており，皮膚バリアが低下した乳児の皮膚は樹状細胞を介して感作刺激を受けやすい．母乳栄養児の場合は，顔についた母乳に含まれる食物抗原が感作刺激となるかも知れない．また，いったん感作が成立すれば，母乳から入ったわずかな食物抗原が軽度の蕁麻疹や瘙痒を惹起し，授乳期には持続的な皮膚病変が形成されるため，アトピー性皮膚炎と診断される状態を作り出す可能性はある．そして，授乳中の母親が当該食物を除去することで皮膚状態が改善するというのはあり得ることである．しかし，母乳から入る抗原刺激は微量であり，ステロイド外用薬を塗布することで消失させ得る程度の皮疹しか生じないのであれば，乳児ならば顔に4群，体幹や四肢には3群のステロイド外用薬を塗布すれば皮疹は速やかに消失する．そして，皮疹をなくした後は保湿薬の塗布により皮膚バリアを強化し，ステロイド外用薬は間欠塗布として副作用を回避していれば，母親の食物制限をしなくても，次第に経口免疫寛容が成立して食物による皮疹が生じなくなる．しかし，いったん母親が長期に食物制限を行うと，経口免疫寛容が失われ，再び摂取したときや児に直接当該食物を与えた

ときに，明らかな即時型反応を生ずる可能性が高くなる．

生後5カ月頃までは母親の食物制限で皮疹が改善したが，生後半年以降はその効果がはっきりと感じられなくなったというような母親の話は以前からよく聞く．乳児期に発症した早期の食物アレルギーの症状は，除去食により改善する可能性があるが，本格的なアトピー性皮膚炎は食物除去だけでは治療困難である．乳児期には免疫の状態も皮膚状態も急速な変化を遂げる．比較的月齢の早い乳児を診察する機会の多い小児科医と，月齢の遅い乳児や幼児を診察する皮膚科医とが受ける印象が異なるのは，上述したような機序によるのではないかと推察される．両者ともありのままを報告しているのであって，作為があるわけでないので，激しい論争が展開されたのであろう．

3．今後の乳児と母親への指導に関する提言

今われわれが必要としているのは，そうしたかつての論争に戻ることではなく，新しいパラダイムの構築である．すなわち，乳児の湿疹やアトピー性皮膚炎に対して，母親と患児それぞれに対してどのような食事指導を行うことが適切なのかという，議論の根拠となるパラダイムの更新が必要な時期に差し掛かっていると思われる．児に対しては新たな食物への皮膚感作を防ぐべく湿疹を速やかに治療すべきであり，授乳中の母親に対しては母乳を介した経口免疫寛容を誘導すべく，やむを得ない場合を除き（授乳後に明らかな症状を呈する場合や，ステロイド外用薬の連日塗布から脱出できない場合など），母親への食物制限を行わないことを提案したい．

しかしながら，現在の先進国で普及した加工品中心の食事内容はアトピー性皮膚炎対策としてはあまり好ましいものではない．脂肪酸のバランスや腸内細菌叢の正常化を促すような伝統的な和食への回帰が，グルメやロハスの特権ではなく，一般庶民の食生活の改善というレベルで実現するまでは，ある程度の食事指導を行った方がよいと思われる．これは食物除去指導とは全く異なるものであることを強調しておきたい．

これらの指導は，既存のアトピー性皮膚炎診療ガイドラインや食物アレルギーの手引きに矛盾するものではない．むしろ，明確な記述がないために不適切な除去指導や制限が行われている現状を懸念するものである．まだRCTレベルのエビデンスがあるわけではないが，コホート研究レベルのエビデンスに反する過剰な除去指導が横行している現状を改める意味で，今後の改訂で取り上げてもらいたい話題である．

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TABLE I. Sensitivity and specificity* for Ara h 2 and whole peanut extract

Test	Cutoff point (kU$_A$/L)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
Ara h 2	0.30	100.00	90.20	93.75
	0.32	100.00	94.12	95.00
	0.35	100.00	96.08	97.50
	0.38	96.55	96.08	96.25
	0.40	93.10	98.04	96.25
	0.55	93.10	100.00	97.50
	0.87	89.66	100.00	96.25
Whole extract	0.35	96.55	26.92	51.85
	3.91	79.31	84.62	82.72
	5.00	75.86	90.38	85.19
	5.30	75.86	94.23	87.65
	5.96	72.41	94.23	86.42
	7.81	72.41	96.15	87.65
	15.00	55.17	96.15	81.48
	43.86	34.85	98.08	75.31

Analysis included all children with available data (81 for sIgE to whole peanut extract and 80 for sIgE to Ara h 2).

*Sensitivity refers to the proportion of subjects who have peanut allergy and give positive test results. Specificity refers to the proportion of subjects without the target condition and a negative test result for peanut allergy.

peanut allergy and 50 are peanut-tolerant. By using sIgE to component Ara h 2 with a cutoff point of 0.35 kU$_A$/L, all children with peanut allergy would be correctly classified. The specificity of this test is given as 96.1% (Table I). In this example we expect 2 children who are not allergic to peanuts to be misclassified as having peanut allergy and the other 48 children to have a negative result. By using this cutoff point, 97.5% of the population is correctly classified. A similar proportion of children would be correctly classified by using a cutoff point of 0.55 kU$_A$/L; however, in this case 3 children with peanut allergy would be misclassified as tolerant. This cutoff point corresponds to a gain in specificity (100%) but a loss in sensitivity (93.1%). Given the importance of not misdiagnosing children with peanut allergy as being tolerant, we propose that the optimal cutoff point in our population is 0.35 kU$_A$/L.

The cutoff for whole peanut sIgE of 5.30 kU$_A$/L provides the maximum proportion of correctly classified subjects (87.6%), with a sensitivity of 75.9% and a specificity of 94.2%. However, approximately 24% of children with peanut allergy would be inappropriately classified as peanut-tolerant. The cutoff of 15 kU$_A$/L has excellent specificity, with 96.2% of children at greater than this level being correctly classified as allergic; however, this decision point has relatively poor sensitivity, with almost half of the subjects with peanut allergy being classified as tolerant. These data suggest that in our population the quantification of whole peanut sIgE has lower accuracy in discriminating peanut allergy from tolerance compared with quantification of sIgE to Ara h 2.

In conclusion, having identified sIgE to Ara h 2 as an important predictor of clinical reactivity to peanut using microarray technology,[5] we have now demonstrated the value of its quantification using a routinely available laboratory test. Among school-aged children in the United Kingdom, a cutoff of 0.35 kU$_A$/L Ara h 2 IgE confers 100% sensitivity and 96.1% specificity. By using this cutoff point, 97.5% of the subjects in our study population were correctly classified, with all children with peanut allergy given the correct classification. The importance of Ara h 2 has

been suggested in studies from other Central and Northern European countries[7,8]; however, in other populations and geographic areas, IgE to other components might be relevant (eg, Ara h 9 in the Mediterranean[9]). Our findings need to be replicated in other populations and age groups before general application.

Nicolaos Nicolaou, MD, PhD[a]
Clare Murray, MD[a]
Danielle Belgrave, MSc[a,b]
Maryam Poorafshar, PhD[c]
Angela Simpson, MD, PhD[a]
Adnan Custovic, MD, PhD[a]

From [a]the University of Manchester, Manchester Academic Health Science Centre, NIHR Translational Research Facility in Respiratory Medicine, University Hospital of South Manchester NHS Foundation Trust, Manchester, United Kingdom; [b]the Biostatistics Group, School of Community-Based Medicine, University of Manchester, Manchester, United Kingdom; and [c]Phadia AB, Uppsala, Sweden. E-mail: nic. nicolaou@googlemail.com.

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Four distinct subtypes of non–IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms

To the Editor:

Although most food allergies are IgE-mediated, there are a number of non–IgE-mediated gastrointestinal food allergies that affect mainly infants and young children.[1,2] Because most such
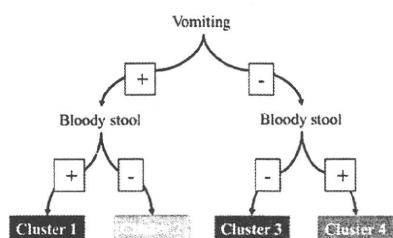
FIG 1. Tree analysis using 2 variables (vomiting and bloody stool at initial presentation) enables assignment of patients into 4 clusters.

patients develop the allergy more than 2 hours after ingestion of the offending food and show negative skin prick tests and/or absence of serum specific IgE against the offending food, these allergies are thought to be cell-mediated. However, the precise pathogenetic mechanisms of these disorders remain poorly understood. Several investigators have described different subtypes of non–IgE-mediated gastrointestinal food allergies: food protein-induced enterocolitis syndrome (FPIES),[3] food protein-induced proctocolitis syndrome (hereafter referred to as "proctocolitis"),[4] food protein-induced enteropathy syndrome (hereafter referred to as "enteropathy"),[5] celiac disease, and allergic eosinophilic gastroenteropathies.

Presumably because the main target organ of these syndromes is the gastrointestinal tract, patients with non–IgE-mediated gastrointestinal food allergies often exhibit similar symptoms, such as vomiting and diarrhea. However, it remains unclear whether these syndromes have the same pathogenesis and merely differ in severity, or whether the pathogenesis of each is distinct, meaning that they should be classified as separate clinical entities.

We applied cluster analysis to the clinical and laboratory findings to characterize these non–IgE-mediated food allergies and determine whether they are made up of distinct clinical entities. A total of 176 patients with detailed clinical records who had been registered in the database of the Japanese Research Group for Neonatal, Infantile Allergic Disorders from 2007 to 2010 were enrolled. Among them, 136 patients fulfilled 3 of the Powell[6] criteria: (1) a switch to therapeutic milk led to resolution of symptoms, (2) differential diagnosis from other disorders was possible, and (3) there was verified body weight gain. Definitive diagnosis was possible for 46 patients by oral food challenge tests that were performed after complete resolution of the initial symptoms (see this article's Fig E1 in the Online Repository at www.jacionline.org). These 46 patients were subjected to further analysis. Details of food challenge test are available in this article's Food challenge test, method section in the Online Repository at www.jacionline.org. Our total cohort included 15 patients who developed the most severe reactions, including ileus, shock, and developmental retardation. The clinical characteristics of those patients are summarized in this article's Table E1 in the Online Repository at www.jacionline.org. Because of the medical and ethical justification, even though these patients fulfilled 3 elements of the Powell[6] criteria, oral challenge tests were not performed. Thus, these patients were excluded from this cluster analysis of 46 patients. This study was approved by the Ethics Committee of the National Center for Child Health and Development.

We omitted clinical and laboratory findings found only in a few patients and finally selected 5 variables: birth weight, age at first presentation (days after birth), severity of vomiting (ranked as 0, none; 1, 1-2 times a day; 2, 3-5 times a day; and 3, more than 5 times a day or bilious vomiting) and severity of bloody stool (0, none; 1, spotty; 2, intermediate; and 3, massive) at first presentation, and milk-specific IgE antibody titer (class 0-6). Unsupervised cluster analysis and discriminant analysis were performed by using SPSS version 18 software (SPSS, Inc, Chicago, Ill). The Wald minimum-variance hierarchic clustering method was performed by using an agglomerative (bottom-up) approach and Ward's linkage. The squared Euclidean distance was used as a proximity measure. Values were transformed by a maximum magnitude of 1. ANOVA, the Tukey-Kramer test, and the χ^2 test were used for parametric continuous, nonparametric continuous, and categoric variables. As a result, the 46 definitively diagnosed patients were classified into 4 distinct clusters, and a dendrogram was generated (see this article's Fig E2 in the Online Repository at www.jacionline.org).

Stepwise discriminate analysis identified the 2 strongest discriminatory variables for cluster assignment: vomiting and bloody stool (Fig 1). Cluster 1 was the patient group with vomiting and bloody stool at initial presentation. Cluster 2 had vomiting but not bloody stool. Cluster 3 had neither vomiting nor bloody stool. Cluster 4 had bloody stool but not vomiting. One patient initially assigned to cluster 3 in fact had clear bloody stool, and was thus reassigned to cluster 4 in accordance with Fig 1. As a result, clusters 1 through 4 consisted of 14, 16, 5, and 11 patients, respectively.

Table I presents the demographic data for each cluster. Cluster 3 showed a significantly lower birth weight and later onset of disease. Clusters 1 and 4 both had bloody stool, but they had normal birth weight and a somewhat earlier onset (median of 7 days after birth).

The laboratory data generated within the initial several days after onset showed that the peripheral blood eosinophil ratio was high in all clusters, with no significant differences among them. In contrast, eosinophils were found in the stool mainly of patients in clusters 1 and 4, in which all patients, by definition (Fig 1), had bloody stool. The presence of eosinophilia suggests that patients with non–IgE-mediated gastrointestinal food allergies tend to have a T_H2-prone immune deviation at baseline, but some additional factors such as overproduction of eosinophil-attracting chemokines are probably necessary to induce immune responses involving eosinophils in the gut (see this article's Fig E3 in the Online Repository at www.jacionline.org).

A positive milk-specific IgE antibody titer was observed in 37% of the patients, with no statistically significant differences among any of the clusters. In addition, almost all symptoms at initial presentation as well as in oral food challenge tests began to manifest at more than 2 hours after ingestion of the offending food, whereas no patients developed typical IgE-mediated symptoms such as urticaria or wheeze. These results strongly suggest that the presence of milk-specific IgE antibody neither causes the gastrointestinal symptoms nor rules out a diagnosis of non–IgE-mediated gastrointestinal food allergy.

One of the most notable findings of this study was the remarkably high reproducibility of symptoms provoked in the oral food challenge tests and those found at the initial presentation in all 4 clusters, even though the oral challenge tests were performed several months after the initial presentation (Table I). This observation suggests that the upper or lower gastrointestinal tract–specific hypersensitivity and perhaps the responsible

TABLE I. Demographic data of the patients (total = 46) whose diagnosis was confirmed by oral food challenge tests

Clinical characteristics		Cluster 1 (n = 14)		Cluster 2 (n = 16)		Cluster 3 (n= 5)		Cluster 4 (n = 11)	P value
Birth weight (g)		2642 (2410-3030)		2745 (2223-3079)		1008 (907-2491)		2678 (2512-3170)	.03*
Male/female (n)		6/8		9/7		2/3		5/6	.95
Initial presentation									
Day of onset		7.5 (3-23)		16.5 (9.5-33.5)		37 (8.5-132)		7 (2-56)	.17
Vomiting (%)		100		100		0		0	.000*
Bloody stool (%)		100		0		0		100	.000*
Fever (%)		7.1		18.8		20.0		0	.45
(Laboratory data)†	n		n		n		n		
Blood eosinophil ratio (%)‡	13	15 (3.0-23)	14	7 (3.9-19.3)	5	27 (3.2-39.3)	11	14 (4.5-25)	.63
WBC (×10³/mL)§	13	18.4 (13.7-22.7)	14	15.7 (11.4-21.9)	5	21.8 (11.0-27.7)	11	13.1 (8.2-18.3)	.64
Total IgE (IU/mL)‖	14	5.2 (4.8-28.3)	16	11.4 (5.0-80.8)	5	7.4 (5.5-653.5)	10	5.0 (2.0-5.8)	.36
Positive for milk-specific IgE (class ≥1) (%)	14	57	16	37.5	5	40	11	9	.28
C-reactive protein (% positive, ≥0.5)	13	46	14	50	5	40	10	30	.47
Stool eosinophil (% positive)	8	50	6	33	3	0	7	100	.01*
Diet (reaction to each milk, %)									
Cow's milk	14	100	16	100	5	100	10	100	1.00
Breast milk	8	38	7	0	2	50	7	27	.40
Hydrolyzed formula	9	0	10	20	2	0	8	63	.02*
Oral food challenge test									
Onset of reaction (h)		6 (1.8-12)		10 (2-24)		48 (24-60)		24 (24-48)	.17
Vomiting (%)		85.7		81.3		0		9.1	.000*
Bloody stool (%)		28.6		6.3		0		72.7	.001*
Diarrhea (%)		21.4		31.3		60.0		18.2	.33

WBC, White blood cell count.
Data are shown as the median and the interquartile range.
*P < .05.
†n, Number with medical records.
‡Normal range of blood eosinophils is 0% to 4%. However, it is known to rise to some degree in the neonatal period, especially in low-birth-weight infants.[10]
§Normal range of WBC in neonatal period is 7.0 to 25.0 × 10³/μL.
‖Normal range of total IgE in infantile period is less than 20 IU/mL.

immune cells remain in the same part of the gastrointestinal tract even after several months' remission.

Because the patients in clusters 1 and 2 had vomiting that was provoked at relatively early time points, they are likely to be diagnosed as having FPIES, although the bloody stool and eosinophilia seen mainly in cluster 1 patients were not emphasized in earlier reports.[7,8] The nearly simultaneous manifestation of vomiting and bloody stool suggests that FPIES may affect both the upper and lower gastrointestinal tracts.

The main symptoms of the patients in cluster 3 were poor weight gain and diarrhea and were similar to those found in patients with enteropathy. The significantly lower birth weight and marked eosinophilia characteristically found in cluster 3 patients imply the involvement of immature gastrointestinal function in the pathogenesis of this syndrome.

Bloody stool was the main symptom of the patients in cluster 4. Some patients in this cluster had no systemic manifestation other than bloody stool, whereas others also had diarrhea and/or poor weight gain. Therefore, these patients may be diagnosed as having proctocolitis or early onset of allergic eosinophilic gastroenteropathies, respectively. However, the pathogenetic similarity and/or disparity of proctocolitis and allergic eosinophilic gastroenteropathies need to be studied further.

In our cohort, 3 children with exclusive breast-feeding have developed FPIES. This information is available in this article's Breast-feeding and FPIED section in the Online Repository at www.jacionline.org.

Elevated serum C-reactive protein levels were found in 30% to 50% of patients with non–IgE-mediated gastrointestinal food allergies. In addition, some patients developed a fever during oral food challenge tests, suggesting that TNF-α and other proinflammatory cytokines may be involved in the pathogenesis of these syndromes.[9]

To confirm the results of cluster analysis, we performed the same analysis for the aforementioned 136 patients who fulfilled 3 of the Powell[6] criteria (consisting of the 46 patients definitively diagnosed by oral food challenge and 90 patients not subjected to oral food challenge; Fig E1). We obtained exactly the same results: the patients were assigned to 4 clusters in accordance with the tree analysis shown in Fig 1. The patients' demographics (see this article's Table E2 in the Online Repository at www.jacionline.org), birth weight (see this article's Fig E4 in the Online Repository at www.jacionline.org) and peripheral blood eosinophils (see this article's Fig E5 in the Online Repository at www.jacionline.org) confirmed the earlier cluster analysis findings.

In our ongoing cohort, 52% of the patients acquired tolerance to the offending food by 1 year of age, 88% by 2 years, and 94% by 3 years. Therefore, assuming that identification and elimination of the offending food had been done properly, it can be assumed that most patients outgrew their allergy by the age of 2 to 3 years. On the other hand, just like patients with severe IgE-mediated food allergy, patients with non–IgE-mediated gastrointestinal food allergies may develop severe reactions

(Table E1). Thus, early diagnosis is very important, and refinement of the diagnostic method is truly necessary.

Our findings clearly demonstrated that patients with these non–IgE-mediated gastrointestinal food allergies showed similar T_h2-prone laboratory data (eosinophilia and presence of specific IgE antibody), but the disease entities of each cluster had distinct clinical features and may have different pathogenetic mechanisms.

Ichiro Nomura, MD, PhD[a,d]
Hideaki Morita, MD[d,e]
Shinichi Hosokawa, MD[f]
Hiroaki Hoshina, MD[g]
Tatsuki Fukuie, MD[a]
Misa Watanabe, MD, PhD[h]
Yoshikazu Ohtsuka, MD, PhD[i]
Tetsuo Shoda, MD[j]
Akihiko Terada, MD, PhD[k]
Tetsuya Takamasu, MD[l]
Katsuhiro Arai, MD[b]
Yushi Ito, MD[c]
Yukihiro Ohya, MD, PhD[a]
Hirohisa Saito, MD, PhD[d]
Kenji Matsumoto, MD, PhD[d]

From the Divisions of [a]Allergy, [b]Gastroenterology, and [c]Neonatology, National Center for Child Health and Development, Tokyo; [d]the Department of Allergy and Immunology, National Research Center for Child Health and Development, Tokyo; [e]the Department of Pediatrics, Keio University School of Medicine, Tokyo; [f]the Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka; [g]the Department of Pediatrics, Kyorin University School of Medicine, Tokyo; [h]the First Department of Pediatrics, Toho University Omori Medical Center, Tokyo; [i]the Department of Pediatrics, Juntendo University School of Medicine, Tokyo; [j]the Department of Pediatrics, Yokohama City Minato Red Cross Hospital, Yokohama; [k]the Department of Pediatric Allergy, Daido Hospital, Nagoya; and [l]the Department of Allergy, Kanagawa Children's Medical Center, Yokohama, Japan. E-mail: nomura-i@ncchd.go.jp and matsumoto-k@ncchd.go.jp.

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FOOD CHALLENGE TEST, METHOD

Generally, oral challenge tests were performed at 4 to 6 months of age. First, 4 mL milk/kg body weight was administered. If no reaction occurred, the dose of milk was increased daily until symptoms manifested. If the reaction had been evoked by a very small volume of milk in the initial presentation, the test was started using a lesser volume to avoid a serious reaction. Because of the medical and ethical justification for oral food challenge tests, patients with the most severe reactions were excluded from the initial cluster analysis. Their clinical characteristics are summarized in Table E1.

BREAST-FEEDING AND FPIES

Six of the 46 patients were exclusively breast-fed. Three of them were included in cluster 1 and can be diagnosed as FPIES. Those 3 patients showed a positive reaction to cow's milk as well as breast milk even after their mothers stopped consuming milk products. These patients also developed symptoms when orally challenged with rice and/or soy. Therefore, these findings indicate that not only proctocolitis but also FPIES can develop even in children who are exclusively breast-fed. A recent case report supports our findings.[E1]

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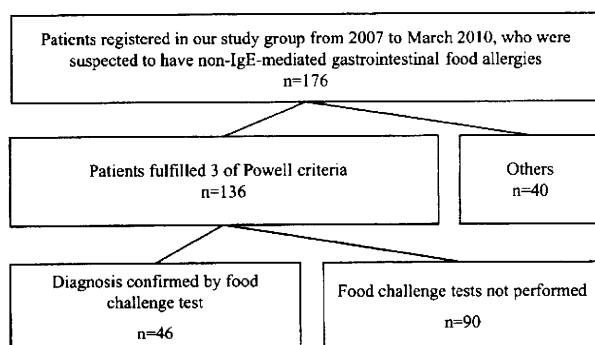
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┌─────────────────────────────────────────────────────┐
│  Patients registered in our study group from 2007 to  │
│  March 2010, who were suspected to have non-IgE-      │
│  mediated gastrointestinal food allergies             │
│                    n=176                              │
└─────────────────────────────────────────────────────┘

┌──────────────────────────────────┐   ┌──────────────┐
│  Patients fulfilled 3 of Powell  │   │   Others     │
│  criteria                        │   │   n=40       │
│              n=136               │   │              │
└──────────────────────────────────┘   └──────────────┘

┌──────────────────────────────┐  ┌──────────────────────────────┐
│  Diagnosis confirmed by food  │  │  Food challenge tests not     │
│  challenge test               │  │  performed                    │
│              n=46             │  │              n=90             │
└──────────────────────────────┘  └──────────────────────────────┘
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FIG E1. A total of 176 patients with gastrointestinal symptoms who were suspected of having non–IgE-mediated allergy from 1999 to 2009 were registered by doctors of the Japanese Research Group for Neonatal, Infantile Allergic Disorders. Of them, 136 patients fulfilled elements 1 through 3 of the Powell criteria. Forty-six patients underwent food challenge tests and had a positive result, whereas the remaining 90 patients were not tested. Seventeen patients showed no reaction in the oral challenge tests. However, it was unclear whether this was because the patients had outgrown their allergy or because of misdiagnosis. Those 17 patients were excluded from further analysis in this study.
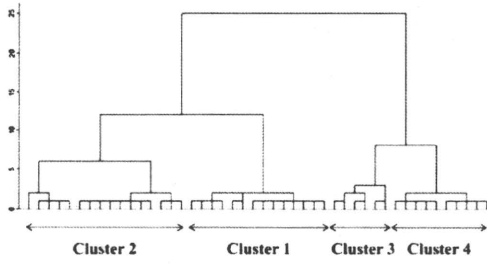
FIG E2. The 46 patients definitively diagnosed with non–IgE-mediated food allergies were analyzed for 5 variables by using an agglomerative (bottom-up) approach and Ward's linkage, and a dendrogram was generated.
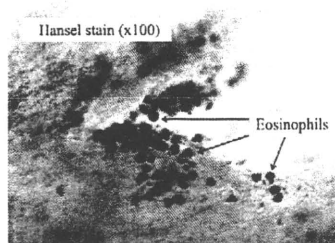
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Hansel stain (x100)

Eosinophils

FIG E3. Detection of accumulations of eosinophils in the stool mucus. The mucous part of the stool was thinly smeared on a glass slide and stained by using Hansel stain. The stool sample was taken from a patient in cluster 2 after a positive food challenge test. Representative images were found in a total of 13 patients (Table I).
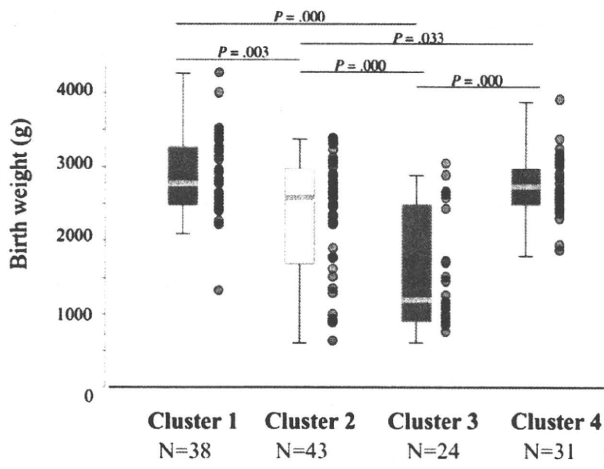
FIG E4. The birth weights in each cluster of the 136 patients who fulfilled 3 elements of the Powell criteria for a non–IgE-mediated allergy are shown.[E2] The birth weights in cluster 3 were significantly lower than in the other clusters. Moreover, 2 subgroups seem to be identified in cluster 3: a lower birth weight group and a normal birth weight group.
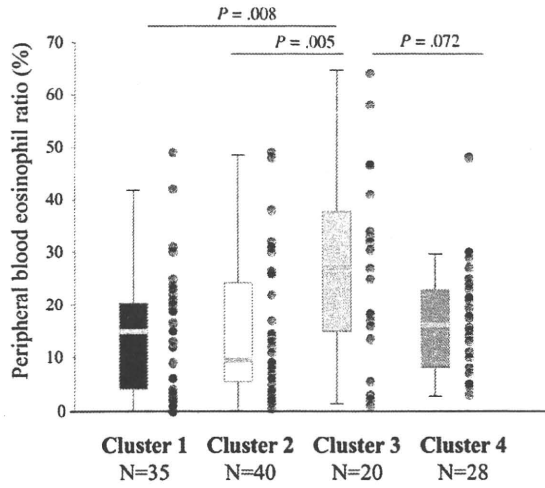
FIG E5. The peripheral blood eosinophil ratios in each cluster of the 136 patients who fulfilled 3 elements of the Powell criteria are shown.[E2] Although eosinophilia was found in all 4 clusters, the eosinophil ratios of the patients in cluster 3 were significantly higher than those of the patients in clusters 1 and 2.

TABLE E1. Clinical features of most severe cases of non–IgE-mediated gastrointestinal food allergies*

Patient no.	Sex	Cluster	Complication	Day of onset	Diet right before the onset of complications	Remarks
1	F	1	Ileus	8	Cow's milk 7 d	
2	M	1	Ileus	5	Cow's milk 3 d, breast milk 6 d	Relieved by surgical operation
3	F	1	Ileus	8	Breast milk 9 d	Relieved by surgical operation
4	F	1	Shock	2	Cow's milk 2-3 times	Massive bloody stool, blood infusion required
5	F	1	Shock	21	Breast milk 18 d	Massive bloody stool, disseminated intravascular coagulation
6	F	2	Ileus	14	Breast milk 2 d	
7	F	2	Shock	36	Breast milk 30 d	Apnea, vomiting
8	M	2	Shock	30	Cow's milk 50 mL by chance	Vomiting
9	M	2	Shock	241	Soy food 2-3 times	Vomiting and diarrhea, ICU admission
10	M	3	Ileus	61	Breast milk 45 d	Cholestasis
11	F	3	Shock	22	Cow's milk 21 d, breast milk 21 d	ICU admission
12	F	3	Severe weight loss	12	Breast milk several months	Developmental retardation
13	M	3	Severe weight loss	46	Cow's milk 30 d, breast milk 30 d	Developmental retardation
14	F	4	Ileus	2	Cow's milk 6 d, breast milk 3 d	Stenosis of sigmoid colon
15	F	4	Ileus	7	Cow's milk 10 d	

F, Female; *ICU*, intensive care unit; *M*, male.

*These patients fulfilled 3 elements of the Powell criteria,[E2] but oral challenge tests were not performed.

TABLE E2. Demographics of the 136 patients who fulfilled 3 elements of the Powell criteria[E2]

Clinical characteristics		Cluster 1 (n = 38)		Cluster 2 (n = 43)		Cluster 3 (n = 24)		Cluster 4 (n = 31)	P value
Birth weight (g)		2823 (2501-3267)		2581 (1779-3016)		1363 (1023-2611)		2778 (2512-3100)	.000 *
Male/female		19/19		28/15		13/11		12/19	.16
Initial presentation									
Day of onset		6 (4-8)		29 (7.5-52)		16.5 (9.5-37.5)		7 (2-35)	.01*
Vomiting (%)		100		100		0		0	.000*
Bloody stool (%)		100		0		0		100	.000*
(**Laboratory data**)†	n		n		n		n		
Blood eosinophil ratio (%)	35	15 (3.5-21.0)	40	9 (5.3-25.0)	20	26 (14.1-39.3)	28	17 (8.5-23.8)	.005*
WBC (×10³/mL)	32	18.7 (14.5-23.5)	40	13.8 (10.4-22.1)	23	15.9 (13.9-24.4)	27	13.9 (11.4-19.5)	.16
Total IgE (IU/mL)	32	5.2 (4.1-23.1)	40	5.8 (4.0-17.8)	22	13.2 (5.5-122.9)	28	5.0 (3.3-6.0)	.001*
Positive for milk-specific IgE (class ≥1) (%)	31	41.9	38	23.7	20	50	27	19	.24
C-reactive protein (% positive, ≥0.5)	36	61	40	45	20	70	27	33	.69

WBC, White blood cell count.
Data are shown as the median and the interquartile range.
*P < .05.
†*n,* Number with medical records.

PEDIATRIC ALLERGY AND IMMUNOLOGY

World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines

Alessandro Fiocchi, (Chair), Jan Brozek, Holger Schünemann, (Chair), Sami L. Bahna, Andrea von Berg, Kirsten Beyer, Martin Bozzola, Julia Bradsher, Enrico Compalati, Motohiro Ebisawa, Maria Antonieta Guzmán, Haiqi Li, Ralf G. Heine, Paul Keith, Gideon Lack, Massimo Landi, Alberto Martelli, Fabienne Rancé, Hugh Sampson, Airton Stein, Luigi Terracciano and Stefan Vieths

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Correspondence to: Alessandro Fiocchi, MD, Paediatric Division, Department of Child and Maternal Medicine, University of Milan Medical School at the Melloni Hospital, Milan 20129, Italy E-mail: allerg@tin.it.

Authorship

Alessandro Fiocchi, MD, Pediatric Division, Department of Child and Maternal Medicine, University of Milan Medical School at the Melloni Hospital, Milan 20129, Italy.

Holger J. Schünemann, MD,[a] Department of Clinical Epidemiology & Biostatistics, McMaster University Health Sciences Centre, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada.

Sami L. Bahna, MD, Pediatrics & Medicine, Allergy & Immunology, Louisiana State University Health Sciences Center, Shreveport, LA 71130.

Andrea Von Berg, MD, Research Institute, Children's department, Marien-Hospital, Wesel, Germany.

Kirsten Beyer, MD, Charité Klinik für Pädiatrie m.S. Pneumologie und Immunologie, Augustenburger Platz 1, D-13353 Berlin, Germany.

Martin Bozzola, MD, Department of Pediatrics, British Hospital-Perdriel 74-CABA-Buenos Aires, Argentina.

Julia Bradsher, PhD, Food Allergy & Anaphylaxis Network, 11781 Lee Jackson Highway, Suite 160, Fairfax, VA 22033.

Jan Brozek, MD,[a] Department of Clinical Epidemiology & Biostatistics, McMaster University Health Sciences Centre, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada.

Enrico Compalati, MD,[a] Allergy & Respiratory Diseases Clinic, Department of Internal Medicine, University of Genoa, 16132, Genoa, Italy.

1

Motohiro Ebisawa, MD, Department of Allergy, Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Kanagawa 228-8522, Japan.

Maria Antonieta Guzmán, MD, Immunology and Allergy Division, Clinical Hospital University of Chile, Santiago, Chile. Santos Dumont 999.

Haiqi Li, MD, Professor of Pediatric Division, Department of Primary Child Care, Children's Hospital, Chongqing Medical University, China, 400014.

Ralf G. Heine, MD, FRACP, Department of Allergy & Immunology, Royal Children's Hospital, University of Melbourne, Murdoch Children's Research Institute, Melbourne, Australia.

Paul Keith, MD, Allergy and Clinical Immunology Division, Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Gideon Lack, MD, King's College London, Asthma-UK Centre in Allergic Mechanisms of Asthma, Department of Pediatric Allergy, St Thomas' Hospital, London SE1 7EH, United Kingdom.

Massimo Landi, MD, National Pediatric Healthcare System, Italian Federation of Pediatric Medicine, Territorial Pediatric Primary Care Group, Turin, Italy.

Alberto Martelli, MD, Pediatric Division, Department of Child and Maternal Medicine, University of Milan Medical School at the Melloni Hospital, Milan 20129, Italy.

Fabienne Rancé, MD, Allergologie, Hôpital des Enfants, Pôle Médicochirurgical de Pédiatrie, 330 av. de Grande Bretagne, TSA 70034, 31059 Toulouse CEDEX, France.

Hugh Sampson, MD, Jaffe Food Allergy Institute, Mount Sinai School of Medicine, One Gustave L. Levy Place, NY 10029-6574.

Airton Stein, MD, Conceicao Hospital, Porto Alegre, Brazil.

Luigi Terracciano, MD,[a] Pediatric Division, Department of Child and Maternal Medicine, University of Milan Medical School at the Melloni Hospital, Milan 20129, Italy.

Stefan Vieths, MD, Division of Allergology, Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines, Paul-Ehrlich-Str. 51-59, d-63225 Langen, Germany.

[a]Member of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group

Revision Panel

Amal Assa'ad, MD, Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

Carlos Baena-Cagnani, MD, LIBRA foundation Argentina, Division of Immunology and Respiratory Medicine, Department of Pediatric, Infantile Hospital Cordoba, Santa Rosa 381, 5000 Cordoba, Argentina.

GR Bouygue, MSc, Pediatric Division, Department of Child and Maternal Medicine, University of Milan Medical School at the Melloni Hospital, Milan 20129, Italy.

Walter Canonica, MD, Allergy & Respiratory Diseases Clinic, Department of Internal Medicine. University of Genoa, 16132, Genoa, Italy.

Christophe Dupont, MD, Service de gastroentérologie et nutrition, Hôpital Saint Vincent de Paul, 82, avenue Denfert-Rochereau, 75674, Paris CEDEX 14, France.

Yehia El-Gamal, MD, Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Matthew Fenton, MD, Asthma, Allergy and Inflammation Branch, National Institute of Allergy and Infectious Diseases, NIH, 6610 Rockledge Dr., Bethesda, MD 20892.

Rosa Elena Huerta Hernandez, MD, Pediatric Allergy Clinic, Mexico City, Mexico.

Manuel Martin-Esteban, MD, Allergy Department, Hospital Universitario La Paz, Madrid, Spain.

Anna Nowak-Wegrzyn, MD, Jaffe Food Allergy Institute, Mount Sinai School of Medicine, One Gustave L. Levy Place, NY 10029-6574.

Ruby Pawankar, MD, Department of Otolaryngology, Nippon Medical School, 1-1-5 Sendagi, Tokyo, 113 Japan.

Susan Prescott, MD, School of Pediatrics and Child Health, University of Western Australia, Princess Margaret Hospital for Children, Perth, Australia.

Patrizia Restani, PhD, Department of Pharmacological Sciences, Università degli Studi di Milano.

Teresita Sarratud, MD, Department of Pediatrics, University of Carabobo Medical School at the Carabobo Hospital, Valencia, Venezuela.

Aline Sprikkelmann, MD, Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital Academic Medical Centre, Amsterdam, The Netherlands.

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Sections

Section 1: Introduction

Allergy and clinical immunology societies have issued guidance for the management of food allergy.[1,2] Guidelines are now regarded as translational research instruments, designed to provide cutting-edge benchmarks for good practice and bedside evidence for clinicians to use in an interactive learning context with their national or international scientific communities. In the management of cow's milk allergy (CMA), both diagnosis and treatment would benefit from a reappraisal of the more recent literature, for "current" guidelines summarize the achievements of the preceding decade, deal mainly with prevention (3–6), do not always agree on recommenda-

tions and date back to the turn of the century (7, 8). In 2008, the World Allergy Organization (WAO) Special Committee on Food Allergy identified CMA as an area in need of a rationale-based approach, informed by the consensus reached through an expert review of the available clinical evidence, to make inroads against a burdensome, world-wide public health problem. It is in this context that the WAO Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines was planned to provide physicians everywhere with a management tool to deal with CMA from suspicion to treatment. Targeted (and tapped for their expertise), both on the DRACMA panel or as nonsitting reviewers, were allergists, pediatricians (allergists and generalists), gastroenterologists, dermatologists, epidemiologists, methodologists, dieticians, food chemists, and representatives of allergic patient organizations. Ultimately, DRACMA is dedicated to our patients, especially the younger ones, whose burden of issues we hope to relieve through an ongoing and collective effort of more interactive debate and integrated learning.

Definitions

Adverse reactions after the ingestion of cow's milk can occur at any age from birth and even among infants fed exclusively at the breast, but not all such reactions are of an allergic nature. A revision of the allergy nomenclature was issued in Europe in 2001 (9) and was later endorsed by the WAO (10) under the overarching definition of "milk hypersensitivity," to cover nonallergic hypersensitivity (traditionally termed "cow's milk intolerance") and allergic milk hypersensitivity (or "cow's milk allergy"). The latter definition requires the activation of an underlying immune mechanism to fit. In DRACMA, the term "allergy" will abide by the WAO definition ("*allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms*"). In most children with CMA, the condition can be immunoglobulin E (IgE)-mediated and is thought to manifest as a phenotypical expression of atopy, together with (or in the absence of) atopic eczema, allergic rhinitis and/or asthma. A subset of patients, however, have non-IgE mediated (probably cell-mediated) allergy and present mainly with gastro-intestinal symptoms in reaction to the ingestion of cow's milk.

References, Section 1

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