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HOW GUT MICROBIOTA MAY MEDIATE THE ANTI-SEIZURE EFFECTS OF KETOGENIC DIET IN PEDIATRIC DRUG-RESISTANT EPILEPSY: A NARRATIVE REVIEW

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Abstract

Drug-resistant epilepsy (DRE) affects a substantial proportion of children with epilepsy, with cumulative incidence estimates reaching approximately 25% according to the International League Against Epilepsy (ILAE) consensus definition. This review aims to synthesize current evidence on the epidemiology and definition of pediatric DRE, the clinical efficacy of the ketogenic diet (KD) as an established therapeutic option, and the emerging mechanistic role of the gut-brain axis in mediating KD's anti-seizure effects. A non-systematic literature search was conducted, focusing on key studies addressing the relationship between KD, gut microbiota, and seizure outcomes in pediatric DRE, with literature on the gut-brain mechanism primarily drawn from the past decade, reflecting when substantive research in this area began to emerge. Findings indicate that KD produces clinically meaningful seizure reduction across randomized controlled trials and multicenter cohort studies, with a generally favorable safety profile. Beyond ketosis and elevated beta-hydroxybutyrate (BHB), preclinical evidence demonstrates that an intact gut microbiota, particularly Akkermansia muciniphila and Parabacteroides, is required for KD's anti-seizure efficacy, acting through short-chain fatty acid production and modulation of the hippocampal GABA/glutamate ratio. This mechanism converges with that of a conventional antiseizure medication, topiramate, supporting the gut-brain axis as a biologically plausible therapeutic pathway. Furthermore, distinct microbiota signatures have been associated with treatment response, suggesting potential utility as predictive biomarkers. These findings support the continued use of KD in pediatric DRE and highlight the gut microbiota as a promising target for future mechanistic and translational research.

Keywords: Drug-Resistant Epilepsy; Pediatric Epilepsy; Ketogenic Diet; Gut-Brain Axis; Gut Microbiota

1 Introduction

With an annual incidence of about 44 per 100,000, epilepsy is recognized as one of the most common neurological conditions affecting the pediatric population [1]. According to the International League Against Epilepsy (ILAE) 2010, a

patient is considered to have drug-resistant epilepsy (DRE) when seizures persist despite treatment with two appropriate antiseizure medications (ASM), used either alone or in combination, administered at correct doses and tolerated by the patient, yet still failing to achieve sustained seizure freedom [2]. Existing studies stated that roughly two-thirds of patients (60%–70%) respond to ASM treatment, whereas 30%–40% go on to become drug-resistant. [3,4]. Meanwhile, the cumulative incidence of DRE in pediatric studies was found to be approximately 25.0%, indicating that roughly one in four children with epilepsy will go on to develop drug resistance during the observation period [5].

Since its introduction in the 1920s, the ketogenic diet (KD) has re-emerged over the past few decades as a validated treatment for pediatric DRE [6]. The pediatric population represents a particularly compelling focus for KD research and clinical application in DRE. First, KD is the treatment of choice for GLUT1 deficiency syndrome and is recommended for early consideration in several other pediatric-onset syndromes, including Dravet syndrome and infantile spasms (West syndrome) [7,8]. Second, children generally exhibit higher rates of dietary adherence under close caregiver supervision compared with adolescents and adults [9].

Evidence from systematic reviews of randomized controlled trials has shown clinically significant seizure reduction of more than 50% in a substantial subset of treated children [10]. These clinical benefits are further supported by objective improvements in electroencephalogram (EEG) background rhythm and epileptiform discharge frequency [11,12]. Regarding safety, adverse effects associated with KD are predominantly mild and gastrointestinal, and long-term studies have shown that lipid profiles and growth parameters generally remain within acceptable limits under close medical supervision [11]. Collectively, this evidence base supports KD as a proven, effective, and reasonably safe therapeutic option in the management of children with DRE.

Although the anti-seizure efficacy of the ketogenic diet (KD) has traditionally been attributed to ketosis and elevated beta-hydroxybutyrate (BHB) levels, this metabolic explanation alone does not fully account for its mechanism of action. Recent preclinical evidence has shown that depleting the gut microbiota abolishes KD's seizure-protective effects even when BHB levels remain elevated, indicating that ketosis is necessary but not sufficient to explain the diet's efficacy [13]. Despite this, evidence on gut microbiota as a mediator of KD's anti-seizure effects in pediatric DRE, the population in which KD is most widely used, remains scattered and has not been comprehensively synthesized. This narrative review therefore aims to synthesize current evidence on the role of gut microbiota, particularly microbiota-derived short-chain fatty acids, as a mediator of KD's anti-seizure effects in pediatric DRE, and to identify key gaps warranting further research.

2 Methods

Relevant literature was identified through a non-systematic search of the biomedical literature, focusing on key studies addressing the relationship between ketogenic diet, gut microbiota, and seizure outcomes in pediatric drug-resistant epilepsy. Literature addressing this relationship was primarily drawn from studies published within the past decade (2017 onward), as this period marks when research substantively began addressing the link between gut microbiota and the mechanisms underlying ketogenic diet efficacy in epilepsy. Studies were selected based on relevance, methodological quality, and publication recency, with additional references identified through citation tracking of key papers.

3 The Gut-Brain Axis in Ketogenic Diet-Mediated Seizure Control

While the clinical efficacy and safety of the KD in pediatric DRE are well established, the mechanisms underlying its anti-seizure effects remain incompletely understood. Traditionally attributed to ketosis and elevated BHB levels, this explanation alone appears insufficient. This section examines the gut-brain axis as a key mediator of KD efficacy, from its general role in epilepsy to the specific microbial, metabolic, and neurochemical pathways involved, and their potential as predictors of clinical response.

3.1 The Gut-Brain Axis in Epilepsy: A General Overview

Research consistently supports a clear gut-brain connection, with substantial evidence indicating that the microbiota influences brain morphology and function. Germ-free animals, for example, develop structural brain abnormalities in the absence of microbial colonization. A comparative study demonstrated this directly, showing that germ-free mice exhibit altered motor activity and anxiety-like behavior compared with conventionally colonized mice, along with corresponding changes in brain gene expression. Interestingly, the effects of microbial colonization depended on the timing of exposure. Introducing gut bacteria early in life was able to normalize the altered behavioral patterns, whereas colonization during adulthood did not produce the same effect. These findings suggest that early life may represent a critical developmental period during which gut microbiota influence brain maturation and subsequent behavior [14].

These gut-brain interactions occur through several interconnected pathways. Neural communication depends on direct anatomical connections through the vagus nerve or indirect connections via the enteric nervous system, although the underlying neuronal circuits have not been fully elucidated. Immune communication occurs primarily through cytokines released by immune cells into the circulation, while endocrine communication, the broadest route, encompasses the hypothalamic-pituitary-adrenal (HPA) axis. Humoral mediators, including short-chain fatty acids (SCFAs), may also influence brain function by modulating inflammatory processes, neurotransmitter signaling, and gut barrier integrity [15]. Together, these pathways provide a biological basis through which alterations in gut microbial composition may influence brain function, a relationship of particular relevance to epilepsy.

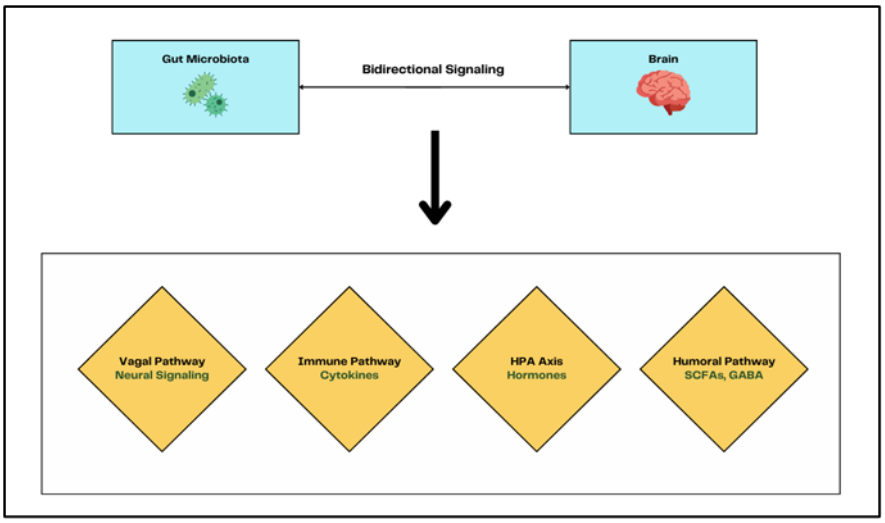


Figure 1: Communication pathways of the gut-brain axis

Bidirectional signaling between the gut microbiota and the brain occurs through neural, immune, endocrine (HPA axis), and humoral pathways [15].

This bidirectional gut-brain communication has increasingly been implicated in epilepsy, with the gut microbiota now recognized as a potential contributor to seizure susceptibility and neuronal excitability [16]. Supporting this link, clinical studies in the pediatric population have identified clear microbial dysbiosis in children with intractable epilepsy compared with healthy controls. One study reported that children with intractable epilepsy exhibited significantly reduced gut microbial diversity, alongside a lower relative abundance of Bacteroidetes and a higher abundance of Actinobacteria, relative to age-matched healthy children [17]. These findings suggest that alterations in gut microbial composition are not merely incidental but may actively contribute to the pathophysiology of pediatric epilepsy, providing a rationale for investigating microbiota-targeted interventions such as the ketogenic diet.

3.2 Gut Microbiota as a Necessary Mediator of KD Efficacy

The causal role of the gut microbiota in mediating KD efficacy was first established in a landmark study by Olson et al. [13] using two independent mouse seizure models: the acute electrically induced 6-Hz psychomotor seizure model and a model of spontaneous tonic-clonic seizures. In conventionally colonized specific pathogen-free (SPF) mice, the KD significantly increased seizure thresholds compared with control diet-fed mice. This protective effect was completely abolished in germ-free mice and in SPF mice pretreated with a broad-spectrum antibiotic cocktail, despite these mice remaining in a state of ketosis. This finding provided direct evidence that an intact gut microbiota, rather than ketosis or elevated BHB alone, is necessary for the anti-seizure effects of KD.

Beyond establishing necessity, the study identified which specific microbial taxa were responsible for this effect. 16S rRNA sequencing revealed that KD feeding markedly enriched two bacterial genera, Akkermansia muciniphila and Parabacteroides (including P. merdae and P. distasonis), with A. muciniphila relative abundance increasing from approximately 2.8% to 36.3% within 4 days of KD initiation. Importantly, introducing the two identified bacterial taxa simultaneously into germ-free mice was sufficient to restore the seizure-protective effect of the KD. In contrast, introducing either bacterial taxon alone did not restore this protective effect. These findings suggest that the presence of both bacterial taxa, rather than either taxon individually, may be required for the gut microbiota to mediate the anti-seizure effects of the KD. Moreover, direct transplantation of the KD-associated microbiota, or treatment with A. muciniphila and P. merdae alone, conferred seizure protection even in mice fed a standard control diet, demonstrating that these bacteria are sufficient to recapitulate the anti-seizure phenotype independent of the diet itself [13].

Olson et al. [13] further investigated how KD-associated bacteria may contribute to seizure protection through changes in neurochemical metabolism. Colonization with Akkermansia and Parabacteroides was associated with reduced levels of systemic gamma-glutamylated amino acids and an increased gamma-aminobutyric acid (GABA) to glutamate ratio in the hippocampus. These changes were not observed in germ-free or antibiotic-treated mice, suggesting that they were dependent on the presence of gut microbiota. Because GABA is the major inhibitory neurotransmitter in the central nervous system, an increased GABA to glutamate ratio may reduce neuronal excitability and contribute to a higher seizure threshold. Together, these findings suggest a possible gut-brain pathway through which KD-associated bacteria influence systemic metabolism and, in turn, alter brain neurotransmission involved in seizure control.

Collectively, these findings position the gut microbiota not merely as a bystander of dietary change but as an essential mediator of KD's antiseizure mechanism, challenging the long-held assumption that ketosis and elevated BHB alone are sufficient to explain the diet's efficacy. This causal evidence, although derived from preclinical mouse models, has since motivated a growing body of clinical research investigating microbiota alterations in children undergoing KD therapy for DRE.

3.3 Effects of KD on Gut Microbiota Composition in Children

Since 2017, a growing number of pediatric clinical studies have shown that KD induces measurable shifts in gut microbiota composition, although the specific taxonomic changes vary across cohorts, likely reflecting differences in patient age, epilepsy etiology, sequencing method, and regional dietary background. See Table 1.

Table 1: Studies of gut microbiota changes in children with epilepsy treated with KD

Author (Year)	Design	Population	Duration	Key microbiota changes	Clinical outcome	Ref
Xie et al. (2017)	Retrospective observational study; 16S rDNA sequencing	14 infants with refractory epilepsy; 30 healthy infants as controls	1 week	↓ Proteobacteria (including Cronobacter); ↑ Bacteroides, Prevotella, Bifidobacterium	64% of infants showed improvement; ≥50% seizure frequency reduction	[18]
Zhang et al. (2018)	Prospective observational study; 16S rDNA sequencing	20 children with refractory epilepsy	6 months	↓ Firmicutes; ↑ Bacteroidetes; ↓ alpha diversity	2 seizure-free, 3 with ≥90% reduction, 5 with 50–89% reduction; 10 had <50% reduction. All 10 responders showed EEG improvement	[19]
Lindefeldt et al. (2019)	Prospective observational study; shotgun metagenomic sequencing	12 children with severe DRE	3 months	No significant change in alpha diversity; ↓ Bifidobacterium as well as E. rectale and Dialister; ↑ E. coli;	Taxonomic and functional focus, not a primary clinical outcome	[20]
Wang et al. (2026)	Prospective observational study; 16S rRNA Sequencing	34 children with DRE; 16 responders, 18 non-responders	3 months	Responders: higher baseline Lachnoclostridium and Barnesiella; ↑ Parabacteroides and Akkermansia after KD. Non-responders: persistently higher Catenibacterium	Lachnoclostridium and Barnesiella proposed as predictive biomarkers of KD response	[21]

Xie et al. [18] were among the first to characterize this in infants with refractory epilepsy, reporting that gut microbiota structure differed markedly from that of healthy controls at baseline. After one week of KD, 64% of infants showed a clinical response (≥50% seizure reduction), accompanied by a marked decrease in Proteobacteria and an increase in Bacteroides, Prevotella, and Bifidobacterium. Zhang et al. [19], in a prospective study of 20 children with refractory epilepsy, reported reduced alpha diversity and decreased Firmicutes abundance after six months of KD, with all ten clinical responders showing EEG improvement.

Lindefeldt et al. [20] studied 12 children with DRE using shotgun metagenomic sequencing and found no significant change in alpha diversity after three months, but detected altered taxonomic and functional composition, including reduced Bifidobacterium, increased Escherichia coli, and significant changes in carbohydrate metabolism. Notably, the direction of some changes differed between studies (for example, Bifidobacterium increased in Xie et al. but decreased in Lindefeldt et al.), underscoring the heterogeneity of existing cohorts.

More recently, Wang et al. [21] extended this line of evidence by comparing microbiota trajectories in responders and non-responders: following KD initiation, Parabacteroides and Akkermansia increased in responders but remained unchanged in non-responders. Whether baseline composition itself can predict this differential response is discussed further in Section 3.6.

3.4 Short-Chain Fatty Acids as Molecular Mediators

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are produced by bacterial fermentation of dietary substrates and are a leading candidate for linking the gut microbiota to neuronal excitability. SCFAs exert neuroprotective effects through several converging mechanisms, including activation of G-protein-coupled receptors, inhibition of histone deacetylases (HDACs), and preservation of blood-brain barrier integrity through upregulation of tight junction proteins such as occludin and Zonula Occludens-1 [22].

Direct causal evidence for SCFAs in seizure modulation comes from a recent study which demonstrated that chronic supplementation with a balanced mixture of acetate, propionate, and butyrate produced disease-modifying effects in a murine model of drug-resistant epilepsy, markedly attenuating seizure progression, reducing the emergence of new seizure clusters, and improving memory performance. These functional benefits were accompanied by clear neuroprotective effects at the hippocampal level, including normalization of aberrant neurogenesis, preservation of inhibitory interneurons, and reduced reactive gliosis and neuroinflammation [23].

Whether KD itself acts through SCFAs, however, remains unresolved. In a small clinical study, it was found that one month of classic KD significantly reduced fecal SCFA concentrations in patients with epilepsy, including a 55% reduction in total SCFAs, which contrasts with the assumption that KD increases SCFA production. SCFAs therefore represent a mechanistically plausible mediator of gut-brain signaling in epilepsy, supported mainly by preclinical evidence, but their role in KD-mediated seizure control requires confirmation in studies that measure SCFAs alongside clinical response [24].

3.5 The GABA/Glutamate Pathway and Supporting Evidence from Other Therapies

Beyond dietary interventions, emerging evidence suggests that even conventional ASMs may partly exert their effects through modulation of the gut microbiota, converging on the same GABA/glutamate pathway implicated in KD efficacy. One study demonstrated that oral administration of topiramate, a well-established ASM used in both monotherapy and drug-resistant focal epilepsy, significantly increased the abundance of the probiotic species Lactobacillus johnsonii in the gut microbiome of mice. Notably, co-treatment with topiramate and L. johnsonii together, but not either alone, reduced seizure susceptibility in a pentylenetetrazol (PTZ)-kindling model. This enhanced protection was accompanied by an increased abundance of the butyrate-producing family Lachnospiraceae and elevated butyrate levels in the gut, as well as a significantly increased GABA/glutamate ratio in the cortex [25]. These findings closely parallel the mechanistic pathway identified by Olson et al. [13] for KD, in which microbiota-mediated increases in hippocampal GABA relative to glutamate underlie seizure protection. Together, this convergence across two mechanistically distinct interventions, a dietary therapy and a apharmacological ASM, strengthens the broader hypothesis that microbiota-driven modulation of central inhibitory-excitatory neurotransmitter balance represents a shared, generalizable pathway relevant to seizure control in DRE.

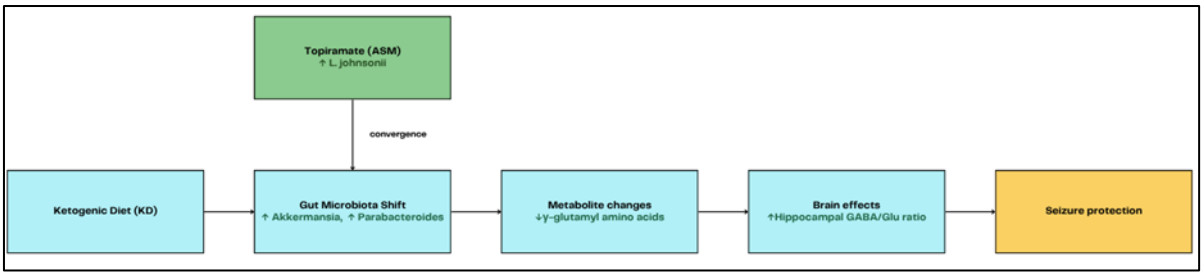


Figure 2: Proposed mechanism linking the ketogenic diet, gut microbiota, and seizure protection.

Based mainly on mouse models. KD enriches Akkermansia and Parabacteroides, linked to a higher hippocampal GABA/glutamate ratio [13] while topiramate acts at the microbiota level by increasing Lactobacillus johnsonii [25].

3.6 Microbiota Signatures as Predictors of Clinical Response

A more recent and clinically translational line of research has moved beyond characterizing microbiota changes to identifying specific microbial signatures that may predict, rather than merely accompany, treatment response in pediatric DRE. In a case-control study comparing medication-resistant (MR) and medication-sensitive (MS) pediatric epilepsy patients of genetic and presumed genetic etiology against age-matched healthy controls, identified a distinct gut microbiota signature specifically associated with medication resistance, using 16*S* rRNA sequencing alongside dietary and gastrointestinal symptom assessment. Comparing the epilepsy groups with healthy controls, Hungatella was found to be significantly increased in both MS and MR patients relative to controls. Within the epilepsy cohort itself, however, the [Eubacterium] siraeum group differed between the MS and MR subgroups, pointing to a taxon that may specifically distinguish medication response rather than epilepsy status alone [26]. Complementing this, a cohort study found that responders had higher baseline abundances of Lachnoclostridium and Barnesiella than non-responders and showed increased Parabacteroides and Akkermansia after KD initiation, whereas non-responders showed persistently higher Catenibacterium. Responders also had significantly higher Parabacteroides than non-responders as early as one month after starting KD, suggesting that baseline and early on-treatment microbiota composition may hold predictive value for eventual clinical response [21].

These findings collectively support the hypothesis that gut microbiota profiling could, in the future, serve as a non-invasive biomarker to identify children with DRE most likely to benefit from KD or to develop pharmacoresistance, potentially enabling more personalized and timely treatment selection, though such findings require validation in larger, prospective, and mechanistic studies.

4 Conclusion

DRE remains a significant clinical challenge in the pediatric population, affecting an estimated one in four children with epilepsy according to the ILAE's consensus definition. Among available therapeutic options, the KD has emerged as a well-established, evidence-based intervention, supported by randomized controlled trials and multicenter cohort studies demonstrating clinically meaningful seizure reduction alongside a generally favorable safety profile. Importantly, this review highlights that the therapeutic efficacy of KD is unlikely to be fully explained by ketosis and elevated beta-hydroxybutyrate levels alone. Preclinical evidence points to the gut microbiota as a necessary and active mediator of KD's anti-seizure effects in mice, acting through specific bacterial taxa, such as Akkermansia muciniphila and Parabacteroides, and through modulation of the hippocampal GABA/glutamate balance, while short-chain fatty acids remain a plausible but unresolved additional mediator. In children, clinical studies confirm that KD alters gut microbiota composition, although the observed changes are heterogeneous and their links to treatment response remain associative. The overlap between this microbiota-mediated mechanism and the effects of the conventional antiseizure medication topiramate in mouse models further supports the potential role of the gut–brain axis in seizure control.

Taken together, these findings carry important clinical and translational implications. First, they reinforce the rationale for continued use of KD in children with DRE, particularly in conditions where it is best established, such as Dravet syndrome, infantile spasms (West syndrome), and GLUT1 deficiency syndrome. Second, the identification of distinct microbiota signatures associated with treatment response, such as higher baseline Lachnoclostridium and Barnesiella in responders, raises the possibility of using gut microbiota profiling as a predictive biomarker, potentially enabling more personalized and timely treatment decisions in the future. Nevertheless, much of the mechanistic evidence to date, particularly regarding microbiota necessity and causality, remains derived from preclinical animal models, and pediatric clinical studies are still limited by small sample sizes, observational designs, and heterogeneous methodologies. Future research should prioritize larger, prospective, and mechanistically-oriented studies in children

to establish causal relationships between specific microbiota alterations and clinical outcomes, as well as to explore the therapeutic potential of microbiota-targeted interventions, such as probiotics or fecal microbiota transplantation, as adjuncts or alternatives to dietary therapy in the management of pediatric drug-resistant epilepsy.

Statements on compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed

CRediT Authorship Contributions

- **Zefanya Aristawidya Putri:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing, Visualization.
- **Wardah Rahmatul Islamiyah:** Supervision, Writing - review & editing

AI Disclosure Statement

During the preparation of this manuscript, the authors used the assistance of AI-based language model (Claude, Anthropic). AI was used to assist with literature retrieval, drafting the framework of the paper, refinement of grammar and sentence structure, as well as the generation of figures. The initial figure outline was AI-assisted, with the final figures independently redesigned by the author. All AI-assisted content was subsequently reviewed, verified against original source publications, and edited by the authors, who take full responsibility for the originality of the manuscript, the accuracy of the scientific information presented, the integrity of the data, the proper citation of all sources, and the verification of all AI-assisted content.

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