Precision intestinal nutrition: knowledge and gaps regarding the role of amino acids during an enteric challenge

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ABSTRACT Poultry nutritionists continually strive for more “precision” nutritional programs that provide the exact balance of nutrients that maximize broiler growth performance without economically and environmentally costly excesses. Many factors affect the precise amount and balance of nutrients needed by the broiler, including genetics, age, sex, and environment. Furthermore, broilers in intensive rearing environments will almost always be subjected to some degree of enteric stress that can alter nutrient needs. Exposure to enteric pathogens such as *Eimeria* spp., the intestinal parasites that cause avian coccidiosis, induces physical damage to the intestinal epithelium and activates immune responses, ultimately resulting in the repartitioning of amino acids (AA) in response to these prioritized demands. Even without any pathogenic challenge, the intestine has an already high demand for many AA, with 30 to 100% of dietary AA extracted during first pass intestinal metabolism. In many cases, increasing dietary protein from intact proteins has been shown to be a viable option to ameliorate impaired AA digestion and absorption and heightened need for certain AA of birds under an enteric stress. However, increasing dietary protein often results in concomitant increases in indigestible protein and carbohydrates that can stimulate the overgrowth of pathogenic bacteria (i.e., *Clostridium perfringens*). Alternative options to increase dietary AA levels are to increase all feed-grade, free AA (e.g., Met, Lys, Thr, Val), or specific individual feed-grade AA. Therefore, the objectives of this paper are to discuss precision nutrition, the dietary AA demands of the intestine, consequences of coccidiosis on AA needs of the intestine, and formulation approaches to meet these altered needs. In summary, increased dietary protein met by intact proteins has consistently demonstrated its benefits during an *Eimeria* spp. infection; however, to further the goal of precision nutritional programs, feeding higher levels of a specific AA to support desired functions such as intestinal recovery or immune function for birds experiencing an enteric stress still require further evaluation.

Key words: intestine, precision nutrition, amino acid, *Eimeria*, broiler

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PRECISION NUTRITION

Precision nutrition has been defined as meeting the nutritional needs of an animal under a specific set of conditions without under or over feeding energy or a single nutrient. Three imperatives for successful implementation of precision nutrition, as proposed by Moss et al. (2021), include ingredient characterization, accurate determinations of daily nutrient requirements of the animal, and rigorous yet careful management of these 2 imperatives. Genetics, age, sex, and environment are all often carefully considered when estimating the daily nutrient requirements of today’s broiler. On the other hand, less emphasis has typically been placed on health status, though it is well-understood that nutrient demand will shift following disease, stress, or injury. While often subclinical, birds will be exposed to some degree of enteric stress in every flock. A better understanding of these altered nutrient requirements could facilitate feeding strategies that alleviate performance losses and support the nutrition and immune functions of the intestine.

FIRST PASS INTESTINAL PROTEIN METABOLISM

First pass intestinal metabolism involves enteral metabolism of digested and absorbed nutrients before they appear in the portal vein and systemic circulation.
COCCIDIOSIS – A PREDOMINANT CULPRIT OF ENTERIC STRESS

Avian coccidiosis, which is caused by *Eimeria* spp., continues to be the most widespread enteric disease for commercial poultry, despite extensive coccidiosis research spanning the last 100 yr (Chapman, 2003). *Eimeria* spp. oocysts are nearly ubiquitous in most environments and have variable behavior and pathogenicity (Williams, 2005). Furthermore, the implementation of antibiotic-free production systems that preclude the use of in-feed ionophore coccidiostats, along with the emergence of drug-resistant field *Eimeria* strains to available chemical anticoccidials, have exacerbated many of these challenges. Consequently, the industry has gradually shifted to greater reliance on vaccination with live *Eimeria* oocysts as a means of coccidiosis control. To ensure immunity to the different species of *Eimeria* potentially encountered in the field, coccidiosis vaccines typically contain multiple *Eimeria* species that infect different parts of the gastrointestinal tract including the duodenum, jejunum, ileum, and ceca.

**PHYSIOLOGICAL, MORPHOLOGICAL, AND METABOLIC CHANGES FOLLOWING *EIMERIA*-INDUCED INTESTINAL STRESS**

*Eimeria* infections elicit physiological, morphological, and metabolic changes to the intestine and its associated immune system. The species and number of *Eimeria* oocysts ingested by the bird dictate the severity of infection, which can be classified as: 1) a mild infection with no adverse effects, also known as “coccidiation”, 2) subclinical coccidiosis that results in reduced weight gain, feed intake, and feed efficiency, and 3) clinical coccidiosis causing diarrhea, markedly impaired growth and feed efficiency, morbidity, and mortality (Williams, 1999, 2005). The extent by which broiler performance is impaired is dependent on many factors including number and pathogenicity of oocysts ingested, age of the bird, environment (e.g., litter conditions), and diet (Willis and Baker, 1981; Lee et al., 2011; Paris and Wong, 2013; Adedokun et al., 2016). Typically, 70 to 75% of the BW reduction following *Eimeria* infections has been attributed to a reduction in feed intake, whereas 25 to 30% stems from impaired nutrient digestion and absorption and the redirected use of nutrients to fulfill immune responses and intestinal repair (Preston-Maffam and Sykes, 1970; Russell Major Jr. and Ruff, 1978; Lillegjød and Trout, 1996).

Intestinal damage from coccidiosis is associated with a reduced number of mucin-secreting goblet cells, reduced mucus thickness, villus atrophy, increased crypt depth, and increased rate of cell movement and turnover along the villus; the severity of this damage can be *Eimeria* dose-dependent (Fernando and McCraw, 1973; Allen, 1987; Tan et al., 2014, 2020). The disruption of the intestinal epithelium during coccidiosis inhibits brush border digestive enzyme activity (Chute et al., 1961;
Russell Major jr. and Ruff, 1978; Adams et al., 1996; Su et al., 2015), downregulates nutrient transporters for AA and peptides, carbohydrates, and Zn (Paris and Wong, 2013; Su et al., 2015; Miska and Fetterer, 2018), and alters pancreatic hormone release (Allen and McMurtry, 1984). Consequently, this reduces absorption of AA as well as minerals, vitamins, lipids, and monosaccharides (Preston-Mafham and Sykes, 1970; Russell Major jr. and Baker, 1983; Adams et al., 1996; Persia et al., 2006; Chapman, 2014; Gautier et al., 2020). Interestingly, the combined downregulation of nutrient transporters and enzymes to increase malabsorption of dietary AA may be a host defense mechanism to alter cellular metabolism to protect against *Eimeria* replication (Paris and Wong, 2013; Su et al., 2015; Miska and Fetterer, 2018).

Several studies have estimated that coccidiosis infection lowers AA digestibility by an average 8% compared with uninfected birds, with the greatest impact on Thr, Val, Cys, Ala, and Ser digestibility, which are key AA for gastrointestinal health and function (Persia et al., 2006; Adedokun et al., 2016; Rochell et al., 2016, 2017a; Yazdanabadi et al., 2020). However, the degree of reduction in AA digestibility caused by coccidiosis has been shown to be influenced by *Eimeria* strain, severity of infection, amount of endogenous losses, and bird age (Teng et al., 2021), and impacts vary among studies. For example, a 4-fold greater magnitude reduction in AA digestibility was reported for young (21 d) vs. older (42 d) broiler subjected to a coccidia infection, likely because the older birds had more mature gastrointestinal and immune systems (Adedokun et al., 2016).

The increased flow of undigested dietary AA and endogenously-secreted AA (e.g., sloughed cells, plasma AA, mucin, enzymes) following *Eimeria* infection cause opportunistic pathogens like *Clostridium perfringens* to proliferate and move proximally in the digestive tract, predisposing birds to necrotic enteritis, the second most problematic disease in poultry (USAHA, 2019). Indeed, coccidiosis and *C. perfringens* typically operate in tandem, and coccidiosis has been used as an infection model for necrotic enteritis (Williams, 2005). Growth of *C. perfringens* can be further influenced by dietary protein source and AA composition, as well as cereal grain source and non-starch polysaccharide content and composition (Kaldhusdal and Skjerve, 1996; Drew et al., 2004; Moore, 2016; Xue et al., 2017). Moreover, the disruption and dysfunction of the mucosal and epithelial barrier cause host inflammation involving vasodilation and increased intestinal permeability via altered gene expression of tight junctions, adheren junctions, gap junctions, and desmosomes (Tan et al., 2014; Teng et al., 2020). Although this mechanism facilitates the rapid accumulation of immune cells, it also gives pathogens an opportunity to cause systemic inflammation if not controlled.

Following infection, intestinal epithelial cells communicate closely with immune cells to activate both the innate and acquired immune systems. This leads to the diversion of dietary and peripheral tissue AA that would otherwise be used for muscle deposition (Selvaraj, 2012). For example, inflammatory responses can consume 30 to 65% of TSAAs for glutathione synthesis (Grimble and Grimble, 1998; Selvaraj, 2012). Other specific immune responses or metabolic changes induced by coccidiosis and other enteric infections include increased proliferation of immune cells and their effector molecules and production of acute phase proteins. The amount of individual AA required to support many of these responses appears to often differ from that needed to maximize muscle protein synthesis (Reeds et al., 1994; Yaqoob et al., 2018; Oxford and Selvaraj, 2019; Mund et al., 2020). Even under conditions of dietary deficiency for key substrate AA, prioritization of immune molecules synthesis can take priority over growth, as has been shown for prioritization of Arg for nitric oxide production in *Eimeria*-infected birds fed Arg deficient diets (Rochell et al., 2017b). Nonetheless, impaired immune response and increased disease susceptibility can occur when birds are fed reduced protein diets with unbalanced AA profiles (Grimble and Grimble, 1998; Li et al., 2007; Kamely et al., 2020).

### APPROACHES FOR INCREASING AA SUPPLY DURING COCCIDIAL INFECTIONS

The compounding effect of reduced AA absorption and the redirection of AA to repair intestinal damage and support immune responses may create conditional AA deficiencies in coccidiosis-infected birds, thereby warranting diet modulation. Furthermore, birds that are given a live oocyst vaccine may not compensate for early growth reduction by market weight age because of the relatively short growing period of broilers (Waldenstedt et al., 1999; Williams, 2002; Lee et al., 2009; Lehman et al., 2009; Arczewska-Wlozek et al., 2017). Higher AA density diets created to address altered AA needs following *Eimeria* infection can be formulated in 3 primary ways: 1) by increasing total AA density with proteinaceous feed ingredients, 2) by increasing total AA density with feed-grade, free AA, or 3) by increasing specific “functional” AA. Increasing total AA density can be accomplished by greater inclusion levels of proteinaceous feed ingredients, such as soybean meal, to meet a certain CP or digestible Lys level. Indeed, increasing total AA by intact proteins can provide a margin to prevent an AA limitation of conditionally essential AA; however, this approach results in the greatest excess of AA that can contribute to enteric stress in addition to negative economic and environmental consequences. These effects are certainly counter to the goals of precision nutrition. To increase AA density with minimal increases in dietary CP, feed-grade AA that are currently economically feasible to use, including Met, Lys, Thr, Val and perhaps Ile and Arg, can be increased with minimal changes to overall dietary nitrogen or diet composition. However, as opposed to increasing total dietary CP with proteinaceous feed ingredients, less-limiting essential and nonessential AA,
many of which have been shown to support intestinal development and repair (e.g., Gly, Pro, and Gln), may be under-supplied with this approach. Lastly, feeding a higher level of individual “functional” AA such as Thr, Arg, Gly, or Gln can supply substrates for a specific metabolic or immune function. Therefore, it would be ideal to provide the bird with the exact AA that is needed to improve gut and immune function while preventing AA waste.

**INCREASED AA DENSITY FOR EIMERIA-INFECTED BROILERS**

Sharma et al. (1973) were among the first to report that daily weight gain and feed efficiency of birds subjected to a coccidiosis infection were improved when fed increased dietary CP levels (16, 20, and 24%), despite higher CP diets causing increased oocyst shedding. It should be noted that disease suppression and improved performance are not always achieved in concert. Indeed, lowering CP has been shown to reduce coccidiosis-related mortality, oocyst shedding, and coccidiosis lesions, perhaps due to the role of trypsin in oocyst excystation, but increasing CP protects birds from weight loss and provides AA for intestinal repair and immune function (Britton et al., 1964; Mathis et al., 1995).

Others have also consistently shown that increasing total dietary CP or balanced digestible AA levels support broiler performance when birds are infected with a coccidia challenge or administered a live oocyst vaccine (Table 1). Specifically, increasing CP from 20 to 24% (0–27 d; Lee et al., 2011), 24 to 26% (0–32 d; Bryan et al., 2019), average of 21 to 23% (0–42 d; Arczewska-Włosek et al., 2017), or increasing digestible Lys from 1.15 to 1.25% (0–19 to 21 d; Cloft et al., 2019a; b) have been shown to assist coccidiosis-vaccinated broilers in compensating for losses in performance. Notably, work by Cloft et al. (2019a, b) indicates that feeding increased AA density only during the first 3 wk, when the impacts of vaccinal Eimeria oocysts cycling are the greatest, has sustained benefits on broiler performance at market weight. In each of these experiments, increased CP or AA density was achieved partly or totally with increased dietary soybean meal. As a result, concomitant increases in indigestible protein and carbohydrates (i.e., non-starch polysaccharides and oligosaccharides) may have limited the positive responses to increased AA density due to their propensity to stimulate undesirable bacteria fermentation and proliferation (Gilbert et al., 2018; Bryan et al., 2019; Adhikari et al., 2020). Although fermentation of certain dietary fiber fractions can benefit broiler health, excess soluble NSP and protein fermentation are generally detrimental. Increases in AA density achieved with ingredients such as soy protein isolate, free AA, or other highly digestible, low non-starch polysaccharides feed-stuffs might prove more advantageous to Eimeria-vaccinated or challenged broilers. Adedokun et al. (2016) quantified the impacts of a Eimeria vaccine challenge (12x the dose recommended for newly-hatched chicks) on AA digestibility and conducted a subsequent experiment in which similarly challenged broilers were fed diets with higher levels of soybean meal, Biolys, DL-Met, L-Thr, Val, Ile, and L-Trp to compensate for expected reductions in AA digestibility. Feed efficiency from 14-21 d, but not d 21 BW, was improved, though an uninfected group fed the same diets was not included to confirm these responses were specifically beneficial to the Eimeria-challenged birds.

Currently, there is increasing pressure to implement low CP diets, which has been reviewed elsewhere (Lemme et al., 2019; Lee et al., 2020). Work by Lehman et al. (2009) reported that vaccinated broilers fed a low CP diet with supplemental gelatin performed equivalent to broilers fed higher CP diets met by greater inclusion levels of soybean meal. These authors stated that the high content of Gly, Ser, Pro, and the marginal increases in other essential AA from gelatin was a viable alternative to increasing soybean meal inclusion levels.

| Authors                  | Experimental diet | Period (d) | Challenge model | Protein change | Growth performance response |
|--------------------------|-------------------|------------|-----------------|----------------|-----------------------------|
| Sharma et al., 1973      |                   | 0-29       | *E. acervulina* or *tenella* | 16 to 24% CP   | - Improved overall BWG & FCR |
| Lehman et al., 2009      |                   | 0-56       | Vaccine         | 2% CP unit dec. + gelatin | - Improved overall FCR |
|                          |                   | 0-27       | *E. acervulina, maxima, & tenella* | 20 to 24% CP  | - Improved overall BWG & FCR |
| Arczewska-Włosek et al., 2017 |            | 0-42       | 1x vaccine dose | 2% CP unit inc. | - Improved 22 to 42 d BWG |
| Bryan et al., 2019       |                   | 0-32       | Vaccine         | 24 to 28% CP   | - Improved overall FCR & pectoralis minor meat yield |
| Cloft et al., 2019a      |                   | 0-21       | 1x vaccine dose | 1x vaccine dose | - Improved overall BWG, FCR, & total breast weight & yield |
| Cloft et al., 2019b      |                   | 0-19       | 1x vaccine dose | 1x vaccine dose | - Improved 0 to 19 d FCR, overall BWG, & total breast meat weight |

Abbreviations: BWG, body weight gain; CP, crude protein; dec., decrease; dLys, digestible Lys; FCR, feed conversion ratio; inc., increase.
Recent work by Teng et al. (2021) evaluated lower CP diets from 12-23 d and with feed-grade Met, Thr, Arg, or Gln increased individually or all together (combination diet) when fed to *Eimeria* spp. challenged broilers. When compared to the challenged birds fed the control diet, offering the low CP diet showed no adverse effects on intestinal health or growth, and increasing Arg improved intestinal permeability and gene expression of AA transporters; Gln and Thr lowered gene expression for tight junction proteins; and the combination diet lowered gene expression for tight junction proteins but decreased villus height to crypt depth ratio. Interestingly, increasing Met or the combination diet exacerbated infection severity. Beyond these reports, there has been a limited amount of research to evaluate approaches for increasing overall dietary AA density (essential, conditionally essential, and nonessential AA) without also markedly increasing indigestible protein and dietary non-starch polysaccharides content.

Increasing specific individual AA over recommended levels in standard CP diets have been studied for Met/TSAAs (Southern and Baker, 1982; Lai et al., 2018; Ren et al., 2020), Thr (Kidd et al., 2003; Wils-Plotz et al., 2013), Arg (Perez-Carbajal et al., 2010; Tan et al., 2014; Castro et al., 2020; Yazdanabadi et al., 2020), and Gln (Mussini et al., 2012; Oxford and Selvaraj, 2019). Challenge models varied among these studies with one or a mixed *Eimeria* spp. used, but general conclusions can be made. Increasing dietary TSAAs, Thr, Arg, or Gln can improve growth performance; TSAAs, Arg, or Gln can improve intestinal integrity and morphology; and TSAAs, Thr, Arg, or Gln may improve immune response and anti-inflammatory effects that are detailed in Table 2. Supplementation of specific feed-grade AA can increase the digestibility of the respective AA but may interfere with digestibility of other AA (Teng et al., 2021). Interestingly, Met requirements were lower for vaccinated vs. medicated broilers to optimize performance and immune response (Lai et al., 2018). Although, Southern and Baker (1982) disagree whereas Ren et al. (2020) agrees that coccidia infected broilers do not respond with greater Met/TSAAs concentrations. Conflicting reports on Thr have been documented where Kidd et al. (2003) found that the Thr requirement was not affected by an infection of *E. acervulina* (3 × 10^6 or 1 × 10^7), whereas Wils-Plotz et al. (2013) noted that *E. maxima* (1.5 × 10^7) infection increased Thr needs by 25% for performance and immune response. Gottardo et al. (2016, 2017) fed increased Thr, Arg, and Gln in combination from 11-42 d to broilers challenged with mixed *Eimeria* spp. (14 d) and *E. coli* (16 d) challenge. These authors reported improvements in weight gain, FCR, mucosal cell proliferation, goblet cells, villus height to crypt depth ratio, and immune function with a combined increase in dietary Thr, Arg, and Gln.

### Table 2. Summary of published research evaluating increased individual dietary feed-grade amino acids when fed to broilers challenged with *Eimeria* spp.

| Authors                        | Period (d) | Experimental feed | Total growth | Challenge model            | Amino acid | Growth performance | Response                                                                 |
|--------------------------------|------------|-------------------|--------------|-----------------------------|------------|--------------------|-------------------------------------------------------------------------|
| Lai et al., 2018                | 0-22       |                   | E. tenella   | Met                         | Higher Met requirement for medicated vs. vaccinated broilers | Improved BWG & FCR | For medicated, inc. antioxidant capacity, glutathione peroxidase, IL-2, IgA, CD4, CDS, TNF, interferon-γ, VH: CD, Dec. intestinal lesion scores |
|                                |            |                   |              |                             |            |                    | - Dec. jejunal IgA                                                       |
| Ren et al., 2020                | 11-21      |                   | Mixed *Eimeria* | TSAA                        | No Improvements | Improved BWG & FCR | Inc. proinflammatory cytokines & interferon-γ                               |
| Kidd et al., 2003               | 2 or 3-15  |                   | E. acervulina | Thr                         | Thr needs are not increased | Improved BWG & FCR | Dec. intestinal lesion scores                                               |
| Wils-Plotz et al., 2013         | 0-16       |                   | E. maxima    | Thr                         | Thr needs are not increased | Improved BWG & FCR | Inc. nitric oxide and heterophils & monocytes                             |
| Perez-Carbajal et al., 2010     | 0-28       | 1 × vaccine dose & mixed *Eimeria* | Arg          |                             | Improved BWG & FCR | (Inc. serum IgG and IgM)                                                  |
|                                |            |                   |              |                             |            |                    | Inc. proinflammatory cytokines & interferon-γ                               |
| Tan et al., 2014                | 0-21       |                   | 20 × vaccine dose | Arg                        | Improved BWG & FCR | Improved goblet cell, VH, CD, mucosal density, & inflammation             |
|                                |            |                   |              |                             |            |                    | - Dec. apoptosis                                                         |
| Yazdanabadi et al., 2020        | 0-42       |                   | Mixed *Eimeria* | Arg                        | Improved BWG & FCR | Improved goblet cell, VH, CD, mucosal density, & inflammation             |
| Castro et al., 2020             | 0-26       |                   | Mixed *Eimeria* | Arg                        | Improved BWG & FCR | Dec. intestinal lesion score                                               |
| Oxford and Selvaraj, 2019       | 0-21       |                   | 20 × vaccine dose | Gln                       | No improvements | Improved BWG & FCR | Inc. tight junction proteins & VH:CD                                       |
| Gottardo et al., 2016, 2017     | 11-42      |                   | Mixed *Eimeria* & *E.coli* | Thr, Arg, & Gln | Improved FCR | Inc. VHC:CD, intestinal cell proliferation, & goblet cell               |
|                                |            |                   |              |                             |            |                    | Lower IgA                                                               |

Abbreviations: BWG, body weight gain; CD, crypt depth; Dec., decrease; FCR, feed conversion ratio; Inc., increase; VH, villus height.
In our own lab, we have directly compared feeding increased AA diets achieved primarily with soybean meal, several essential feed grade AA (Met, Lys, Thr, Val, Ile, and Arg), or select AA (Val, Ile, or Thr) (unpublished data). Specifically, digestible Lys levels were increased from 1.24 to 1.32% in the starter and from 1.11 to 1.19% in the grower period, with other essential AA ratios relative to Lys held constant. In one diet series, soybean meal was allowed to increase (37.1 to 40.6% in the starter) to meet increased digestible AA minimums, whereas with the other approach, soybean meal was held constant (37.1%) and feed-grade Met, Lys, Thr, Val, Ile, and Arg were used to match digestible levels of these AA with the high soybean meal diet. We determined that coccidiosis vaccinated broilers responded positively and similarly when fed increased essential AA density from either soybean meal or feed grade AA. Similar to Cloft et al. (2019a,b), these higher AA diets that were provided early (0–26 d) resulted in sustained benefits to market weight age. Given that performance was improved with both approaches, we concluded that the greater amount of less limiting essential AA, conditionally essential AA, and nonessential AA in the soybean meal provided no advantage over feeding only the first 6 limiting essential AA, nor did the increase in indigestible protein and carbohydrate fractions of the soybean meal elicit any negative effects. Furthermore, the same benefits were not seen with only increasing Val, Thr, and Arg.

CONCLUSIONS

Enteric stress from pathogens such as *Eimeria* will be a continual problem for the poultry industry for years to come. Existing data consistently demonstrate that either increased dietary protein or AA density is beneficial to the performance of *Eimeria*-infected broilers. However, it must be recognized that gut health is multifactorial, and *Eimeria* infection, especially when subclinical, is often only one factor of many that influence overall gastrointestinal health. The potentially negative consequences of over-feeding nitrogen in attempt to meet increased AA needs of *Eimeria*-infected broilers cannot be overlooked. Thus, additional research is needed to close the gap between the consistent positive responses of *Eimeria*-infected broiler to increased AA density and the less consistent responses to individual AA. Furthermore, understanding how any newly identified feeding strategies ultimately impacts the susceptibility of broilers to necrotic enteritis or other gastrointestinal health challenges must also be considered. Finally, precision nutrition approaches can only be implemented if they can be applied to targeted flocks that are most likely to benefit. This will require responsiveness, flexibility, and coordination among stress/disease diagnosis, ingredient characterization, feed formulation, and feed manufacture and delivery. Only then will the true potential of precision nutrition be fully realized.

DISCLOSURES

There are no conflicts of interest to declare.

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