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AMINO ACID-BASED ENTERAL DIETS

For Canine Adverse Food Reactions And Gastrointestinal Disease

Viszla and lysine crystals

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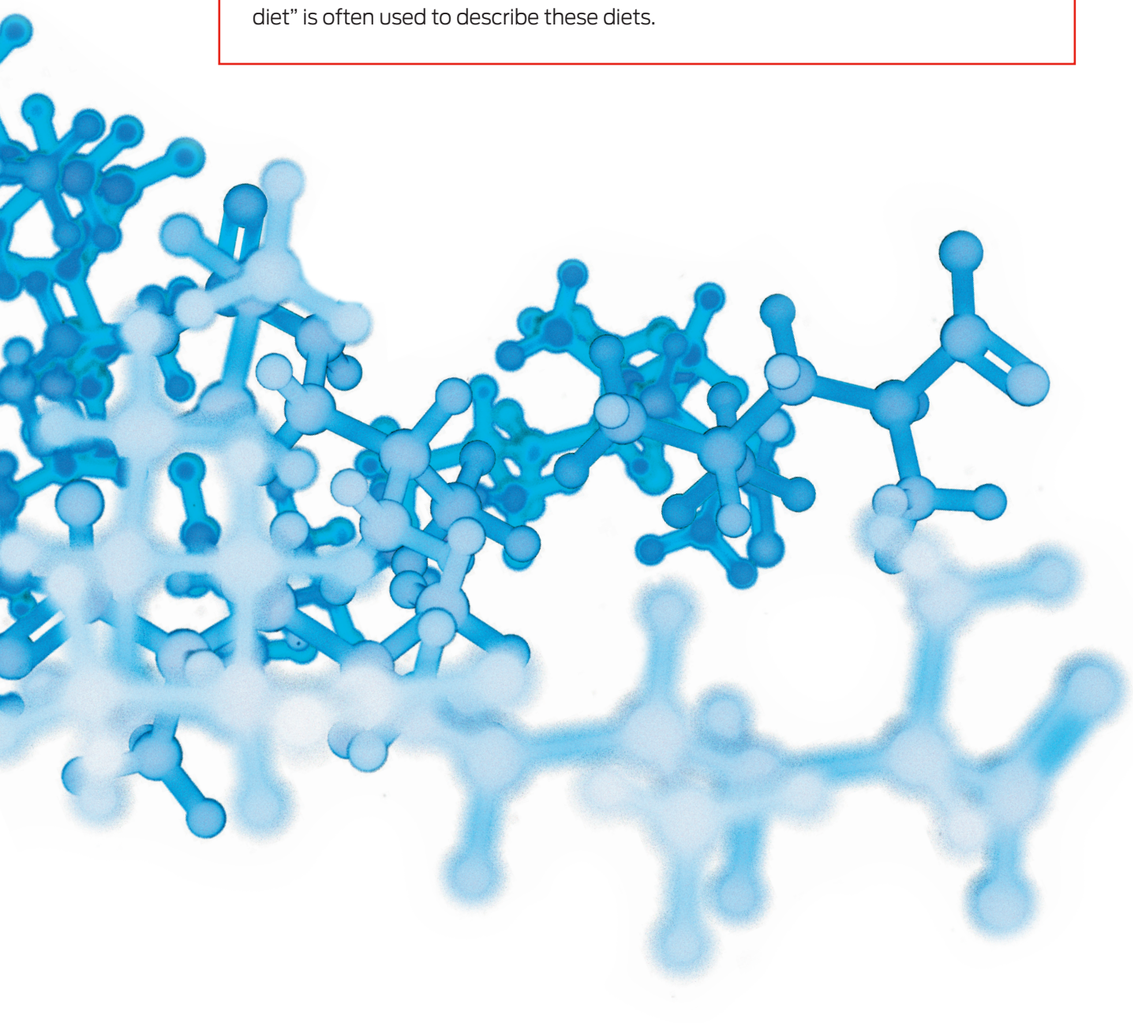
Amino acid-based enteral diets provide protein in its simplest form: amino acids.[1] Fat is usually provided in small amounts as fatty acids, or often as medium-chain triglycerides.[1-7] As a consequence of this simplicity, these diets do not require intact digestive capabilities for their breakdown and absorption.[8] The term “elemental diet” is often used to describe these diets.



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HISTORY OF AMINO ACID-BASED AND ELEMENTAL DIETS

Amino acid-based diets were introduced into human medical practice in 1960, and the first studies emerged as a result of the space program.[9,10] The first planned use of these elemental diets was to provide nutrition for astronauts on prolonged space voyages, hence the early name "space diets."[5]

In human medicine, amino acid-based diets gained popularity because they offered a number of advantages over total parenteral nutrition (TPN) including: ease of administration; improved ability to meet the patient's nutritional needs; reduced sepsis and other infectious complications; reduced labor associated with monitoring and care; and improved return of gastrointestinal function.[1,9] One of the principal benefits of enteral nutrition, including amino acid-based diets, is the provision of luminal nutrients to support the gastrointestinal mucosa.[11] The presence of nutrients within the gut lumen is critical for intestinal mucosal growth, repair and integrity.[12] The absence of luminal nutrients (due to TPN and/or forced avoidance of oral intake) leads to a number of detrimental effects including mucosal atrophy, increased intestinal permeability, and increased pro-inflammatory responses.[12]

Positive outcomes were reported for use of amino acid-based elemental diets in human patients with gastrointestinal fistulas; short bowel syndrome; chronic pancreatic insufficiency; partial intestinal obstruction; enteropathy associated with radiation or chemotherapy; malabsorptive and maldigestive states (including inflammatory bowel disease and Crohn's disease) unresponsive to conventional therapy; and postoperative management following bowel resection.[4,9,13]

NOT ALL HYDROLYSATES ARE CREATED EQUAL

Hydrolysis uses proteases and specific pH and temperatures to reduce intact proteins to small polypeptides, with the goal of providing polypeptides sufficiently small enough to avoid eliciting an allergic response.[14-21] Hydrolysates were first introduced more than 50 years ago for use in formulas for infants and children with cow's milk allergies.[18,22] Hydrolysates have been in use in pet nutrition since the mid-1990s.[11]

Purina's leadership: In 1998, Purina launched the first hydrolyzed veterinary therapeutic diet to nutritionally manage food allergies.

Due to differences in the parent (original source) protein, the specificity of the proteolytic enzymes used, the method and degree of hydrolysis, and any further processing of the hydrolysate during manufacture, hydrolysates can be quite variable – resulting in potential variability in clinical response.[11,23-27] Even hydrolysates of the same parent protein may differ in the respective amounts of oligopeptides, di- and tri-peptides, and free amino acids.[28] **Only extensive hydrolyzation to yield very small peptide sequences or free amino acids can minimize the antigenicity and allergenicity of the diet.**[19,21,25,27,29,30,32]

AMINO ACID-BASED DIETS FOR SELECTED CONDITIONS

Adverse food reactions (AFRs)

Adverse food reactions are reactions to an otherwise harmless component of the diet and include immunological mechanisms, such as food allergy, as well as non-immunologic conditions such as food intolerance and intoxication.[11,18,32-36]

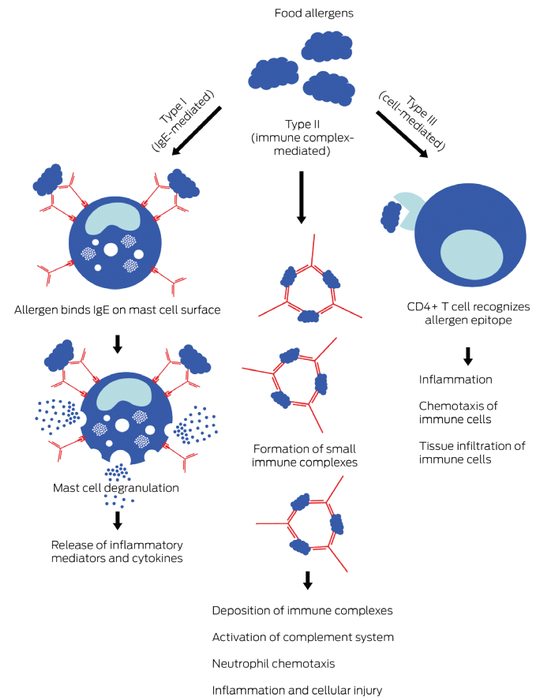
The exact pathophysiological processes underlying AFRs are not well described, but type I, III and/or IV hypersensitivity reactions may be involved.[28,34-36,39,42-44]

The etiologies of AFR vary, but the clinical signs are usually indistinguishable.[25,37] Although associated with dietary antigens, AFRs result in gastrointestinal signs in approximately 10-30% of cases.[15,32-35] Increased fecal frequency, tenesmus, diarrhea, and mucus or blood in the feces may be observed.[38] AFRs commonly result in dermatologic conditions and are one of the most common causes of nonseasonal allergic skin disease in dogs.[15,32-35,39,40] The dermatologic signs associated with AFRs are variable and non-specific, and mimic other dermatoses including atopy.[32,34,35,37,39,40] Otitis externa (often bilateral) is one of the most commonly reported clinical signs associated with AFRs.[41]

The gold standard of AFR diagnosis in dogs is the resolution of clinical signs while fed an elimination diet, followed by a return of clinical signs when fed a provocative challenge of the offending antigen.[32,36,45-48] Dogs with GI signs may show clinical improvement within several weeks, but cutaneous AFR often requires 8-12 weeks or longer on the elimination diet.[32,36,45-48]

It is common for dogs to be sensitized to more than one food allergen, which may limit options for elimination diet components.[36,38,49,50] Comparisons of the advantages and disadvantages of the most common elimination diets are provided in the table below:

Figure 1:
Schematic of types I, III and IV hypersensitivity reactions following ingestion of a food allergen



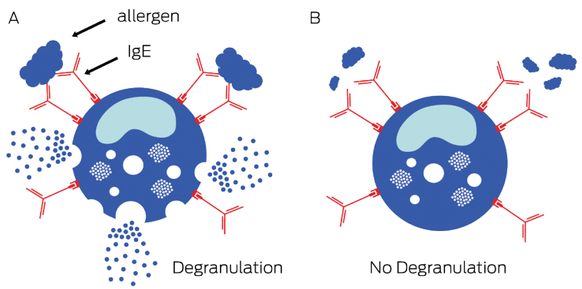
Diet type	Advantages	Disadvantages
Home-cooked diets	■ Most appropriate[16,37,39,40,51] ■ Can be limited to one protein source, one carbohydrate source[36] ■ Ability to tailor diet on individual's nutritional history[36] ■ Owners feel more involved[36]	■ Not balanced for long-term feeding[16,37,39,40,51] ■ Effort-intensive, time-consuming[16,36-38,59] ■ Expensive[59] ■ Higher risk of failure/non-compliance[16,37,39,40,51,59] ■ Novel ingredients might not be readily available[16,36-38] ■ Not adequate for maintenance after diagnosis[16,36-38] ■ Not adequate for diagnosis in young, growing dogs[16,36-38] ■ Potential challenges with acceptance[16,36-38] ■ Possible GI upset[16,36-38]
Selected/ limited protein commercial diets	■ Complete and balanced[36,57] ■ Less expensive than home-cooked[36] ■ Variety of foods available[36] ■ Easy to obtain[36] ■ Practical[36]	■ Variable efficacy[36,58] – only effective if diet does not contain any proteins to which the dog is sensitized ■ Risk of allergenicity due to undeclared ingredients or additives[16,19,36,37,40,54-56,58] ■ May not provide novel food protein source suitable for an individual[36]
Hydrolized commercial diets	■ Complete and balanced[40,45] ■ Easy to obtain[36] ■ Effective and well tolerated[52] ■ May be tolerated by dogs sensitized to parent protein[36]	■ Risk of persistent or increased immunogenicity/ allergenicity[11,36,52,53,55,56,58] ■ Reduced palatability[11,36,52]

All dietary proteins are antigenic, but only a fraction of the total ingested protein content is allergenic.[36,60] Epitopes are specific sites on the protein that are recognized by the immune system.[61,62] Linear epitopes consist of sequential, covalently linked amino acids (peptide sequences) and conformational epitopes are formed by amino acids made adjacent by the tertiary (three-dimensional) structure of the protein.[60,62] The number of amino acids forming an epitope varies, but the minimal number is six.[60,63]

Hydrolysis is the most reliable method of reducing the allergenicity of a diet without changing the nutritional value of the dietary protein.[11,16,34,37] Ideally, the peptide sequences are cleaved within the epitopes to produce immunologically inactive polypeptides.[11] Many B cell epitopes are conformational; therefore, destruction of the protein's tertiary structure by denaturation and/or hydrolysis will destroy these epitopes.[11,61,64] However, linear epitopes may still remain after hydrolysis, resulting in an immune response that leads to continuation or recurrence of the AFR signs.[11,30,31] In addition, linear epitopes that were previously obscured by the protein's tertiary structure may become exposed following disruption of that structure; or new conformational epitopes may be formed during partial refolding of the protein, contributing sources of additional antigenic (and potentially allergenic) stimulation.[11,31,64,65] Type IV hypersensitivities, mediated by T-lymphocytes recognizing peptides too small to bridge IgE and trigger type I hypersensitivity reactions, have been observed in dogs with food hypersensitivity.[31,43,44]

Figure 2:

Peptide fragments large enough to bind and bridge two or more IgE molecules trigger mast cell degranulation and type I hypersensitivity reactions (A). Sufficient hydrolysis eliminates these larger peptides; although intact epitopes may still bind IgE, the peptides are not large enough to bridge IgE molecules and trigger degranulation (B).



Many dogs will tolerate hydrolyzed diets even if sensitized to the parent protein[11,52] but continuation, worsening or relapse of cutaneous signs has occurred in some dogs fed hydrolysates of the parent protein to which they were sensitized.[17,18,45,66,67] Ensuring that a hydrolysate contains peptides smaller than 3 kDa, or even 1 kDa, would ensure the greatest chance of eliminating protein immunogenicity; the provision of amino acids and very small peptides meets this goal.[11,52,53]

Amino acid-based diets for adverse food reactions

Amino acid-based diets offer a dual advantage of providing adequate nutritional support with complete removal of dietary protein antigens.[69] Although hydrolyzed diets are markedly less antigenic than intact protein diets and are generally well tolerated, they may still contain peptides of sufficient length to be immunogenic in highly sensitized individuals.[30] All of the studies evaluating hydrolysates for AFR have had one or more dogs whose clinical signs did not improve on the hydrolysate; although the reason for dietary failure in these dogs was not investigated, these findings support the possibility of persistent antigenicity. There are documented cases of human infants with cow's milk allergy (CMA) experiencing relapse of GI symptoms when fed casein hydrolysates, with subsequent remission on an amino acid diet.[22,69,70] An amino acid-based diet facilitated the diagnosis of cutaneous AFR in 7 dogs who had previously failed to improve on hydrolyzed (1 dog), novel protein (3 dogs), and home-cooked (2 dogs) diets.[30]

A key benefit unique to amino acid-based diets is a lack of antigenic constituents.[3,68] Essentially, these diets provide complete, yet protein-free, nutrition.[4] These features make amino acid-based diets ideal candidates for use as elimination diets.

Amino acid-based diets may have immunomodulatory effects. In rodent studies, use of amino acid-based enteral diets decreased intraepithelial lymphocytes; reduced the size of Peyer's patches throughout the small intestine; reduced the cellularity of the intestinal lamina propria; and increased villus height without inducing a change in the depth of the intestinal crypts.[71] The absence of dietary protein antigens in amino acid-based diets may lead to downregulation of the influx or proliferation of cells in the lymphoid tissue.[71] Amino acid-based formulas improved symptoms and intestinal barrier function and reduced intestinal inflammation and protein loss in infants with cow's milk allergy.[72] An amino acid-based elemental diet reduced eosinophil counts and improved cutaneous lesions in six human patients with atopic dermatitis.[73] In another study, improvement was seen in 27 of 37 (73%) children with refractory atopic eczema when an elemental diet was fed for 30 days as part of a strict allergen avoidance regimen.[74]

Figure 3:

The allergenicity of food proteins decreases as the degree of hydrolysis increases. Partially hydrolyzed proteins may still retain linear epitopes that bind antibodies or T cell receptors, triggering hypersensitivity reactions. Extensively hydrolyzed products have smaller fragments that are less likely to bind antibodies or cell receptors, and amino acids present the lowest allergenicity.

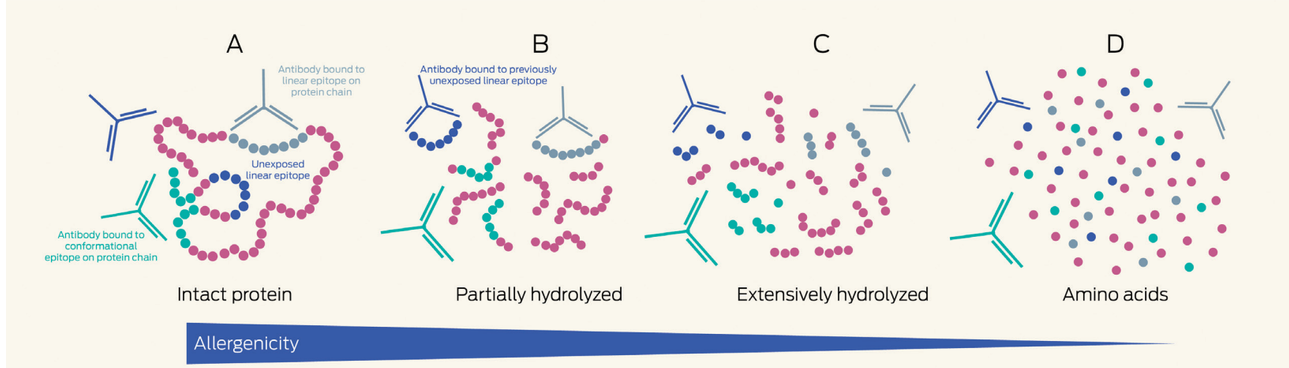
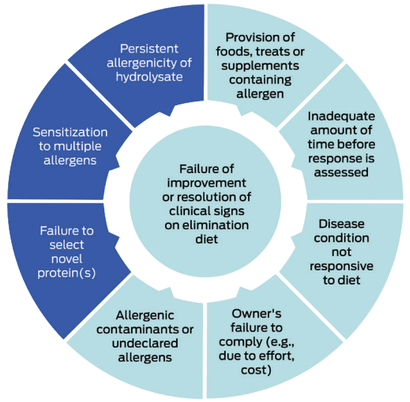


Figure 4:

Reasons for failure of response to elimination diets. The darker boxes represent factors where amino acid-based diets offer distinct advantages.



Chronic Enteropathies

Chronic enteropathies are subclassified into food- or diet-responsive; antibiotic-responsive; or corticosteroid-, steroid-, or immunosuppressive-responsive enteropathies based on their response to treatment.[27,75,76] Despite different etiologies, the clinical signs often overlap and may be indistinguishable.[75,76] The exact pathogenesis of steroid-responsive chronic enteropathy is unknown, but a number of factors have been proposed including dysregulation of mucosal immunity; inflammatory cell infiltration of the intestinal lamina propria; intestinal barrier dysfunction; depletion of the protective mucus layer; dysbiosis; and impaired bacterial clearance.[37,77-79]

Based on a meta-analysis of 11 randomized clinical trials investing dietary intervention for chronic enteropathy, Makielski et al[75] stated there is strong evidence to support a recommendation to feed elimination diets to dogs with chronic enteropathy. The dogs typically responded within 1-2 weeks of starting the elimination diet.[75] In a review of 53 published studies, Dandrieux et al[27] reported that response to diet was 60-100% with the exception of one study reporting remission in 45% of dogs.

Steroid-responsive chronic enteropathy in dogs closely resembles Crohn's disease, which is a variant of inflammatory bowel disease in humans.[27] Enteral nutrition is effective for inducing remission in Crohn's patients, and

has shown value as a primary treatment for Crohn's disease since the 1980s.[3,80,81] In a study of six dogs with refractory chronic enteropathy/inflammatory bowel disease, four of the six dogs showed improvement with a soy hydrolysate diet alone.[82] Due to their lack of antigenicity, amino acid-based diets are promising as elimination diets for initial or long-term management of chronic enteropathies.

Benefits of amino acid-based diets for chronic enteropathies

The majority of patients with GI disease benefit from a highly digestible diet with moderate fat restriction and either a novel or hydrolyzed protein source.[51] Amino acid-based elemental diets offer a theoretical advantage for chronic enteropathies, even non-food-responsive enteropathies, due to their lack of antigenicity. Larger polypeptides and proteins in less-hydrolyzed or intact protein diets may provide consistent antigenic stimulation that promotes inflammation.[3] By reducing the antigenic load confronting the GI tract's immune cells, amino acid-based diets can exert an indirect anti-inflammatory role.[83] In addition, given the possibility that adverse food reactions may trigger, or be triggered by, chronic enteropathy, amino acid-based elemental diets offer an advantage by eliminating the dietary antigens that could elicit an immune response.[25]

There is strong evidence to support a recommendation to feed elimination diets to dogs with chronic enteropathy.[75]

Mansfield et al[68] reported a higher remission rate for Crohn's patients treated with elemental versus polymeric diets (75% vs 36%, respectively). In the same study, two of five patients who failed to enter remission on a polymeric diet subsequently entered remission when switched to an elemental diet.[68] The elemental diet was also associated with a significant reduction in Crohn's Disease Activity Index (CDAI) score that was not observed with a polymeric (intact protein) diet.[68]

Amino acid-based elemental diets may also have beneficial immunomodulatory effects. Nucleotide-deficient diets (such as amino acid-based diets) are thought to be immunosuppressive, which could be beneficial for Crohn's disease and colitis treatment.[84] Highly digestible diets reduce the protein content entering the colon, resulting in reduced ammonia generation; in excess, ammonia is toxic to the large intestinal mucosa.[84,85]

As low-residue, highly digestible diets, amino acid-based elemental diets can serve as a "medical bypass" of affected GI segments while still providing adequate nutrition.[3,84,85] Amino acid-based diets elicit reduced gastric, pancreatic, biliary and intestinal secretions compared to intact protein diets, which may reduce the propagation of mucosal damage by these secretions.[84-86]

PREVENTING SECONDARY SENSITIZATION TO FOOD ANTIGENS

The GI tract has physical and physiological barriers to the absorption of antigenic, and potentially allergenic, dietary components.[32,87,88] When these barriers are compromised or breached, oral tolerance – the active process of establishing immune nonreactivity to a dietary antigen – may be impaired and the risk of sensitization increases.[14,84,89]

Intestinal infection and inflammation may compromise oral tolerance by disrupting the integrity of the mucosal barrier or the function of antigen-presenting cells or immune cells of the GALT.[90] Disruption of one or more steps in the development of oral tolerance, or a failure of the complex cellular interactions necessary to maintain it, may lead to inflammatory conditions including food hypersensitivity and allergy.[36,37,77,87,88,91] The persistence of luminal antigens elicits immunological responses and inflammation in the affected intestine.[3,7,12,68,85,92] These exaggerated responses may lead to subsequent relapses or delayed recovery of inflammatory conditions such as chronic enteropathies.

A proposed secondary aim of hydrolyzed diets is to provide a diet that does not elicit an immune response that may lead to sensitization in a naïve individual.[11,52] There is evidence to support concerns that dogs with inflammatory GI conditions and adverse food reactions develop secondary sensitization to proteins.[89] Some dogs with AFR develop dietary sensitivities to novel proteins within 1-3 years of their initial sensitivity.[34] Some veterinarians recommend switching away from the dog's original diet during acute gastroenteritis to a "sacrificial" novel protein source to reduce the likelihood of acquired sensitization to proteins in the original diet and perpetuation of the intestinal inflammation.[51,84,85] Hydrolysates have been recommended to achieve this goal,[84] but amino acid-based diets offer the advantage of meeting nutritional needs while eliminating dietary protein immunogenicity that may lead to the subsequent development of secondary sensitization or persistent inflammation.

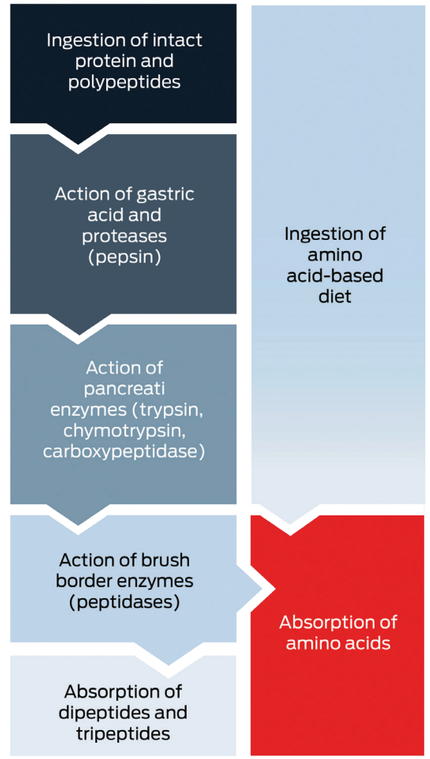
A key benefit unique to amino acid-based diets is a lack of antigenic constituents.[3,68] Essentially, these diets provide complete, yet protein-free, nutrition.[4] These features make amino acid-based diets ideal candidates for use as elimination diets.

ADDITIONAL GASTROINTESTINAL BENEFITS OF AMINO ACID-BASED DIETS

Additional proposed advantages of amino acid-based elemental diets include the following:

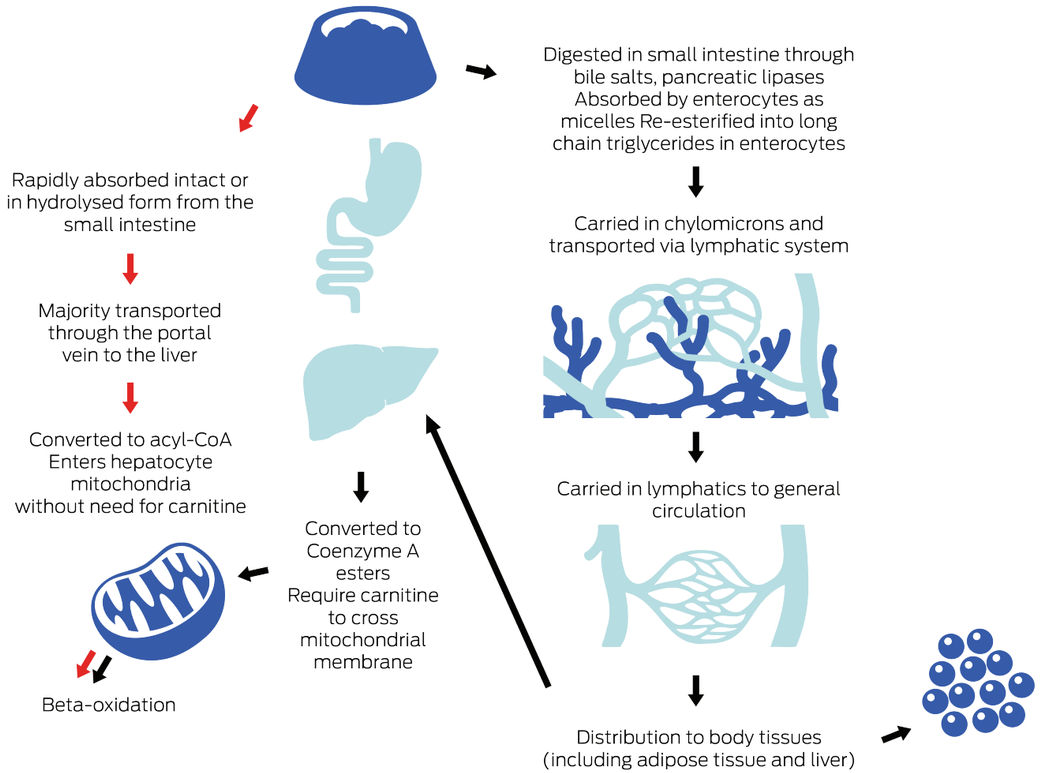
- Require minimal demand on the patient's digestive system, providing a highly digestible diet that allows "gastrointestinal rest"[4,7-9]
- Provide readily available nutrients directly to the enterocytes[7,93]
- Provide a nutritionally adequate diet to maintain positive nitrogen balance[9]
- Reduce bile and pancreatic exocrine secretions that could induce mucosal damage[3,7,9,13,93-95]
- Reduce gastric acid secretion[86]
- Serve as low-residue diets that meet the patient's nutritional needs with reduced intestinal volume and fecal bulk[4,96]
- Low fat levels have been associated with less favorable outcomes in a review of published studies[92]

Figure 5:
Schematic representation of the digestive process for intact proteins compared to ingested amino acids



The inclusion of **medium-chain triglycerides** as the primary fat source brings additional benefits. Medium-chain triglycerides (MCTs) provide fat in a readily available form that can be more quickly oxidized than long-chain triglycerides, even in protein-deficient states and gastrointestinal compromise.[70,97,98] Unlike long-chain triglycerides, the majority of MCTs are directly absorbed without the need for hydrolysis or micellar formation.[85,97] MCTs do not stimulate cholecystokinin secretion; do not require bile or pancreatic enzymes for digestion; and do not require carnitine for transport into mitochondria.[97] A number of botanical oils, such as coconut oil, provide excellent sources of MCTs.[98] Minimizing long-chain triglyceride (LCT) content in enteral diets for gastrointestinal disease may improve the therapeutic benefit: efficacy and remission rates have been negatively associated with the LCT content of the enteral diet.[7,99-101]

Figure 6:
Diagram depicting the different digestion, absorption, and metabolism of long-chain fatty acids (LCFA) versus medium-chain fatty acids (MCFA). The flow of processes involved in LCFA metabolism is indicated by the black arrows, whereas the simpler metabolism of MCFAs is indicated by the red arrows.

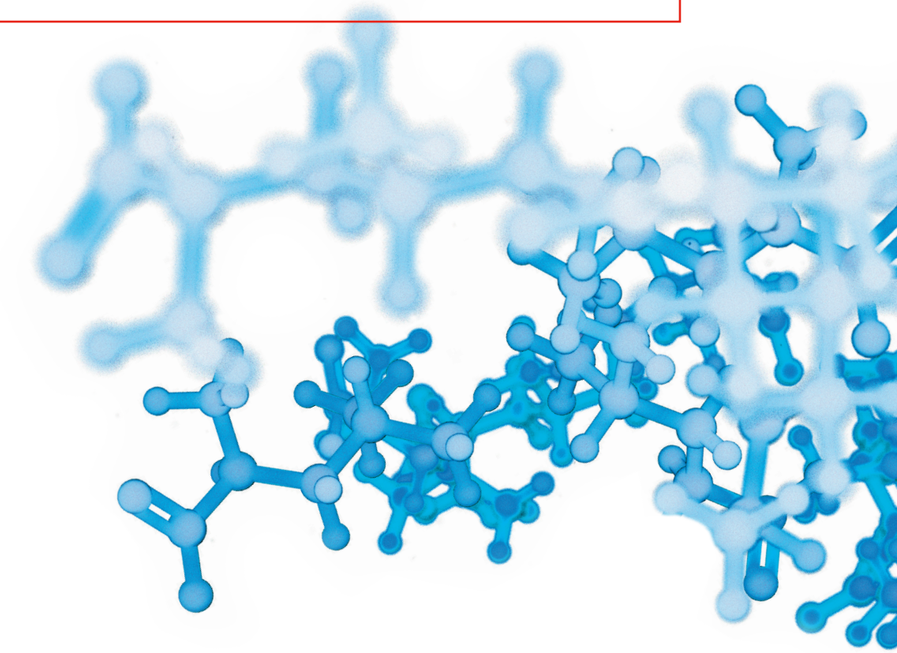


Although technically long-chain fatty acids, **omega-3 fatty acids** (such as those in fish oil) have numerous reported health benefits including anti-inflammatory and immune enhancement or immunomodulatory properties.[85,102-104] Appropriate dietary n-3 omega fatty acid intake is essential for numerous organ and tissue functions, and diets with optimal n-6:n-3 ratios are likely to be of benefit in the management of inflammatory, skin and gastrointestinal diseases in dogs.[84,102,104] Due to their anti-inflammatory effects, n-3 omega fatty acids may have steroid-sparing effects when used in management of inflammatory gastrointestinal conditions.[104]

Supplementation of enteral diets with glutamine, a conditionally essential amino acid, provides additional benefits. Glutamine is the principal fuel source for small intestinal enterocytes, and supplementation has been shown to attenuate the alterations in intestinal permeability associated with inflammation.[105]

These features make amino acid-based diets appealing for the management of other gastrointestinal conditions such as short bowel syndrome;[106] lymphangiectasia;[77,97] malabsorption;[7,107] pancreatitis and pancreatic exocrine insufficiency;[7,13,94,95,97,108] colitis;[84] and protein-losing enteropathy.[84,85,109,110]

Amino acid-based diets provide complete, protein-free nutrition to meet patients' nutritional needs without antigenic stimulation. As a result, amino acid-based diets are ideal elimination diets for adverse food reactions and a number of gastrointestinal conditions.



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