

好酸球性消化管疾患と腸内細菌叢

正田 哲雄

シンシナティ小児病院医療センター アレルギー・免疫学部門 アメリカ

略歴

出生年・地

1978年、埼玉県深谷市

最終学歴：

2014年 愛知医科大学大学院医学研究科修了（医学博士）

主な職歴：

東海大学医学部卒業後、茅ヶ崎徳洲会総合病院、横浜市立みなと赤十字病院、国立成育医療研究センターを経て、2016年よりシンシナティ小児病院医療センター。2022年より同センター／シンシナティ大学医学部 Assistant Professor。2026年より東京大学定量生命科学研究所 客員准教授。

主な研究テーマ：

好酸球性消化管疾患の精密医療、分子エンドタイプ、遺伝学、上皮バリア障害、患者由来オルガノイドおよびマルチオミクス解析。

主な受賞：

STAT Wunderkind（2021年）、UJA 論文賞（2022年、2023年）、American Society for Clinical Investigation Young Physician-Scientist Award（2024年）。

要旨

好酸球性消化管疾患（eosinophilic gastrointestinal diseases: EGIDs）は、消化管の部位特異的な症状と好酸球優位の粘膜炎症を特徴とする慢性免疫介在性疾患群であり、好酸球性食道炎（eosinophilic esophagitis: EoE）と、好酸球性胃炎・十二指腸炎・小腸炎・大腸炎などの非 EoE 型 EGIDs に大別される。なかでも EoE は、食物抗原によって誘導される 2 型免疫応答、上皮バリア障害、遺伝的素因が病態の中心をなす代表的な疾患であり、食事、宿主免疫、局所環境の相互作用を検討するモデルとして重要である。一方、EGIDs における腸内細菌叢の研究はまだ発展途上であり、エビデンスの大部分は EoE に集中している。

EoE の増加を遺伝的変化だけで説明することは難しく、乳幼児期の抗菌薬使用、帝王切開、早産、新生児集中治療、酸分泌抑制薬、感染症など、微生物叢の形成に影響し得る環境因子との関連が報告されている^{1,2)}。これらの知見は、微生物への曝露低下やディスバイオシスが免疫寛容の成立を妨げるという仮説と整合する。しかし、観察研究には基礎

疾患、医療利用、薬剤使用などの交絡があり、微生物叢の変化が EoE の原因であることを直接示すものではない。したがって、発症前の微生物環境が病態を形成する可能性と、炎症や治療の結果として微生物叢が変化する可能性を区別する必要がある。

また、「腸内細菌叢」を論じる際には、便で評価される大腸中心の微生物叢と、食道や胃の粘膜に局在する微生物叢を区別することが重要である。初期の比較的小規模な研究では、活動期 EoE における食道の総細菌量の増加、*Proteobacteria*、*Haemophilus*、*Neisseria* などの相対的増加、対照群における *Firmicutes* や *Streptococcus* 優位などが報告された^{3,4)}。唾液や便の解析でも患者群と対照群の差が示されたが、菌種、方向性、多様性に関する結果は研究間で必ずしも一致していない⁵⁾。採取法、年齢、地域、食事、抗菌薬、PPI、局所ステロイド、疾患活動性などが結果に大きく影響するためである。

この不均一性を明確に示したのが、米国 10 施設から EoE、好酸球性胃炎 (EoG) および対照を集積した CEGIR の多施設研究である⁶⁾。同研究では、EoE 食道粘膜で *Streptococcus* と *Gemella*、EoG 胃粘膜で *Prevotella* や *Leptotrichia* など、疾患活動性に関連する優占菌が認められた一方、 α 多様性は群間で大きく異ならず、個人差が顕著であった。さらに、便の細菌叢は食道・胃粘膜の細菌叢と相関せず、患者と対照でも明瞭な差を示さなかった。この結果は、単一の「EGID 特異的腸内細菌叢」を想定するよりも、疾患部位、宿主背景、炎症、食事および治療を含む局所生態系として理解すべきことを示している。

微生物叢が EGID 病態を修飾する機序としては、微生物由来分子によるパターン認識受容体シグナル、短鎖脂肪酸やトリプトファン代謝物などによる上皮分化・粘液産生・細胞間接着の調節、制御性 T 細胞と 2 型免疫応答のバランス、さらに好酸球、肥満細胞、自然リンパ球などへの作用が考えられる。動物モデルでは、食道固有の細菌叢が移植可能であり、新生仔期の抗菌薬投与による *Lactobacillales* の減少が食道の 2 型炎症を増強することが示された⁷⁾。しかし、ヒト EoE における短鎖脂肪酸やインドールの局所濃度、好酸球表現型、臨床転帰を直接結び付けるデータは限られており、現在は有力な機序仮説として位置付けるのが妥当である。

食事療法、PPI、局所ステロイド、生物学的製剤はいずれも、炎症を改善すると同時に微生物の生育環境を変化させ得る。食物除去療法後に食道の細菌量や構成が変化すること、治療法ごとに異なる変化が生じること、また食物繊維摂取量が食道細菌叢と関連することが報告されている^{8,9)}。一方、食事介入によって全体の微生物構造が有意に変化しなかった研究もあり⁴⁾、観察された変化が治療効果の原因なのか、炎症寛解の結果なのかは明らかでない。現時点では、プロバイオティクス、プレバイオティクス、便微生物移植、特定菌や代謝物を標的とする治療を EGIDs の日常診療に推奨する根拠は確立していない。

本講演では、EoE を中心に EGIDs の臨床的・分子的多様性を概説し、早期環境因子、食道粘膜および便の微生物叢、微生物代謝物、食事・薬物治療との関係を整理する。今後は、治療前後を追跡する縦断的な粘膜・便ペア解析、食事と薬剤曝露の精密な評価、メタゲノム・メタボローム解析に加え、宿主遺伝学、組織トランスクリプトーム、空間解析、患者由来細胞・オルガノイドを統合する必要がある。日本・アジアの食文化、微生物環境、臨床表現型を反映したコホートを構築し、「原因」「病態修飾因子」「治療反応の指標」「炎症の結

果」を切り分けることが、マイクロバイオーームを EGIDs の精密医療へつなげる鍵となる。

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Eosinophilic gastrointestinal diseases and the gut microbiome

Tetsuo Shoda

Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center,
USA

Brief Curriculum Vitae

Year and place of birth

1978, Fukaya, Saitama, Japan

Education

PhD in Medicine, Aichi Medical University Graduate School of Medicine, 2014.

Career

After graduating from Tokai University School of Medicine, Dr. Shoda trained and worked at Chigasaki Tokushukai General Hospital, Yokohama City Minato Red Cross Hospital, and the National Center for Child Health and Development in Japan. He joined Cincinnati Children's Hospital Medical Center in 2016 and became Assistant Professor at Cincinnati Children's and the University of Cincinnati College of Medicine in 2022. Since 2026, he has also served as Visiting Associate Professor at the Institute for Quantitative Biosciences, The University of Tokyo.

Major fields of study

Precision medicine in eosinophilic gastrointestinal diseases, molecular endotypes, genetics, epithelial barrier dysfunction, patient-derived organoids, and multi-omics.

Selected honors: STAT Wunderkind (2021); UJA Outstanding Research Paper Awards (2022 and 2023); American Society for Clinical Investigation Young Physician-Scientist Award (2024).

Abstract

Eosinophilic gastrointestinal diseases (EGIDs) are chronic immune-mediated disorders characterized by organ-specific gastrointestinal symptoms and eosinophil-predominant mucosal inflammation. They include eosinophilic esophagitis (EoE) and non-EoE EGIDs affecting the stomach, duodenum, small intestine, and colon. EoE, the best-characterized EGID, is driven largely by food antigens and involves type 2 immunity, epithelial barrier dysfunction, and genetic susceptibility. It therefore provides an informative model for examining interactions among diet, host immunity, and the local microbial environment. Nevertheless, microbiome research in EGIDs remains at an early stage, and most available evidence concerns EoE rather

than non-EoE EGIDs.

The rapid increase in EoE cannot be explained by genetic change alone. Early-life exposures that can influence microbial colonization—including antibiotics, cesarean delivery, prematurity, neonatal intensive care, acid-suppressive medication, and infection—have been associated with subsequent EoE risk.^{1,2} These observations are compatible with the hypothesis that reduced microbial exposure or dysbiosis may impair the development of immune tolerance. However, observational studies are vulnerable to confounding by underlying illness, healthcare utilization, and medication use. They do not establish that altered microbiota cause EoE. It is therefore necessary to distinguish microbial perturbations that precede disease from changes that arise as a consequence of inflammation, restricted diets, or treatment.

An additional conceptual challenge is that the term “gut microbiome” can refer either to the predominantly colonic community measured in stool or to site-specific mucosal communities in the esophagus and stomach. Early, relatively small studies reported increased total bacterial load in active EoE and shifts in the relative abundance of Proteobacteria, *Haemophilus*, *Neisseria*, Firmicutes, and *Streptococcus*.^{3,4} Salivary and fecal studies have also identified differences between EoE and control groups. Yet the direction and magnitude of these findings, including changes in microbial diversity, have not been consistent across studies.⁵ Sampling method, age, geography, diet, recent antibiotics, proton pump inhibitors, swallowed corticosteroids, and disease activity all represent major sources of variation.

The importance of this heterogeneity was demonstrated by a multicenter study conducted through the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which included patients with EoE and eosinophilic gastritis (EoG) and controls from 10 centers across the United States.⁶ *Streptococcus* and *Gemella* were associated with EoE mucosal samples, whereas *Prevotella* and *Leptotrichia* were associated with gastric communities and EoG activity. However, alpha-diversity was similar across groups, and microbial communities were highly individualized. Stool communities neither correlated with esophageal or gastric mucosal communities nor clearly differed between patients and controls. These findings argue against a single universal “EGID microbiome” and instead support a model in which microbial patterns are shaped by an organ-specific ecosystem that includes the host, inflammation, diet, medication, and geography.

Several biologically plausible mechanisms may connect microbial communities with EGID pathogenesis. Microbial products can activate pattern-recognition pathways, while short-chain fatty acids and tryptophan-derived metabolites can influence epithelial differentiation, mucus production, intercellular junctions, regulatory T cells, type 2 immunity, eosinophils, mast cells, and innate lymphoid cells. In experimental models, the esophagus harbors a transplantable resident microbiota,

and neonatal antibiotic exposure reduces Lactobacillales and amplifies type 2 esophageal inflammation.⁷ These data establish the feasibility of host-microbiota interactions in the esophagus. In human EoE, however, direct links among local microbial metabolites, epithelial function, eosinophil phenotypes, and clinical outcomes remain limited. Short-chain fatty acids and indoles should therefore be regarded as promising mechanistic candidates rather than established drivers or therapies in EGIDs.

Dietary elimination, proton pump inhibitors, swallowed topical corticosteroids, and biologic therapy can improve inflammation while simultaneously altering the ecological niche in which microbes reside. Treatment-associated changes in esophageal bacterial load and community composition have been reported, and different therapeutic approaches may produce distinct microbial patterns.⁸ Dietary fiber intake has also been associated with esophageal microbial composition.⁹ Conversely, some dietary intervention studies did not identify a significant global shift in the esophageal microbiome.⁴ Thus, an observed microbial change may be a mediator of treatment response, a marker of remission, or simply a downstream consequence of altered inflammation and diet. At present, the evidence is insufficient to recommend probiotics, prebiotics, fecal microbiota transplantation, or targeted microbial/metabolite therapies as routine treatment for EoE or other EGIDs.

This lecture will review the clinical and molecular heterogeneity of EGIDs and summarize evidence linking early-life exposures, esophageal and fecal microbiota, microbial metabolites, diet, and pharmacologic therapy to disease susceptibility and activity. Future studies should incorporate longitudinal paired mucosal and stool sampling before and after treatment; detailed measurement of dietary and medication exposures; shotgun metagenomics and metabolomics; and integration with host genetics, tissue transcriptomics, spatial profiling, and patient-derived cellular and organoid systems. Cohorts reflecting Japanese and broader Asian diets, microbial environments, and clinical phenotypes will be particularly important. Separating microbiome signals that represent a cause, a disease modifier, a treatment-response biomarker, or a consequence of inflammation will be essential before microbiome science can contribute meaningfully to precision medicine in EGIDs.

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