20. Review of gut microbiome and hindgut support in PSSM and EPM

Prompt: Conduct a scoping review on gut microbiome, hindgut function, and digestive support in horses with PSSM and EPM. Include forage-first diets, starch overload, hindgut acidosis, probiotics, prebiotics, yeast cultures, medication-associated dysbiosis, fecal microbiome studies, and immune modulation. Use JBI PCC logic: Population = horses with PSSM, EPM, or chronic neuromuscular disease; Concept = gut health and nutritional modulation; Context = clinical management, performance, rehabilitation, and long-term feeding. Extract intervention, microbiome measurement method, digestive outcome, immune outcome, neuromuscular outcome, and evidence level. Determine whether gut-support claims are direct evidence, extrapolated from general equine nutrition, or speculative.

Generated on: April 25, 2026

Excellent! I have gathered comprehensive literature. Now let me create the structure for the review and then write the final comprehensive scoping review. Based on my searches, I have found sufficient literature to conduct this review. Let me organize and write the complete literature review.

Scoping Review: Gut Microbiome and Hindgut Support in Horses with PSSM and EPM

Introduction

Polysaccharide storage myopathy (PSSM) and equine protozoal myeloencephalitis (EPM) represent significant neuromuscular challenges in equine practice, with emerging evidence supporting a complex relationship between gastrointestinal health, nutritional status, and disease management [1], [2], [3]. The pathophysiology of both conditions involves metabolic dysregulation that may be influenced by hindgut function, microbiota composition, and dietary management. While direct evidence linking the equine microbiome to PSSM and EPM remains limited, substantial literature exists regarding nutritional modulation, metabolic disease management, and the role of feed additives in supporting gastrointestinal health. This scoping review applies JBI Population-Concept-Context (PCC) methodology to synthesize evidence on gut microbiome assessment, hindgut function, and digestive support interventions in horses with PSSM, EPM, and related chronic neuromuscular disease, while critically evaluating whether current recommendations represent direct evidence, extrapolation from general equine nutrition, or speculative claims.

1. Population Definition and Disease Context

1.1 PSSM: Genetic Basis and Metabolic Dysfunction PSSM comprises a heterogeneous group of glycogen storage disorders affecting equine skeletal muscle. Type 1

PSSM (PSSM1) is an autosomal dominant glycogen storage disorder caused by the R309H mutation in the glycogen synthase 1 (GYS1) gene [1]. This mutation results in the abnormal accumulation of amylase-resistant polysaccharide within muscle fibers, creating an inability to regulate glucose uptake and glycogen synthesis appropriately [4]. Horses with PSSM1 demonstrate enhanced cellular glucose uptake and heightened sensitivity to insulin, making them particularly susceptible to muscle breakdown when fed high-carbohydrate diets [4], [5]. Type 2 PSSM (PSSM2), identified predominantly in Quarter Horses, presents with intermediate histopathological features and glycogen concentrations between controls and PSSM1-affected horses, though its genetic basis remains unknown [2]. PSSM2 horses similarly benefit from low-starch, fat-supplemented diets and regular exercise, yet approximately one-third continue to show reluctance to go forward and collect under saddle despite dietary intervention [6].

The inflammatory landscape of PSSM differs markedly from other myopathies. Gene expression profiling in PSSM1 muscles reveals significant upregulation of pro-inflammatory genes including IL18, CD44, and FN1, alongside pronounced mitochondrial dysfunction and glycogenesis inhibition [7]. These findings suggest that PSSM is not purely a carbohydrate metabolism disorder but involves chronic muscular inflammation, hypoxia, and immune dysregulation that may have implications for hindgut-mediated inflammatory pathways.

1.2 EPM and Neuroinflammation Equine protozoal myeloencephalitis (EPM), caused by *Sarcocystis neurona*, results in central nervous system inflammation and neuronal damage [8]. While EPM is fundamentally different from PSSM in its pathogenesis, emerging understanding of the gut-brain axis and immune-mediated inflammation suggests that microbiota-derived short-chain fatty acids (SCFAs), endotoxemia, and immune modulation may influence neuroinflammatory processes and treatment response. The relationship between gut dysbiosis and neuroinflammatory disease has been extensively documented in human neurodegenerative conditions but remains underexplored in equine EPM.

1.3 Chronic Neuromuscular Disease Framework For the purpose of this review, the population encompassing horses with PSSM, EPM, and related chronic neuromuscular conditions serves as the foundation for evaluating interventions targeting gastrointestinal health, microbiota composition, and immune modulation.

2. Core Concept: Gut Health, Microbiota, and Hindgut Function

2.1 Hindgut Acidosis and Dysbiosis in Equine Nutrition The equine hindgut harbors a complex microbial ecosystem responsible for fermentation of dietary fiber, production of short-chain fatty acids (primarily acetate, propionate, and butyrate), and modulation of systemic immune function [9]. Hindgut acidosis—a condition characterized by excessive fermentation of carbohydrates and a shift toward pathogenic bacteria—has been proposed as a potential pathophysiological mechanism underlying or exacerbating neuromuscular disease, though direct mechanistic evidence in PSSM and EPM is lacking [10].

High nonstructural carbohydrate (NSC) diets increase the substrate available for fermentation, lower hindgut pH, and promote the proliferation of lactate-producing organisms, potentially compromising intestinal barrier function and increasing systemic endotoxemia [11].

In a seminal study, Borgia et al. demonstrated that horses with PSSM exhibit differential glycemic and insulinemic responses compared to controls when fed hays with varying NSC content [11]. Critically, PSSM horses demonstrated significantly higher glucose and insulin responses to high-NSC hay (17% NSC) compared to low-NSC hay (4% NSC), suggesting that NSC overload in these animals may perpetuate aberrant metabolic signaling that could theoretically interact with hindgut dysbiosis to amplify muscle injury and systemic inflammation [11].

2.2 Forage-First Diets and Carbohydrate Restriction The forage-first dietary approach—prioritizing long-stem forage as the primary energy source while restricting NSC—forms the evidence-based foundation for managing PSSM and, by extension, potentially supporting neuromuscular stability in other chronic conditions [1], [12]. Dietary starch restriction directly reduces glucose and insulin excursions that drive abnormal glycogen accumulation in PSSM muscle, while simultaneously lowering the fermentation substrate in the hindgut [5], [12].

The effect of NSC on postprandial insulin and glucose in control horses further underscores the broad applicability of low-NSC feeding: control horses fed 17% NSC hay demonstrated insulinemic area under the curve of 6891.7 ± 3524.2, compared to only 1185.4 ± 530.2 when fed 4% NSC hay [11]. This metabolic shift—reducing total insulin exposure and avoiding glucose spikes—theoretically reduces fermentation-induced acidosis and supports a more stable hindgut microbiota composition.

2.3 Microbiota and Fecal Composition Studies Direct equine microbiome studies examining PSSM or EPM populations remain absent from the peer-reviewed literature. However, foundational research in aging horses and frailty suggests that reduced microbiota biodiversity, decreased abundance of butyrate-producing species (particularly *Faecalibacterium* and *Bifidobacterium*), and diminished fermentative capacity correlate with reduced grip strength and physical performance [8]. This gut-muscle axis framework, while established in rodent models of sarcopenia and aging humans, has not been specifically investigated in horses with genetic muscle disease.

Animal model data provides indirect evidence: in mice fed high-fat diets, combined probiotic (*Bifidobacterium longum* OLP-01) and exercise training synergistically improved weight, glucose tolerance, fat composition, and exercise-related oxidative stress compared to either intervention alone, suggesting a mechanistic link between microbiota composition and metabolic adaptation to exercise [13]. Extrapolating to PSSM horses, a similar synergy between microbiota optimization and structured exercise might enhance metabolic recovery and reduce muscle inflammation, though this remains speculative without equine-specific data.

3. Diagnostic and Measurement Approaches

3.1 Methods for Assessing Hindgut Microbiota Fecal microbiome analysis via 16S rRNA gene sequencing represents the standard approach for quantifying equine microbiota composition. However, no published studies have applied this methodology to characterize microbiota differences in PSSM-affected or EPM-affected horses versus healthy controls. Limitations of fecal sampling include its inability to directly assess the cecal and colon microbiota in situ, reliance on culturable and non-culturable organism characterization, and substantial inter-individual variation even within healthy horses.

Metagenomic and transcriptomic approaches have been employed in human inflammatory bowel disease and neuroinflammatory conditions to quantify functional gene expression related to SCFA production, lipopolysaccharide (LPS) synthesis, and antimicrobial peptide production. Such approaches have not been systematically applied to equine populations with neuromuscular disease. Additionally, measurement of fecal SCFA concentrations and plasma lipopolysaccharide (LPS) levels may serve as biomarkers of hindgut dysbiosis and intestinal permeability, respectively, but normative data and clinical utility in horses with PSSM or EPM are undefined.

3.2 Clinical Assessment of Digestive Outcomes Clinical digestive outcomes in equine myopathy studies are rarely measured. The aforementioned colic scoping review identified that early reintroduction of forage-based, low-starch diets was associated with faster recovery post-operatively, supporting the principle that lowering NSC and maximizing forage preserves hindgut motility and microbiota stability [10]. Proxy measures of hindgut health in PSSM populations might include fecal consistency, frequency and quality of defecation, and the absence of clinical colic episodes, though such outcomes are not routinely reported in published PSSM management studies.

4. Interventions: Nutritional Modulation and Feed Additives

4.1 Direct Evidence: Low-Starch, High-Fat Diets The most robust evidence for any intervention in PSSM involves low-starch, fat-supplemented diets. Multiple studies demonstrate that restricting nonstructural carbohydrate (NSC) to <5% of digestible energy while providing >12% of digestible energy as fat significantly reduces serum creatine kinase activity and exertional rhabdomyolysis episodes [5], [6]. Williams et al. reported that 80% of PSSM2 Warmblood horses showed overall improvement in performance with this dietary intervention, including significant decreases in the proportion showing decline in performance and rhabdomyolysis [6].

Mechanistically, this dietary manipulation reduces postprandial insulin excursions and substrate availability for abnormal polysaccharide accumulation within muscle [4]. By corollary, lower dietary NSC also reduces the fermentation substrate reaching the hindgut, potentially stabilizing microbiota composition and reducing acidosis, though this indirect benefit has not been explicitly measured in PSSM horses. The evidence supporting low-starch feeding in PSSM is direct and Level 1 (from randomized controlled trials and observational studies).

4.2 Extrapolated Evidence: Probiotics and Prebiotics Probiotics—live beneficial microorganisms, commonly *Lactobacillus* and *Bifidobacterium* species—are widely marketed for equine digestive health and immune support, yet minimal direct evidence exists for their efficacy in PSSM or EPM. In rodent models of diet-induced obesity and metabolic dysfunction, oral administration of encapsulated *Lactiplantibacillus plantarum* CRD7 increased expression of tight junction proteins (claudin-1, ZO-1, occludin), decreased pro-inflammatory cytokines (TNF-α, MCP-1, IL-6), increased short-chain fatty acid production, and promoted beneficial bacteria while suppressing pathogenic species [14]. This mechanistic package—barrier fortification, pro-inflammatory cytokine suppression, and microbiota rebalancing—aligns theoretically with proposed benefits for horses with neuroinflammatory disease, yet no equine trials have been conducted.

Riboflavin (vitamin B2) supplementation demonstrates anti-inflammatory effects in a DSS-induced colitis mouse model, characterized by inhibition of pro-inflammatory cytokines (TNF-α, IL-1β, CALP), increased anti-inflammatory IL-10, restored tight junction proteins, and elevated short-chain fatty acids including butyrate and propionate [15]. The mechanism involves both immune modulation and microbiota rebalancing, with increased abundance of butyrate-producing *Akkermansia*. While not specifically tested in horses, the anti-inflammatory capacity and SCFA production support warrants future investigation in PSSM populations, particularly those with evidence of systemic inflammation.

Prebiotics—dietary substrates selectively fermented by beneficial microbiota—have not been rigorously studied in horses with muscle disease. Inulin and fructooligosaccharides (FOS) are proposed to increase *Bifidobacterium* abundance, yet excessive prebiotic supplementation in equines has been anecdotally associated with colic and hindgut acidosis, suggesting a careful dose-response relationship exists [10].

4.3 Yeast Cultures and Saccharomyces cerevisiae Yeast culture products, primarily *Saccharomyces cerevisiae*, are claimed to stabilize hindgut pH, enhance microbial fermentation efficiency, and improve digestive outcomes in horses. Despite widespread commercial availability, controlled trials in equine PSSM or EPM populations are absent. The proposed mechanisms—yeast-derived growth factors, β-glucans, and mannan oligosaccharides—may have immunomodulatory properties, but efficacy specific to neuromuscular disease remains unproven. Extrapolation from general equine nutritional literature to PSSM or EPM is tenuous without direct evidence.

4.4 Medication-Associated Dysbiosis and Therapeutic Considerations Antimicrobial therapy—including antibiotics such as metronidazole (used for some intestinal parasites) and anthelmintics—carries potential for disrupting microbial ecosystems [10]. In EPM treatment regimens employing antiprotozoal medications (e.g., diclazuril, toltrazuril), the impact on equine hindgut microbiota has not been systematically evaluated. Given that barrier function and immune tolerance depend on microbial-derived SCFAs and intact tight junctions, dysbiosis secondary to therapeutic medications may theoretically impair recovery. Concomitant probiotic supplementation during or following antimicrobial ther-

apy is a logical extension of clinical practice, yet evidence-based recommendations for equine PSSM or EPM are unavailable.

Nonsteroidal anti-inflammatory drugs (NSAIDs), commonly used to manage muscle pain and inflammation in myopathy patients, can compromise intestinal barrier integrity and increase systemic LPS translocation in certain contexts [10]. While direct evidence in horses is limited, NSAIDs should ideally be used at the lowest effective dose for the shortest duration necessary in PSSM and EPM cases to minimize hindgut disruption.

5. Immune Modulation and Inflammatory Markers

5.1 Cytokine Dysregulation in Muscle Disease PSSM muscle exhibits marked upregulation of pro-inflammatory cytokines, with IL-18 representing one of the most significantly elevated genes in affected tissue [7]. IL-18 is a pleiotropic cytokine that drives interferon-gamma (IFN-γ) production and enhances Th1-mediated immune responses. The systemic consequences of muscle-derived inflammatory cytokines in PSSM have not been extensively characterized, but elevated muscle IL-18 could theoretically amplify hindgut-derived immune signaling, particularly if intestinal barrier integrity is compromised by dysbiosis or high-NSC diets.

Cannabidiol (CBD) treatment in senior horses significantly decreased whole blood inflammatory cytokine expression of IFN-γ at day 60 and IL-6 at days 60 and 90, without affecting other immune parameters or health biomarkers [16]. This selective reduction in specific pro-inflammatory cytokines without generalized immune suppression suggests a potential role for CBD in modulating the chronic inflammation observed in PSSM, though clinical efficacy in PSSM-affected horses has not been evaluated. The immunomodulatory mechanisms appear to involve cytokine downregulation rather than direct effects on microbiota, but the interplay between systemic inflammation and hindgut integrity warrants investigation.

5.2 Muscle-Derived Myokines and Regeneration Skeletal muscle itself functions as an endocrine organ, secreting numerous cytokines (myokines) that regulate myogenic differentiation, inflammatory responses, and systemic metabolism [17]. In the context of PSSM, where chronic polysaccharide accumulation drives inflammation, myokine production is likely pathologically altered. Exercise, a key therapeutic intervention in PSSM management, stimulates myokine production including IL-6 and irisin, which possess anti-inflammatory properties [17]. The hepatic and systemic immune effects of muscle-derived myokines in PSSM horses receiving structured exercise and low-starch diets have not been characterized.

5.3 Hindgut-Derived Immune Signaling and Barrier Function The intestinal epithelial barrier functions as a critical interface between luminal microbiota and systemic immunity. Dysbiosis-associated reduction in butyrate-producing bacteria compromises tight junction protein expression (claudins, occludin, zonula occludens-1) and increases intestinal permeability to lipopolysaccharide (LPS) [15]. Elevated plasma LPS triggers toll-like

receptor 4 (TLR4) signaling, which activates NF-κB and NLRP3 inflammasome pathways, amplifying systemic pro-inflammatory responses [18]. In the context of PSSM, where muscle already exhibits NF-κB activation and NLRP3 inflammasome involvement, additional endotoxemic signaling from dysbiotic hindgut could synergistically exacerbate muscle inflammation.

Direct assessment of intestinal permeability, plasma LPS, and toll-like receptor expression in PSSM and EPM horses remains absent. Interventions specifically designed to restore barrier function—such as glutamine supplementation, zinc supplementation, or probiotics providing barrier-enhancing metabolites—remain untested in these populations, though the theoretical rationale is compelling.

5.4 Exercise, Immune Function, and Anti-Inflammatory Signaling Regular exercise is recommended as a cornerstone of PSSM management [1], [12]. Exercise training in healthy individuals and cancer survivors reduces circulating pro-inflammatory markers including TNF-α and C-reactive protein while modulating immune cell proportions and function [19]. High-intensity interval training in a murine stroke model reduced pro-inflammatory IL-1β and IL-6 in muscle while upregulating anti-inflammatory IL-10 and improving CD4+/CD8+ T cell ratios [20]. The combination of low-NSC diet and structured exercise in PSSM may therefore exert synergistic anti-inflammatory effects at both the muscle and systemic levels, potentially reducing hindgut dysbiosis-associated endotoxemia. However, the immunological benefits of combined dietary and exercise interventions in PSSM horses have not been prospectively evaluated.

6. Synthesis of Evidence Levels and Mechanistic Framework

6.1 Classification of Evidence: Direct, Extrapolated, and Speculative **Direct Evidence (Level 1: Established in PSSM/EPM or relevant equine disease)** - Low-starch, high-fat diets reduce exertional rhabdomyolysis and improve performance in PSSM [1], [5], [6] - Genetic testing (GYS1 mutation) accurately identifies PSSM1 [1], [21] - Regular exercise combined with low-starch diet improves PSSM outcomes [1], [6]

Extrapolated Evidence (Level 2-3: Established in related animal models or human disease, mechanistically applicable) - Probiotics and specific *Lactobacillus*/*Bifidobacterium* strains enhance barrier function and reduce systemic inflammation in mice and humans [14], [15] - Riboflavin supplementation reduces pro-inflammatory cytokines and enhances SCFA production [15] - Combined probiotic and exercise interventions synergistically improve metabolic parameters [13] - Hindgut dysbiosis-associated endotoxemia contributes to systemic inflammation and potentially muscle disease progression [8] - Forage-based, low-NSC diets preserve hindgut microbiota stability and reduce acidosis [10]

Speculative Evidence (No direct equine data; theoretical mechanism only) - Yeast culture products improve PSSM-related hindgut dysfunction - Specific probiotic strains improve EPM neuroinflammation or recovery - Cannabidiol supplementation reduces PSSM muscle inflammation beyond systemic cytokine effects - Prebiotic supplementation im-

proves muscle recovery in PSSM without increasing colic risk - Restored barrier function via microbiota optimization directly improves PSSM phenotype

6.2 Proposed Mechanistic Framework: The Gut-Muscle-Immune Axis in PSSM A coherent mechanistic framework emerges from integrating evidence across domains:

1. **Dietary Carbohydrate Overload**: High-NSC diets in PSSM horses drive excessive glucose uptake and polysaccharide accumulation in muscle, while simultaneously providing fermentation substrate for hindgut dysbiosis.
2. **Dysbiosis and Barrier Dysfunction**: Excessive hindgut fermentation reduces pH, promotes pathogenic lactate-producing organisms, and diminishes butyrate-producing taxa. This dysbiosis compromises intestinal tight junctions and increases systemic LPS translocation.
3. **Endotoxemia and Systemic Inflammation**: Elevated plasma LPS activates TLR4 and NF-κB pathways, amplifying systemic pro-inflammatory cytokine production and recruitment of immune cells to muscle.
4. **Myocellular Inflammation and Energy Deficit**: PSSM muscle exhibits mitochondrial dysfunction, glycogenesis inhibition, and chronic inflammation independent of dietary effects. Systemic endotoxemia and pro-inflammatory signaling further compromise energy metabolism and myocellular integrity.
5. **Exercise Intolerance and Rhabdomyolysis**: The combination of metabolic susceptibility, inflammation, and energy deficits renders PSSM muscle acutely vulnerable to breakdown during exercise, manifesting as rhabdomyolysis.
6. **Therapeutic Intervention: Low-NSC Diet + Microbiota Optimization**: Low-NSC feeding reduces polysaccharide accumulation and hindgut fermentation substrate, allowing dysbiotic microbiota to recover. Concomitant probiotic/prebiotic supplementation accelerates restoration of barrier-protective and SCFA-producing organisms, reducing systemic endotoxemia and enabling anti-inflammatory immune remodeling.

This framework, while largely speculative for PSSM, is grounded in robust mechanistic understanding from comparative pathophysiology and highlights critical gaps requiring equine-specific investigation.

6.3 EPM and the Gut-Brain-Immune Axis For EPM, a parallel framework suggests potential therapeutic targets:

1. **Neuroinflammation**: *Sarcocystis neurona* infection triggers CNS-resident immune cell activation and pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6, IFN-γ), resulting in neuronal dysfunction and death.
2. **Systemic Immune Dysregulation**: Peripheral immune cells exhibit heightened activation and inflammatory cytokine production in EPM patients.

3. **Potential Microbiota-Immune Link**: Dysbiotic microbiota are less efficient at SCFA production, impairing intestinal barrier function and increasing systemic LPS exposure. Elevated systemic inflammation may inadequately control parasitemia while amplifying bystander neuroinflammation.
4. **Therapeutic Potential**: Microbiota optimization via low-NSC diet and targeted probiotics could theoretically enhance systemic Th1 responses (necessary for parasite control) while reducing dysbiosis-derived endotoxemia that exacerbates neuroinflammation.

This model remains highly speculative for EPM and should not inform clinical practice without direct equine evidence.

7. Critical Evaluation: Gaps and Limitations

7.1 Absence of Equine Microbiome Studies in PSSM and EPM The most glaring limitation is the complete absence of published fecal or cecal microbiota characterization in horses with PSSM or EPM compared to healthy controls. Without baseline microbiota profiling, it is impossible to establish whether dysbiosis exists, which taxa are dysregulated, or whether interventions alter microbiota composition. Future studies must employ high-resolution sequencing and functional metagenomic approaches to address this gap.

7.2 Lack of Mechanistic Studies in Equine Models No published studies have measured plasma LPS, intestinal permeability markers, or tight junction protein expression in PSSM or EPM horses. Similarly, the effects of low-NSC diets on hindgut pH, SCFA production, or microbiota composition in equines with muscle disease remain unmeasured. These mechanistic studies are essential to validate the proposed gut-muscle-immune axis framework.

7.3 Absence of Probiotic Trials in PSSM and EPM Despite widespread use of probiotic and prebiotic supplements in equine practice, no randomized controlled trials have evaluated their efficacy in PSSM or EPM populations. Such trials should employ: - Baseline and post-intervention microbiota profiling - Measurement of clinical outcomes (muscle enzyme levels, exercise tolerance, performance metrics) - Immunological assessment (cytokine profiling, immune cell phenotyping) - Digestive biomarkers (fecal SCFA, plasma LPS)

7.4 Limited Nutritional Intervention Data Beyond Low-NSC Feeding While low-starch feeding is evidence-based, few studies have examined supplemental nutrient interventions (e.g., vitamin E, selenium, omega-3 fatty acids, amino acids) in PSSM. The role of vitamin E and selenium in equine neuromuscular disease is illustrated by enzootic rhabdomyolysis in Transylvania, where selenium and vitamin E deficiency correlated with disease prevalence [22]. Systematic nutritional profiling and supplementation trials in PSSM horses remain absent.

7.5 Lack of Multimodal Intervention Studies No published studies have evaluated combined dietary, probiotic, exercise, and targeted micronutrient interventions in PSSM or EPM. The potential for synergistic effects—as suggested by the probiotic + exercise mouse study—warrants investigation in equine models using well-designed, randomized, controlled trial methodology.

8. Clinical Implications and Future Directions

8.1 Current Evidence-Based Recommendations For PSSM and EPM: 1. **Implement low-NSC (<5% of digestible energy) forage-first diet** (Level 1 evidence for PSSM; theoretical benefit for EPM via microbiota preservation) 2. **Establish structured exercise program** (Level 1 evidence for PSSM; supports general health and immune function for EPM) 3. **Measure baseline nutritional status** (vitamin E, selenium, antioxidant capacity) and supplement if deficient 4. **Monitor fecal consistency and gastrointestinal signs** as proxy indicators of hindgut health 5. **Minimize antimicrobial and NSAID use** unless clinically indicated; if used, consider concurrent probiotic supplementation (Level 2-3 evidence)

8.2 Areas Requiring Further Investigation

1. **Fecal microbiota characterization** in PSSM and EPM populations versus healthy controls
2. **Randomized controlled trials** of specific probiotic and prebiotic interventions with microbiota, immunological, and clinical endpoints
3. **Mechanistic studies** examining plasma LPS, intestinal permeability, and tight junction integrity in PSSM and EPM
4. **Nutritional micronutrient profiling** and targeted supplementation trials (vitamin E, selenium, omega-3 fatty acids, amino acids)
5. **Multimodal intervention trials** combining diet, microbiota optimization, exercise, and immunomodulation
6. **Longitudinal phenotyping** of muscle inflammation, microbiota composition, and clinical outcomes in PSSM horses receiving comprehensive management

8.3 Personalized Medicine Implications Given the substantial inter-individual variability in microbiota composition and immunological responsiveness, future PSSM and EPM management should incorporate baseline microbiota and immune profiling to tailor interventions. Horses with evidence of dysbiosis or systemic inflammation might benefit from targeted probiotics, specific nutrient supplementation (riboflavin, omega-3 fatty acids), or anti-inflammatory compounds (CBD), whereas horses with preserved microbiota diversity but poor clinical response may require alternative mechanistic targets (e.g., mitochondrial support, antioxidant enhancement).

9. Conclusions

The gut microbiome and hindgut function represent potentially modifiable therapeutic targets in equine PSSM and EPM, yet direct evidence linking microbiota composition to

disease pathogenesis or clinical outcomes remains absent. The theoretical foundation for interventions is robust: low-NSC diets preserve hindgut microbiota stability and reduce dysbiosis-associated endotoxemia; probiotics and prebiotics enhance barrier function and anti-inflammatory signaling in comparative models; and exercise synergistically supports metabolic adaptation and immune rebalancing. However, claims regarding specific probiotic strains, yeast cultures, or prebiotic products for PSSM and EPM exceed current evidence and should be classified as speculative until equine-specific data become available.

The strongest evidence supports the continuation and refinement of low-starch, forage-based dietary management combined with regular, structured exercise—interventions that theoretically benefit both muscle metabolism and hindgut microbiota stability. Future research must prioritize microbiota characterization, mechanistic biomarker measurement, and rigorous clinical trials to validate whether microbiota optimization provides additional benefit beyond low-NSC feeding alone. Until such evidence emerges, practitioners should base recommendations on established dietary principles while remaining cautious about extrapolating mechanisms from rodent models or human disease to equine PSSM and EPM populations.

Evidence Summary Table:

Intervention	Evidence Level	Direct Equine PSSM/EPM Data	Microbiota Measurement	Clinical Outcome Measured	Immune/Inflammatory Outcome	Status
Low-NSC, high-fat diet	Level 1	Yes (multiple trials)	No	Performance, CK, rhabdomyolysis	Indirect (reduced inflammation via metabolic effect)	Established
Probiotics (*Lactobacillus*/*Bifidobacterium*)	Level 3	None	No	None in equine	Yes (in mouse models)	Speculative
Yeast culture (*S. cerevisiae*)	Level 3	None	No	None	None	Speculative
Prebiotics (FOS, inulin)	Level 3	None	No	None	None	Speculative

Intervention	Evidence Level	Direct Equine PSSM/ERM Data	Microbiota Measurement	Clinical Outcome Measured	Immune/Inflammatory Outcome	Status
Structured exercise + low-NSC diet	Level 1	Yes (PSSM)	No	Performance, CK, clinical signs	Indirect (improved fitness, myokine production)	Established
Vitamin E + selenium supplementation	Level 2	Yes (in enzootic rhabdomyolysis)	No	CK, rhabdomyolysis prevalence	Indirect (antioxidant defense)	Strongly recommended if deficient
Cannabidiol	Level 3	No (healthy horses only)	No	None in muscle disease	Yes (IFN-γ, IL-6 reduction in seniors)	Speculative
Omega-3 fatty acids	Level 3	None	No	None	Yes (anti-inflammatory in human/rodent)	Speculative

Key Citations by Category:

PSSM Genetics and Pathophysiology: [1], [2], [4], [6], [7]

Nutritional Management: [3], [5], [10], [11], [12]

Microbiota and Gut-Muscle Axis: [8], [13], [14], [15]

Immune and Inflammatory Mechanisms: [16], [17], [18], [19], [20], [23]

Exercise and Metabolic Management: [9], [12], [24]

Micronutrient and Mineral Deficiency: [22]

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