Letters & Reviews in Neurological Sciences

Gut Health and Gut Bacteria in the Treatment of Amyotrophic Lateral Sclerosis / Motor Neuron Disease: A Narrative Review of Mechanisms and Therapeutic Prospects

Dr. Mohamed Afzal Pasha, Ph. D.*

Professor (Retired), Department of Chemistry, Bangalore University, Bengaluru-560056, INDIA

*Present address: Chief-Editor, ESRA Publications Pvt. Ltd., Bengaluru-560094, INDIA

e-mail: chief.editoresra@gmail.com

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), also called motor neuron disease (MND), is a progressive and fatal neurodegenerative disorder for which disease-modifying options remain very limited. Because genetics explains only part of the disease, attention has turned to environmental modifiers, and the gut microbiota has emerged as a leading candidate. Preclinical work shows that SOD1 transgenic mice develop intestinal barrier dysfunction and dysbiosis, that specific commensals can ameliorate (*Akkermansia muciniphila*) or aggravate (*Ruminococcus torques*, *Parabacteroides distasonis*) disease, and that microbial metabolites such as butyrate and nicotinamide modify outcomes [1–3]. In C9orf72-deficient mice, gut bacteria drive systemic and neural inflammation [4]. Human studies are small and heterogeneous but generally report altered microbial composition, intestinal inflammation or abnormal metabolites [5–9]. A six-month probiotic pilot did not change ALS functional decline [9], and a randomised trial of fecal microbiota transplantation has been designed [10]. This review summarises the evidence, proposes an integrated mechanistic scheme, tabulates the major findings and therapeutic strategies, and outlines the research needed before microbiota-directed therapy can be recommended for ALS/MND.

Key words: Amyotrophic lateral sclerosis; motor neuron disease; gut microbiota; microbiota-gut-brain axis; short-chain fatty acids; butyrate; *Akkermansia muciniphila*; nicotinamide; probiotics; fecal microbiota transplantation.

1. Introduction

ALS is characterised by progressive degeneration of upper and lower motor neurons, leading to paralysis and, in most patients, death from respiratory failure within a few years of onset [11,12]. Most cases are sporadic; roughly 5–10% are familial, with mutations in genes such as *SOD1* and *C9orf72* [11]. Approved drugs offer modest benefit, and the need for new therapeutic angles is acute [12].

The incomplete penetrance of ALS-associated mutations and the variable clinical course suggest that environmental factors influence disease expression. The human gut harbours a vast microbial community that communicates with the brain through neural, immune and metabolic routes [13]. This review asks whether gut health and gut bacteria contribute to ALS/MND and whether they can be exploited therapeutically?

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2. The microbiota-gut-brain axis

The microbiota-gut-brain axis is a bidirectional network linking intestinal microbes with the central nervous system (CNS) through the vagus nerve and enteric nervous system, mucosal and systemic immunity, and circulating microbial metabolites [13] (Figure 1). Microbial signals also shape CNS cells: in germ-free mice microglia are immature and functionally impaired, and short-chain fatty acids (SCFAs) help restore their normal state [14]. In a mouse model of Parkinson's disease, the microbiota was required for full expression of motor deficits and neuroinflammation [15], a precedent that motivates similar questions in ALS.

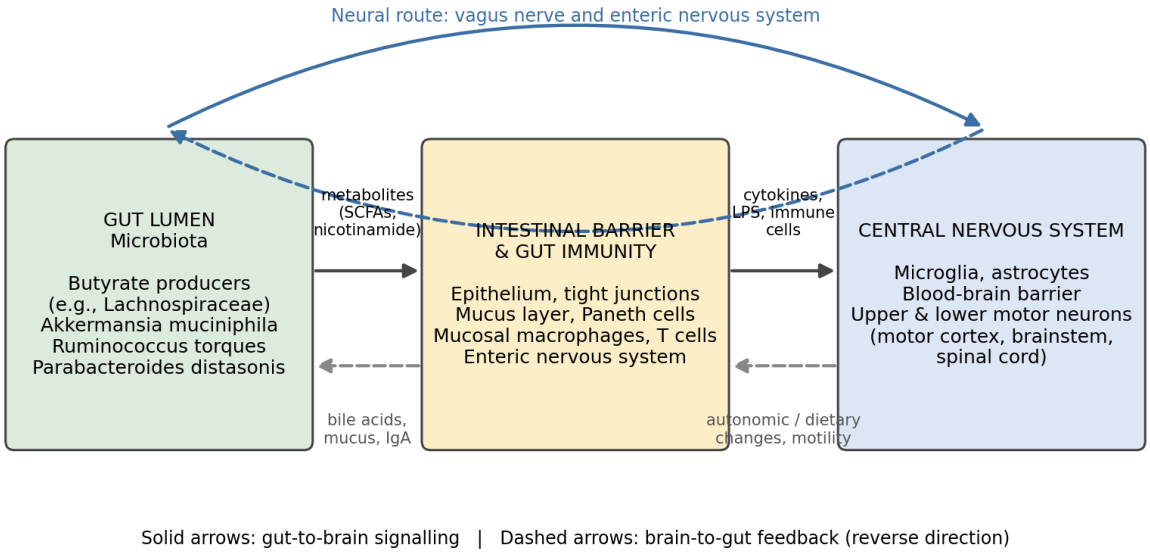


Figure 1. The microbiota–gut–brain axis as it applies to ALS/MND.

3. Evidence linking gut microbiota to ALS/MND

3.1 Animal models

In the SOD1-G93A mouse, increased intestinal permeability, abnormal epithelial features and a shifted microbiome have been reported [1]. Supplementation with the SCFA butyrate was reported to improve gut integrity and to delay onset and prolong survival [2].

Blacher and colleagues showed that SOD1-Tg mice have a pre-symptomatic, vivarium-dependent dysbiosis, and that disease worsens under germ-free conditions or after broad-spectrum antibiotics. Supplying individual commensals to antibiotic-treated mice, *A. muciniphila* ameliorated symptoms whereas *R. torques* and *P. distasonis* exacerbated them; nicotinamide, which accumulated in the CNS of *A. muciniphila*-treated mice, improved motor outcomes when given systemically [3]. A different picture emerged in C9orf72-mutant mice: an environment with fewer immune-stimulating bacteria, antibiotics, and transplantation of protective flora all reduced inflammation and premature mortality [4]. Taken together, the microbiota can be protective or harmful depending on the genetic context, which is critical for any therapeutic plan.

3.2 Human studies

Human observations are summarised in Table 1 and Figure 2. High-throughput sequencing of ALS patients and healthy controls first indicated differences in microbial diversity [5]. A small study of five patients with MND documented dysbiosis together with markers of intestinal inflammation [6]. Later

case-control work reported altered gut microbiome and metabolism [7], and a spouse-controlled design, intended to limit dietary and household confounding, again found community differences [8]. Blacher and colleagues also found reduced nicotinamide in serum and cerebrospinal fluid of ALS patients in a small preliminary comparison with household controls [3]. A prospective longitudinal study found that patients' microbiota differed from controls irrespective of disability and changed during follow-up [9]. Systematic and narrative reviews conclude that findings are not consistent across cohorts, because of small sample sizes, differing methods, and confounders such as diet, constipation, swallowing difficulty, weight loss and medication; they also stress that causality and reverse causation remain unresolved [16,17].

Table 1. Selected preclinical and human studies on gut microbiota in ALS/MND.

Study	Model / design	Main finding (as reported)
Wu et al., 2015 [1]	SOD1-G93A mice	Increased intestinal permeability and altered microbiome.
Fang et al., 2016 [5]	Patients *vs* healthy controls; sequencing	Differences in fecal microbial diversity and composition (small cohort).
Rowin et al., 2017 [6]	Five patients with MND	Dysbiosis with markers of intestinal inflammation.
Zhang et al., 2017 [2]	SOD1-G93A mice, butyrate	Improved gut integrity; delayed onset and prolonged survival reported.
Blacher et al., 2019 [3]	SOD1-Tg mice; small human comparison	*A. muciniphila* protective, *R. torques* and *P. distasonis* harmful; nicotinamide beneficial; reduced nicotinamide in patients.
Burberry et al., 2020 [4]	C9orf72-mutant mice	Gut bacteria drive systemic and neural inflammation; antibiotics and protective flora attenuate it.
Di Gioia et al., 2020 [9]	Prospective longitudinal, patients and controls; 6-month probiotic	Microbiota differed from controls and changed over time; probiotic did not alter ALSFRS-R progression.
Zeng et al., 2020 [7]	Patients *vs* controls	Altered gut microbiome and metabolism.
Hertzberg et al., 2022 [8]	Patients *vs* spouse controls	Differences in gut microbial communities.

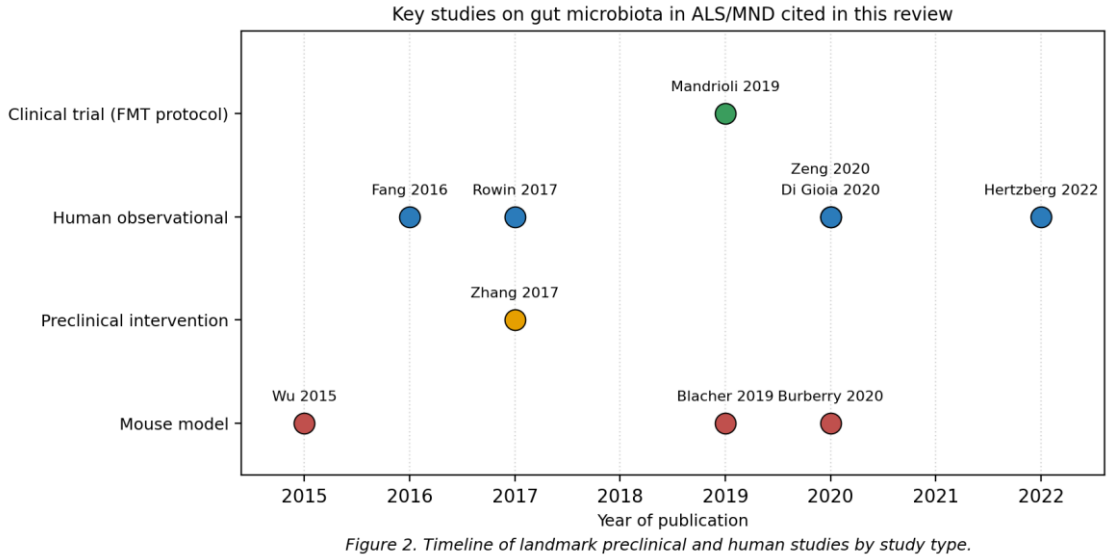


Figure 2. Timeline of landmark preclinical and human studies by study type.

4. Mechanisms of action

Several non-exclusive mechanisms have been proposed (Table 2, Figure 4). They are mainly supported by animal data and should be regarded as working hypotheses in humans.

4.1 Short-chain fatty acids and barrier integrity

Butyrate and other SCFAs are produced by bacterial fermentation of fibre. They support epithelial energy metabolism and barrier function and influence immune and glial cells, partly through histone deacetylase inhibition [**18**]. Loss of butyrate-producing bacteria and a leaky intestine in SOD1 mice, and the benefit of butyrate supplementation, fit this model [**1**,**2**].

4.2 Nicotinamide and metabolic support

A. muciniphila-associated nicotinamide reached the CNS in treated SOD1-Tg mice and improved motor symptoms and spinal cord gene expression; lower nicotinamide levels were seen in patients' serum and cerebrospinal fluid [**3**] (Figure 3). This links a defined microbial metabolite to neuronal energy and redox metabolism.

4.3 Barrier failure, microbial products and neuro-inflammation

When the barrier is weakened, bacterial products such as lipopolysaccharide can reach the circulation, activate innate immune receptors including TLR4, and sustain systemic and CNS inflammation [**13**]. In C9orf72-deficient mice, microbiota-dependent inflammation determined survival, directly implicating gut bacteria in neural inflammation [**4**]. Microglial dependence on microbial signals [**14**] provides a plausible route by which gut changes shape motor neuron vulnerability.

4.4 Reverse direction: the disease shapes the gut

ALS itself may alter the gut through autonomic dysfunction, reduced mobility, dysphagia and dietary change, so some microbial differences may be consequences rather than causes [**16**,**17**]. A vicious cycle, in which dysbiosis aggravates neuro-inflammation and neurodegeneration worsens gut function, is therefore possible.

Table 2. Microbial mediators and proposed actions in ALS/MND.

Mediator	Microbial source	Proposed action	Evidence level
Butyrate / SCFAs	Butyrate-producing Firmicutes	Supports epithelial barrier, modulates immune and glial cells, HDAC inhibition [**2**,**18**].	Mouse model; mechanistic literature
Nicotinamide	*A. muciniphila*-associated	Reaches CNS; improves motor symptoms and spinal cord gene expression [**3**].	Mouse model; small human comparison
Lipopolysaccharide and other microbial products	Gram-negative bacteria; translocation across leaky gut	Innate immune activation (TLR4), systemic and neural inflammation [**4**,**13**].	Mechanistic; C9orf72 mouse data
Pathobiont signals	*R. torques, P. distasonis*	Associated with worse disease in SOD1-Tg mice [**3**].	Mouse model

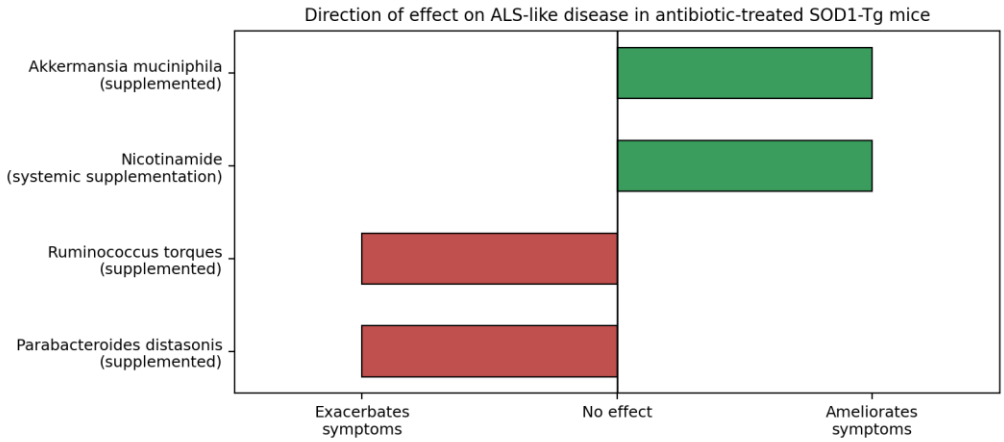


Figure 3. Qualitative direction of effect reported by Blacher et al. (2019); bars show direction only, not magnitude.

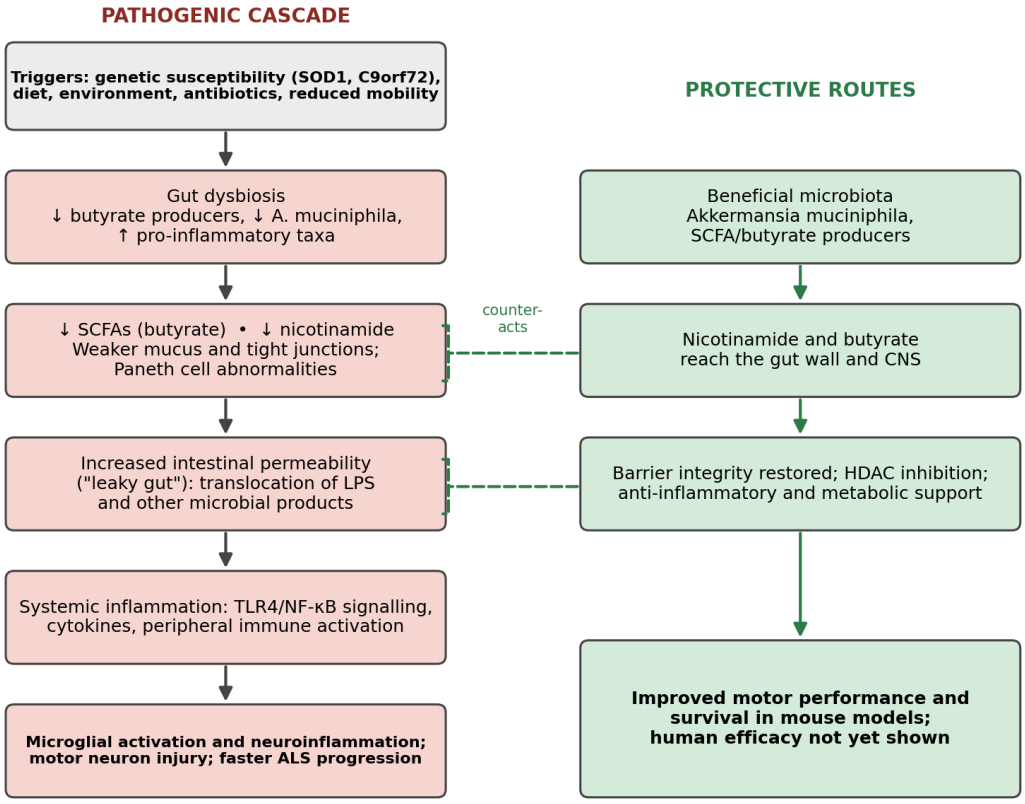


Figure 4. Proposed mechanisms linking gut microbiota to motor neuron degeneration in ALS/MND.

5. Therapeutic strategies targeting the gut microbiota

Strategies under study or proposed are compared in Table 3 and Figure 5.

5.1 Probiotics, prebiotics and synbiotics

Probiotics are live microorganisms that confer a health benefit when given in adequate amounts [19]; synbiotics combine them with substrates selectively used by host microorganisms [20]. In the only prospective longitudinal ALS study cited here, six months of probiotic treatment changed gut microbial composition but did not bring biodiversity close to control values and did not alter progression on the ALSFRS-R [9]. Larger, strain-defined, adequately powered trials are needed.

5.2 Butyrate and defined metabolites

Butyrate supplementation was beneficial in SOD1-G93A mice [2], and nicotinamide improved motor outcomes in SOD1-Tg mice [3]. These small molecules are attractive because dose and exposure are controllable, but human efficacy and safety in ALS remain untested in the studies reviewed here.

5.3 Fecal microbiota transplantation

A multi-center randomised, double-blind trial of fecal microbiota transplantation in ALS has been designed to test effects on immune cell populations, inflammatory status and microbiota, with a view to a later efficacy study [10]. Results are awaited.

5.4 Antibiotics: A cautionary note

Antibiotics worsened disease in SOD1-Tg mice [3] but protected C9orf72-mutant mice [4]. Indiscriminate microbial depletion is therefore not a rational strategy, and any intervention should consider the patient's genetic background.

Table 3. Microbiota-directed strategies in ALS/MND and their current evidence.

Strategy	Rationale	Evidence so far	Stage
Probiotics	Restore balance, support barrier [19]	6-month pilot: microbiota changed, no effect on ALSFRS-R [9]	Human pilot
Butyrate	Replace lost SCFA; barrier and immune support	Delayed onset, longer survival in SOD1-G93A mice [2]	Preclinical
A. muciniphila / nicotinamide	Supply protective commensal or its metabolite	Improved motor outcomes in SOD1-Tg mice [3]	Preclinical
Fecal microbiota transplantation	Re-establish microbial environment, modulate immunity [10]	Randomised trial protocol published [10]	Trial design
Prebiotics / synbiotics	Selectively feed beneficial microbes [20]	No ALS-specific efficacy data in the studies reviewed here	Hypothesis
Antibiotics	Reduce pro-inflammatory bacteria	Harmful in SOD1-Tg mice [3], protective in C9orf72 mice [4]	Context-dependent

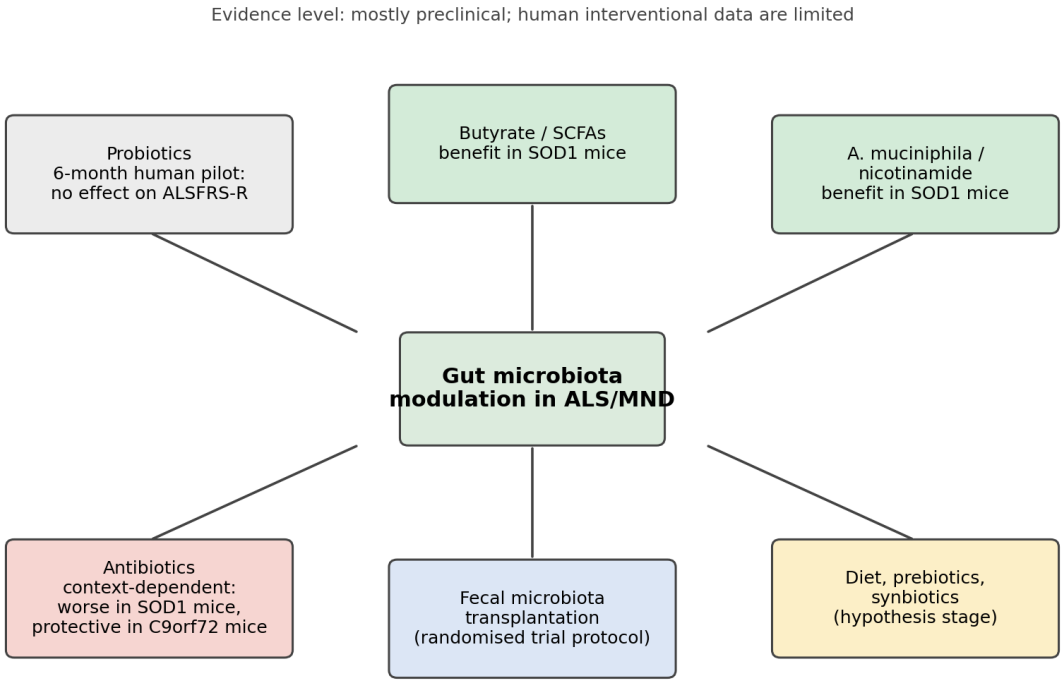


Figure 5. Microbiota-targeted strategies and their current level of evidence.

6. Challenges and future directions

Key limitations are small cohorts, cross-sectional designs, uncontrolled diet and clinical confounders, and variation in sequencing and analysis methods [16,17]. Mouse findings were strongly vivarium-dependent [3], so translation to patients will need care. Priorities include (i). large, prospective, ideally pre-diagnostic cohorts with repeated sampling; (ii). metagenomic and metabolomic profiling rather than composition alone; (iii). stratification by genotype (for example *SOD1* and *C9orf72*) given the opposite effects of antibiotics [3,4]; (iv). mechanistic studies of metabolites such as butyrate and nicotinamide [2,3]; and (v). well-designed, adequately powered clinical trials with standardised endpoints and safety monitoring, including those already planned [10].

7. Conclusions

Evidence from animal models supports a modulatory role for gut bacteria and their metabolites in ALS, and human studies point to altered gut ecology, but the direction of causality and the clinical value of intervention are unproven. Microbiota-directed approaches, including defined metabolites, probiotics and fecal microbiota transplantation, are promising adjuncts to be tested in carefully designed trials rather than recommended for routine use at present.

Conflict of interest and funding

Much of the content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological sciences.

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Data availability: No new datasets were generated or analyzed.

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