

Review

Nitrogen Metabolism and Pathogen Feedback in Intensive Aquaculture: Reframing Ammonia Nitrogen as a Reactive Node

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Abstract

Feeds rich in protein are the dominant nitrogen input in intensive aquaculture, yet only part of dietary nitrogen is retained as animal biomass; the remainder enters water and sediment through uneaten feed, feces, dissolved wastes, mucus, sloughed tissue, and branchial ammonia excretion. This review aims to integrate nutritional, physiological, microbial, and disease-related evidence into an evidence-graded framework that positions ammonia nitrogen as a reactive node linking feed, host, water, sediment, and pathogen risk. To assemble this evidence, we conducted a structured narrative search of Web of Science and PubMed for records in English or Chinese published from 2006 to July 2026, with no restriction on publication type, and classified evidence as direct, indirect, or conceptual. The strongest evidence shows that dietary protein supply, amino acid balance, digestibility, and feeding regime regulate nitrogen retention and ammonia output, while microbial ammonification, nitrification, denitrification, dissimilatory nitrate reduction to ammonium, anammox, and assimilation determine whether reactive nitrogen is regenerated, retained, or removed. Experimental studies further show that ammonia impairs oxidative balance, mucosal barriers, immunity, and disease resistance. In contrast, evidence that pathogen infection quantitatively alters nitrogen retention, ammonia excretion, organic nitrogen release, and sedimentary ammonium regeneration remains limited and largely indirect. Accordingly, ammonia nitrogen is framed as a measurable reactive node rather than a unique source or a universally validated causal loop. Practical management should combine precision nutrition with water, biofloc, sediment, and disease surveillance, while future factorial studies and isotope tracer studies should quantify the complete nitrogen budget under pathogen challenge.

Keywords: nitrogen retention; microbial nitrogen cycling; pathogen feedback; nutritional regulation



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1. Introduction

The rapid expansion and intensification of aquaculture have increased reliance on stocking at high densities, formulated feeds, and continuous nutrient inputs [1]. Nitrogen loading is therefore an inherent consequence of production intensification and a major determinant of animal performance and environmental stability. Intensive aquaculture can be viewed as a system of nitrogen flow rather than solely as an animal production system [2,3]. Dietary protein supplies nitrogen for growth, enzyme synthesis, tissue renewal, osmoregulation, and immune function, but not all feed nitrogen is converted into fish or

shrimp biomass. The unretained fraction enters the farming environment through uneaten feed, feces, urine and other dissolved compounds, mucus, sloughed epithelial material, and branchial ammonia excretion. Feeding regimes and dietary protein levels influence nitrogen metabolism and ammonia release in common carp (*Cyprinus carpio*). In tilapia, feed protein intake affects ammonia production, whereas models of shrimp nitrogen dynamics show that feed and feeding parameters shape retained biomass and dissolved nitrogen pools [4–6]. Nitrogen and phosphorus budgets in biofloc and recirculating systems further identify animal biomass, microbial biomass, sludge, and dissolved inorganic nitrogen as competing nitrogen sinks [7].

Ammonia nitrogen occupies a central position in this system because it is produced by several host and environmental processes. Sources include amino acid deamination, branchial excretion, organic nitrogen mineralization, sedimentary ammonium regeneration, and imbalances between microbial production and consumption [8–12]. It is therefore both an indicator of water quality and a physiological output of host nitrogen metabolism. It also integrates multiple microbial transformations. Aquaculture reshapes nitrogen cycling and microbial communities in coastal tidal flats, while microorganisms that oxidize ammonia are associated with teleost gills; these findings identify both farm environments and host surfaces as compartments where nitrogen is processed [8,9]. Reviews of ammonia sources, toxicity, and defense mechanisms place these processes within a broader physiological and biogeochemical context [10–13]. Nitrogen enrichment also connects aquaculture management with eutrophication, harmful algal blooms, and pollution control [14–16].

A central limitation of current research is that nutrition, ammonia toxicity, microbial nitrogen cycling, and disease are often studied separately. Feed studies usually emphasize growth, feed conversion, and nitrogen retention; ammonia studies focus on oxidative stress, immune damage, behavior, and tissue pathology; microbial studies describe nitrification, denitrification, dissimilatory nitrate reduction to ammonium (DNRA), anammox, or nitrogen cycle genes; and pathogen studies measure mortality, immune gene expression, microbiota, and metabolomic responses. These compartmentalized study designs make it difficult to evaluate how nitrogen moves across the feed, host, water, and sediment continuum during disease events.

Pathogen infection adds another layer to aquaculture nitrogen flow. Infection can reduce feeding and digestion, reallocate amino acids from growth toward defense and tissue repair, damage gill or intestinal barriers, and disrupt the microbiota. These responses may reduce nitrogen retention or increase organic nitrogen release. However, direct evidence linking infection to quantitative changes in nitrogen retention, ammonia excretion, and environmental nitrogen regeneration remains limited. Infection should therefore be treated as a plausible disturbance to nitrogen flow rather than as a resolved causal chain.

Previous reviews have largely addressed aquaculture nutrition, ammonia toxicology, microbial nitrogen cycling, or probiotic health effects as separate topics [3,10–12,17,18]. The unresolved gap is an evidence-graded synthesis that traces nitrogen across feed, host tissues, water, microbiota, and sediment during pathogen challenge while distinguishing measured nitrogen fluxes from inferred links.

This review therefore proposes an evidence-graded nitrogen metabolism and pathogen feedback framework. Its contribution is not a new biochemical pathway, but an integration of established component processes around ammonia nitrogen as a reactive node. Direct evidence is assigned to relationships supported by nitrogen budgets, excretion measurements, process rate assays, or nitrogen-species data; indirect evidence supports biological plausibility; and untested feedback links are explicitly identified as hypotheses.

2. Review Methodology

A structured narrative search was conducted in Web of Science and PubMed. The main search covered the period from 2006 to July 2026, and included records in English or Chinese. No restriction on publication type was applied at retrieval; original articles, reviews, systematic reviews, quantitative evidence syntheses, conference papers, book chapters, and other indexed records were eligible when relevant. Earlier seminal studies identified through backward citation tracking were retained only when they provided foundational evidence on ammonia physiology or nitrogen transformation processes.

Search terms were combined across three concept blocks: (i) aquaculture organisms and systems (aquaculture, fish, shrimp, crustacean, pond, recirculating aquaculture system, RAS, biofloc, and integrated multitrophic aquaculture, IMTA); (ii) nitrogen processes (nitrogen metabolism, nitrogen retention, ammonia, total ammonia nitrogen, ammonification, nitrification, denitrification, dissimilatory nitrate reduction to ammonium, DNRA, and anammox); and (iii) disease and intervention terms (pathogen, infection, disease, immunity, microbiota, probiotic, postbiotic, feed additive, and nutrition). Equivalent Chinese translations of these concepts were also searched.

Records were included when they addressed aquaculture fish or crustaceans and informed at least one component of the framework: dietary nitrogen input or retention, ammonia production or excretion, microbial nitrogen transformation, pathogen-associated metabolic or barrier disturbance, ammonia–pathogen interaction, or nutritional and microecological intervention. Duplicates, non-aquatic studies, and records lacking substantive relevance to nitrogen or disease processes were excluded. Direct evidence quantified connected nitrogen flow components within the same design, indirect evidence supported adjacent components without measuring the complete link, and conceptual evidence denoted biologically plausible but untested connections. Because species, production systems, exposures, and outcomes were heterogeneous, findings were synthesized narratively rather than pooled statistically.

3. Dietary Nitrogen Input, Host Nitrogen Utilization, and Ammonia Nitrogen Excretion

3.1. Dietary Protein Supply and Nitrogen Retention

Dietary protein is the principal nitrogen input in intensive aquaculture, but retention efficiency depends on digestible amino acid availability, energy balance, ingredient quality, feeding status, and environmental conditions. When indispensable amino acids are imbalanced, digestibility is low, energy from nonprotein sources is insufficient, or stress suppresses anabolism, additional protein may increase catabolic nitrogen loss rather than body protein deposition. In yellow catfish (*Pelteobagrus fulvidraco*), dietary protein level affected growth, digestive enzyme activity, nitrogen retention, and TOR signaling [19]. In Nile tilapia, moderate protein reduction with essential amino acid supplementation maintained growth within the tested range, while dietary lysine altered nitrogen retention, digestibility, and growth efficiency [20,21]. Tryptophan optimization in tilapia and isotope studies specific to individual amino acids further show that nitrogen fate depends on amino acid composition and protein quality, not crude protein alone [22,23].

These studies are not directly interchangeable because species, life stage, salinity, diet composition, and outcome definitions differ. Nevertheless, they consistently indicate that nitrogen management should match digestible protein and amino acid supply to anabolic capacity. The relevant targets are nitrogen retention and ammonia output, rather than a universal ‘high’ or ‘low’ crude protein threshold.

3.2. Protein Source Quality, Digestibility, and Fecal Nitrogen

Protein source quality and digestibility determine how much dietary nitrogen is absorbed and how much is discharged as fecal or dissolved organic nitrogen. The ratio of protein to energy and salinity altered nutrient digestibility and fecal characteristics in rainbow trout (*Oncorhynchus mykiss*), while exogenous enzymes improved feed utilization and reduced nitrogen and phosphorus excretion in Japanese seabass (*Lateolabrax japonicus*) [24,25]. Processed soybean ingredients, fermented soybean meal, fermented corn protein, ingredients fermented with lactic acid bacteria, and fermented feeds with low fishmeal content improved growth, intestinal condition, immunity, microbiota, or disease resistance in selected species [26–31]. However, excessive replacement or unsuitable processing impaired intestinal condition in some studies. Insect meal and other alternative proteins also altered nutrient assimilation and internal nitrogen turnover [32].

Unabsorbed nitrogen remains within the production system. Particulate and dissolved organic nitrogen can be mineralized to ammonium and thereby contribute to the ammonia burden in culture water. Ingredient assessment should therefore combine growth and feed conversion with digestibility, fecal stability, particulate losses, and microbial degradability. Comparisons among studies remain limited when fecal nitrogen, total ammonia nitrogen (TAN), and complete nitrogen budgets are not measured together.

3.3. Amino Acid Catabolism and Branchial Ammonia Excretion

After dietary protein is digested and absorbed, the released amino acids are first used for body protein deposition, tissue renewal, enzyme and immune related protein synthesis, antioxidant defense, epithelial repair, and osmoregulation. When amino acid supply exceeds the anabolic demand of the host, or when it is mismatched with energy supply and physiological status, excess amino acids are diverted toward catabolic metabolism and ammonia production. Accordingly, ammonia generation and excretion are not isolated waste elimination processes, but important physiological outcomes that reflect dietary nitrogen utilization efficiency and internal nitrogen allocation. Specifically, amino acids that are not deposited as body protein or functional proteins release nitrogenous groups through transamination and deamination, leading to ammonia formation, which is subsequently eliminated mainly through the gills and kidneys. In fish, the gill is the primary organ for ammonia excretion. It also forms a critical interface between internal nitrogen metabolism and the external aquatic environment.

Branchial ammonia excretion is regulated by Rhesus (Rh) glycoproteins, acid–base transport, H^+ -ATPase activity, sodium transport, renal auxiliary excretion, developmental stage, and water physicochemistry conditions. These mechanisms have been described in fish ammonia physiology and experimental gill studies [12]. From the perspective of nitrogen flow, dietary nitrogen first enters the body through feeding, is then converted into available amino acids through digestion and absorption, and is subsequently allocated to different synthetic pathways according to the requirements for growth, immunity, and homeostatic maintenance. When nitrogen input is matched with the host utilization capacity, more nitrogen is retained in tissue proteins and functional proteins, and ammonia production is relatively reduced. Conversely, when protein intake exceeds retention capacity, or when stress, disease, and environmental challenges suppress anabolic metabolism, amino acid catabolism is enhanced and branchial ammonia excretion increases accordingly. Thus, branchial ammonia excretion represents a key link among dietary nitrogen input, host nitrogen utilization efficiency, and water ammonia nitrogen risk, providing an important theoretical basis for reducing nitrogen loading in intensive aquaculture through nutritional regulation. This host-centered pathway of ammonia nitrogen generation and excretion is summarized in Figure 1.

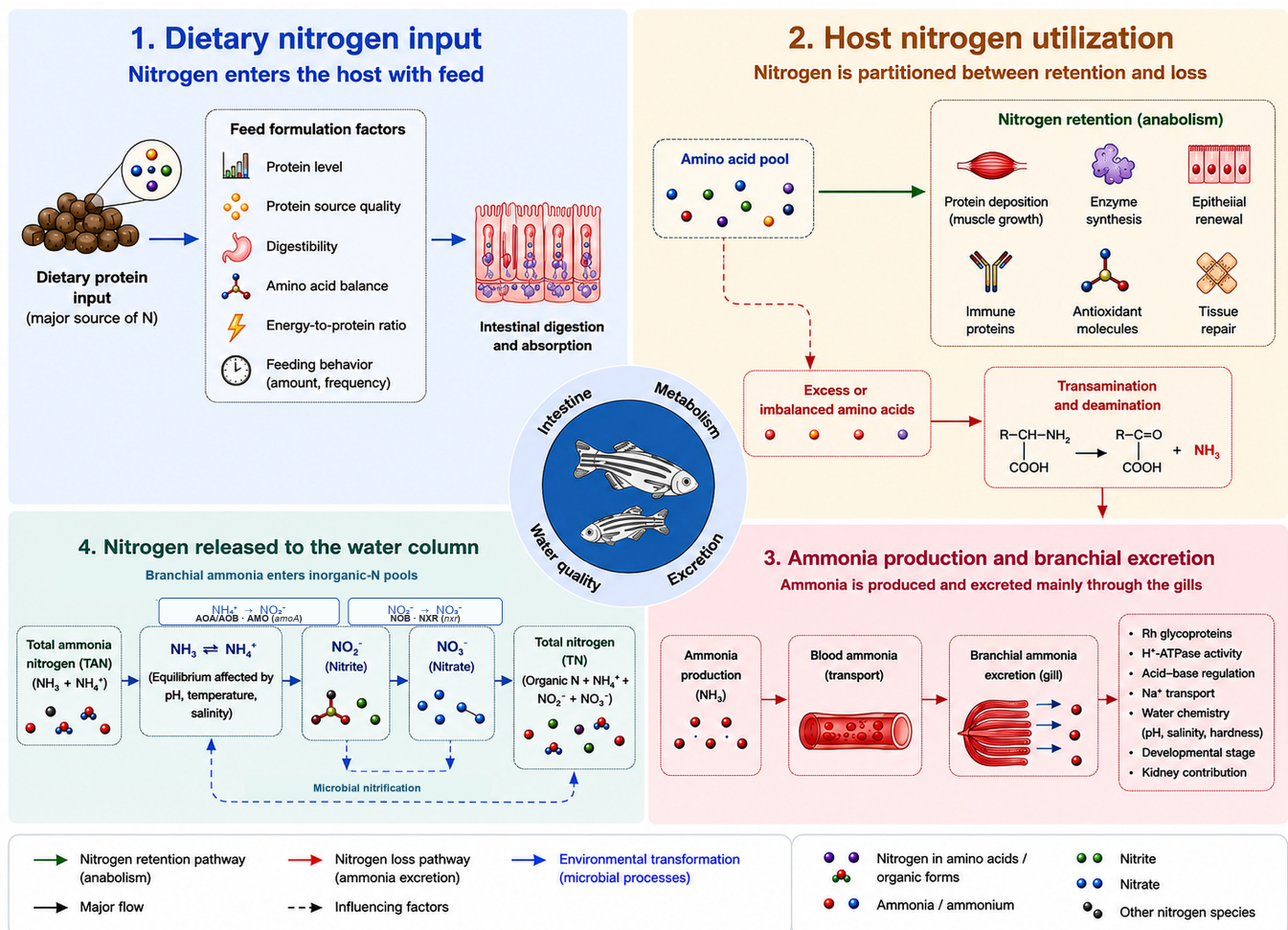


Figure 1. Host-centered nitrogen flow from dietary protein to branchial ammonia excretion and microbial nitrification. Dietary nitrogen is partitioned between anabolic retention and amino acid catabolism. Catabolic ammonia is excreted mainly across the gills, enters the total ammonia nitrogen pool as NH_3 and NH_4^+ , and is transformed under oxic conditions by AOA, AOB, NOB, and comammox *Nitrospira*. Green arrows indicate retention, red arrows indicate ammonia production and excretion, blue arrows indicate microbial transformation, solid arrows indicate major flows, and dashed arrows indicate influencing processes.

4. Microbial Nitrogen Cycling in Aquaculture Water, Gut and Sediment

4.1. Ammonification and Nitrification

Once nitrogen leaves the host, microbial processes determine whether it is recycled, regenerated, retained, or removed. Heterotrophic bacteria and fungi depolymerize proteins and other organic nitrogen through extracellular proteases and peptidases; subsequent amino acid deamination releases NH_4^+ . Under oxic conditions, nitrification converts NH_4^+ first to NO_2^- and then to NO_3^- . This can reduce acute ammonia exposure but creates oxidized nitrogen pools that require assimilation or further removal [8,33–35].

The first step of nitrification is mediated by archaea and bacteria that oxidize ammonia (AOA and AOB), which use ammonia monooxygenase (AMO, commonly tracked by *amoA*) and machinery for hydroxylamine oxidation. Bacteria that oxidize nitrite (NOB), including *Nitrospira* and *Nitrobacter*, use nitrite oxidoreductase (NXR, encoded by *nxr* genes) to convert NO_2^- to NO_3^- . Comammox *Nitrospira* can perform both steps. Gene abundance should be interpreted alongside measurements of nitrogen species, dissolved oxygen and substrate availability, and assays of process rates, because functional potential alone does not establish in situ activity [33–37].

Nitrification is often regarded as beneficial because it reduces ammonia accumulation, but it does not by itself remove nitrogen from the system. Instead, it transfers nitrogen from reduced to oxidized forms. If nitrate is not assimilated or converted to dinitrogen gas, nitrogen remains available for downstream recycling. Nitrogen management must therefore consider the entire transformation chain rather than TAN reduction alone.

4.2. Denitrification, DNRA, and Anammox

Denitrification, dissimilatory nitrate reduction to ammonium (DNRA), and anammox jointly determine the fate of NO_3^- , NO_2^- , and NH_4^+ in sediments and biofilms. Denitrification and anammox remove reactive nitrogen as N_2 , whereas DNRA retains nitrogen by regenerating NH_4^+ .

Studies of freshwater aquaculture sediments, sea cage trout farms, and enriched lake sediments show that organic loading, redox status, electron donors, and trophic conditions regulate the balance between nitrogen retention and removal [38–43]. Sediment should therefore be treated as an active nitrogen reactor rather than an inert waste sink.

Under organic-rich and reducing conditions, disease-derived organic matter, fecal waste, and uneaten feed may favor ammonium regeneration. This possibility is relevant during disease outbreaks but remains insufficiently quantified in aquaculture infection models. The major microbial nitrogen transformations are summarized in Table 1.

Table 1. Major microbial nitrogen transformation processes relevant to aquaculture nitrogen flow management.

Process	Substrate	Main Product	Effect on Nitrogen Fate	Representative Microorganisms, Enzymes/Genes, and Validation	References
Ammonification	Organic nitrogen from feces, uneaten feed, mucus, and carcasses	NH_4^+	Regenerates ammonium and can increase ammonia burden	Heterotrophic bacteria and fungi; extracellular proteases/peptidases and amino-acid deaminases; organic-N loss, NH_4^+ formation, and mineralization rate	[39]
Nitrification	NH_4^+	NO_2^- and NO_3^-	Reduces ammonia but retains nitrogen in oxidized pools	AOA/AOB: AMO (<i>amoA</i>) and hydroxylamine oxidation machinery; NOB (<i>Nitrospira</i> , <i>Nitrobacter</i>): NXR (<i>nxr</i>); comammox <i>Nitrospira</i> ; nitrogen species, oxygen, and rate assays	[33,34,36,37]
Denitrification	$\text{NO}_3^-/\text{NO}_2^-$	N_2	Removes reactive nitrogen from the system	Facultative anaerobes, including <i>Pseudomonas</i> and <i>Paracoccus</i> ; NAR/NAP (<i>narG/napA</i>), NIR (<i>nirS/nirK</i>), NOR (<i>norB</i>), and NOS (<i>nosZ</i>); N flux and nitrate reduction rate	[33,35,37–40,42,43]
DNRA	$\text{NO}_3^-/\text{NO}_2^-$	NH_4^+	Retains nitrogen and may regenerate ammonia	DNRA-capable heterotrophs; nitrate reductases and <i>NrfA</i> (<i>nrfA</i>); NH_4^+ production, redox state, and carbon availability	[38–43]

Table 1. Cont.

Process	Substrate	Main Product	Effect on Nitrogen Fate	Representative Microorganisms, Enzymes/Genes, and Validation	References
Anammox	NH_4^+ and NO_2^-	N_2	Removes nitrogen under anoxic conditions	Anammox Planctomycetota, including Brocadia and Scalindua; hydrazine synthase (<i>hzs</i>) and hydrazine dehydrogenase/oxidoreductase (<i>hdh/hzo</i>); isotope pairing or rate assays	[33,35,37–40,42,43]
Assimilation	NH_4^+ or NO_3^-	Microbial, algal, or extractive biomass	Temporarily stores nitrogen in biomass	Heterotrophic bacteria, microalgae, seaweeds, and biofloc; GS–GOGAT and nitrate assimilation pathways; biomass N, community composition, and uptake rate	[38–43]

Abbreviations: AOA, ammonia-oxidizing archaea; AOB, ammonia-oxidizing bacteria; AMO, ammonia monooxygenase; NOB, nitrite-oxidizing bacteria; NXR, nitrite oxidoreductase; NAR, respiratory nitrate reductase; NAP, periplasmic nitrate reductase; NIR, nitrite reductase; NOR, nitric oxide reductase; NOS, nitrous oxide reductase; DNRA, dissimilatory nitrate reduction to ammonium; GS–GOGAT, glutamine synthetase–glutamate synthase; N, nitrogen; qPCR, quantitative polymerase chain reaction.

4.3. Assimilation, Biofloc, and Engineered Nutrient Recovery

Microbes, algae, bioflocs, and extractive organisms can incorporate NH_4^+ and NO_3^- into biomass, redirecting dissolved inorganic nitrogen into recoverable or trophically useful forms. Biochar-assisted nitrifying bioflocs, nitrogen-removing strains, and biofloc particle size studies illustrate this potential [36,44,45], while microalgae, seaweeds, algal turf scrubbers, and IMTA provide additional recovery routes [37,46–58].

Assimilation is not equivalent to permanent removal. Microbial or algal biomass may be harvested, grazed, deposited in sediment, or remineralized; therefore, short-term nitrogen capture must be distinguished from long-term export. Likewise, gene abundance alone cannot establish process rates without nitrogen-species measurements, redox data, process assays, or isotope tracing.

Cross-study comparison is further constrained by production system and methodological heterogeneity. RAS and biofloc studies often quantify water column TAN and microbial genes under controlled conditions, whereas pond, sea cage, and IMTA studies incorporate sediment fluxes, spatial heterogeneity, or nutrient recovery. Freshwater and marine species also differ in ammonia transport, osmoregulation, feeding ecology, and microbiota. These differences, together with variable exposure durations and endpoints, limit direct extrapolation and can explain apparently inconsistent outcomes.

5. Pathogen Infection as a Disturbance to Host and Environmental Nitrogen Metabolism

5.1. Feed Intake, Nitrogen Retention, and Disease-Associated Nitrogen Loss

Pathogen infection may disturb nitrogen flow through reduced feed intake and altered nitrogen allocation. When feeding declines while maintenance, immune defense, and tissue repair demands rise, a smaller share of dietary nitrogen may be retained as biomass. However, most challenge studies do not measure residual feed, fecal nitrogen, water TAN, nitrogen retention, and pathogen load together [6].

At the farm scale, residual feed, mucus, epithelial shedding, fecal waste, and mortality may redirect nitrogen from host biomass toward microbial mineralization. This pathway remains plausible rather than demonstrated because direct measurements of infection-associated nitrogen redistribution are scarce.

5.2. Immune Metabolism and Amino Acid Reallocation During Infection

Omics studies across bacterial and viral infections show that pathogen challenge can alter arginine, glutamine, amino acid, lipid, and energy metabolism, as well as intestinal microbiota and oxidative responses [59–66]. These findings support metabolic reallocation during infection, but differences in species, pathogens, tissues, sampling times, and analytical platforms preclude a uniform quantitative estimate of nitrogen redistribution.

Amino acids serve both growth and defense, including immune mediators, antioxidant molecules, inflammatory responses, and tissue repair. Infection may therefore shift nitrogen from somatic growth toward defense and survival. Whether this shift consistently increases whole animal amino acid catabolism, reduces nitrogen retention, or elevates ammonia production remains to be tested with direct nitrogen flow measurements.

5.3. Mucosal Damage, Ammonia Excretion, and Organic Nitrogen Release

Gill and intestinal injury provide a potential bridge between infection, ammonia transport, barrier dysfunction, and nitrogen release. Viral gill diseases and bacterial infection alter branchial transporters, physiology, immunity, or bioenergetics, while denitrification genes may also contribute to *Flavobacterium columnare* virulence [67–70].

Because the gill is both an ammonia excretory organ and a mucosal barrier, infection-associated injury could impair ammonia transport and acid–base regulation. Yet, few studies jointly quantify pathogen load, Rh proteins, Na^+/K^+ -ATPase, blood ammonia, excretion rate, and water TAN, so this mechanistic connection remains unresolved.

Disease outbreaks may also increase organic nitrogen inputs through mortality, necrotic tissue, mucus, epithelial shedding, residual feed, and fecal waste [39,41,71–74]. The full sequence from infection to organic nitrogen release, ammonification, DNRA and NH_4^+ regeneration has yet to be quantified within a single aquaculture model.

6. Interaction Between Ammonia and Pathogens: A Potential Feedback Loop Amplifying Health Risks

6.1. Ammonia Stress May Increase Pathogen Susceptibility

Ammonia stress may increase pathogen susceptibility by disrupting barrier integrity, oxidative balance, and immune homeostasis. In fish, ammonia exposure is associated with oxidative stress, inflammation, tissue injury, immune dysregulation, and behavioral alteration [11,75–77]. The gill and intestine are primary interfaces between the host and the aquatic environment; damage induced by ammonia to either tissue may weaken the first line of defense. Studies focused on the gills document physiological, biochemical, metabolic, inflammatory, and oxidative responses in juvenile fourfinger threadfin (*Eleutheronema tetradactylum*) and yellow catfish [76,77]. Ammonia exposure also impaired spleen and head kidney defenses in Wuchang bream (*Megalobrama amblycephala*) [78]. These findings establish ammonia as a physiological stressor, not merely a nitrogenous waste product or endpoint for water quality.

The capacity of ammonia to amplify risk may be more pronounced in combination with other stressors. Combined hypoxia and ammonia exposure exacerbated disturbances in glucose metabolism, oxidative stress, inflammation, and apoptosis in largemouth bass (*Micropterus salmoides*) [79]. Combined exposure to ammonia and infectious hematopoietic necrosis virus produced synergistic effects on immune function and intestinal health in rain-

bow trout [80]. These studies support biological interaction, but they do not demonstrate the complete feedback sequence proposed here.

6.2. Pathogen Infection May Aggravate Ammonia-Associated Stress

Pathogen infection may in turn aggravate ammonia-associated stress by disturbing feeding behavior, intestinal integrity, hepatic metabolism, nitrogen allocation, and branchial excretory function. During infection, nutrients and amino acids are increasingly redirected from growth toward immune defense, acute phase responses, tissue repair, and stress metabolism. This shift may reduce nitrogen utilization efficiency and increase amino acid catabolism, thereby enhancing endogenous ammonia production. At the same time, infection-induced anorexia, intestinal injury, and microbiota disturbance may alter the balance among dietary nitrogen input, nitrogen retention, fecal nitrogen release, and microbial nitrogen transformation.

The evidence is asymmetric. Ammonia exposure studies directly demonstrate oxidative, inflammatory, metabolic, and barrier injury, whereas evidence that infection changes ammonia excretion, organic nitrogen release, or sedimentary ammonium regeneration is largely indirect. Co-exposure studies support biological interaction [79–81], but they do not close the proposed feedback loop. Direct tests must measure feed intake, nitrogen retention, branchial transport, ammonia excretion, water TAN, microbial process rates, and pathogen outcomes in the same design.

6.3. Conceptual Loop Linking Nitrogen, Ammonia, and Pathogens

Based on the available evidence, the interaction between ammonia and pathogens can be conceptualized as a potential feedback loop linking nitrogen utilization, environmental ammonia accumulation, host stress responses, and disease risk (Figure 2). In this loop, low nitrogen utilization efficiency increases amino acid catabolism and ammonia production. Elevated ammonia emission then contributes to TAN accumulation in the culture environment, where the balance among mineralization, nitrification, assimilation, denitrification, sediment regeneration, and dissimilatory nitrate reduction to ammonium determines whether ammonia is removed, transformed, or regenerated. Once ammonia accumulates, it can induce oxidative stress, mucosal damage, inflammatory responses, and immune imbalance, thereby increasing pathogen susceptibility. Subsequent infection may further disrupt feeding, intestinal function, hepatic metabolism, microbiota structure, gill function, and organic nitrogen release, leading to further impairment of nitrogen homeostasis.

This feedback model remains conceptual because current studies have yet to demonstrate every causal step from feed nitrogen input to pathogen susceptibility and back to ammonia regeneration. Nevertheless, it is evidence-based and useful because it integrates processes that are usually studied separately. A rise in ammonia nitrogen may indicate excessive feed nitrogen input, poor nitrogen retention, enhanced tissue catabolism, organic matter mineralization, or an insufficient balance between nitrification and denitrification. At the same time, ammonia may damage host barriers and weaken disease resistance. Therefore, ammonia nitrogen should not be regarded merely as the endpoint of nitrogen metabolism. Instead, it represents a reactive node at which nutrition, physiology, microbiology, and pathology converge, and through which nitrogen imbalance may be amplified into broader health risks in intensive aquaculture systems. The evidence grade assigned to each major relationship in Figure 2 is summarized in Table 2, distinguishing directly measured relationships from indirect biological support and conceptual feedback connections.

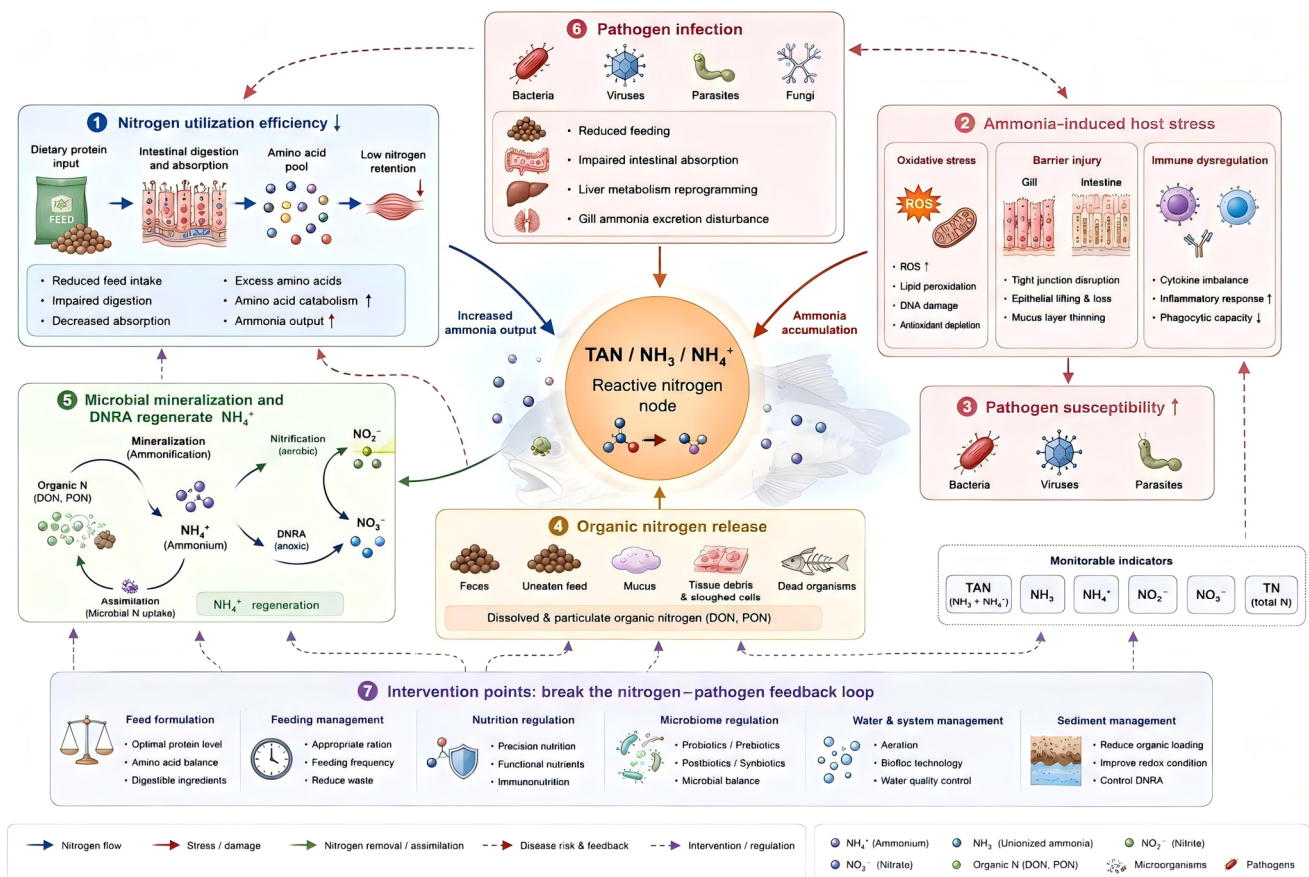


Figure 2. Upward and downward arrows indicate increases and decreases, respectively. Evidence-based framework linking nitrogen utilization, ammonia-associated host stress, pathogen susceptibility, organic nitrogen release, microbial mineralization, and DNRA-mediated ammonium regeneration. Solid blue arrows indicate nitrogen flow, solid red arrows indicate stress or damage, solid green arrows indicate nitrogen removal or assimilation, dashed brown arrows indicate proposed disease feedback, and dashed purple arrows indicate intervention or regulation. Upward and downward arrows (↑ and ↓) indicate increases and decreases, respectively; arrowheads on connecting lines indicate the direction of flow or interaction. The lower panel identifies practical entry points in feed, nutrition, microbiome, water, and sediment management.

Table 2. Evidence grading across the proposed nitrogen and pathogen framework.

Framework Connection	Evidence Grade	Evidence Basis	Principal Limitation
Dietary protein supply to nitrogen retention and ammonia output	Direct	Nitrogen retention, digestibility, and ammonia measurements [4,5,19,21,24,25]	Effects vary with species, diet, life stage, and production conditions
Microbial transformation of inorganic nitrogen	Direct	Nitrogen species, process assays, and functional gene evidence [33,36–39]	Process rates and complete system mass balances remain uneven
Ammonia exposure to oxidative, barrier, and immune injury	Direct	Controlled exposure and combined stress studies [11,75–81]	Species and exposure conditions differ, and the complete feedback is untested
Pathogen infection to altered nitrogen retention or ammonia excretion	Indirect	Metabolic, barrier, transporter, and microbiota responses [59–62,67–70]	Few studies measure nitrogen budgets, excretion, and pathogen load together

Table 2. Cont.

Framework Connection	Evidence Grade	Evidence Basis	Principal Limitation
Disease-derived organic nitrogen to ammonium regeneration	Conceptual	Carcass, fecal waste, mineralization, sediment, and DNRA evidence [39,41,71–74]	No infection model measures the full sequence in one design
Integrated pathogen and ammonia feedback loop	Conceptual	Component evidence assembled in Figure 2 [59,67,71,75,79–81]	The complete causal loop has not been validated in a factorial study

7. Nutritional Strategies for Regulating Nitrogen Flow and Breaking the Feedback

7.1. Precision Protein and Amino Acid Nutrition

Nutritional regulation should be evaluated by its capacity to reshape nitrogen flow rather than only by growth promotion. Precision protein nutrition aims to match digestible nitrogen supply with species, developmental stage, environment, health status, and production goals. Moderate protein reduction with essential amino acid supplementation, dietary lysine optimization, and tryptophan supplementation provide examples of strategies that can improve growth, metabolic status, digestibility, or nitrogen retention while avoiding unnecessary nitrogen input [20–22]. These approaches should be assessed using nitrogen intake, nitrogen retention, protein efficiency, ammonia excretion, and water TAN rather than growth alone.

7.2. Digestible Ingredients and Fermented Feeds

Improving protein digestibility and ingredient tolerance is another way to reduce nitrogen loss. Exogenous enzymes, processed soy ingredients, fermented soybean meal, fermented corn protein, fermentation with lactic acid bacteria, low-fishmeal fermented feeds, and other processed ingredients can improve digestibility, intestinal health, immunity, disease resilience, or feed utilization in selected systems [25–31]. Their effects should be interpreted cautiously because high replacement levels or unsuitable processing may induce intestinal inflammation or dysbiosis. A nitrogen flow-based evaluation should include fecal nitrogen, particulate nitrogen stability, dissolved nitrogen release, ammonia excretion, NO_2^- , NO_3^- , and total nitrogen.

7.3. Functional Feed Additives and Microecological Regulation

Functional nutrients and microbial modulators may preserve barrier integrity, stabilize the gut microbiota, improve immunometabolic coordination, and alleviate ammonia-related stress. N-carbamylglutamate increased ammonia tolerance in juvenile yellow catfish [82], and dietary β -glucan altered the gut microbiota and circulating metabolites while enhancing disease resistance in rainbow trout [83].

The observed effects depended on strain, dose, duration, and host species. For yellow catfish, dietary administration of *Bacillus amyloliquefaciens* at a concentration of 1×10^6 colony-forming units (CFU) per gram of feed for four weeks led to improvements in growth performance, digestive enzyme activities, immune status, microbiota composition, and resistance to bacterial challenge [84]. *Bacillus safensis* NPUST1 at 10^6 – 10^7 CFU/g for 8 weeks improved growth, gut microbiota, innate immunity, and resistance to *Streptococcus iniae* in Nile tilapia [85]. *Bacillus velezensis* BV1704-Y at 1×10^7 CFU/g for 28 days protected zebrafish (*Danio rerio*) against *Aeromonas hydrophila* [86]. *Lactobacillus rhamnosus* JCM1136 and *Lactococcus lactis* subsp. *lactis* JCM5805, administered individually or together

at 1×10^8 CFU/g for 6 weeks, altered growth, intestinal morphology, microbiota, immune responses, and resistance to *Streptococcus agalactiae* in Nile tilapia [87].

Not all additives improve every endpoint. In common carp, *Saccharomyces cerevisiae*, *Pediococcus acidilactici*, or a yeast cell wall prebiotic at 1 g/kg for 60 days altered intestinal morphology and microbiome composition but did not significantly improve growth performance [88]. Across the broader evidence base, probiotics, postbiotics, yeast-derived products, and strain-specific additives improved selected growth, digestibility, immune, disease, microbiota, or water quality outcomes [17,18,84–87,89–105]. These outcomes should not be interpreted as proof of reduced whole farm nitrogen discharge unless TAN, total nitrogen, sediment nitrogen, and complete nitrogen budgets are measured directly.

Broader candidates include polysaccharides, chitin, chitosan, chitooligosaccharides, probiotics, prebiotics, and synbiotics [106–109]. Germ-free and microbiota-oriented fish models can help distinguish direct nutritional effects from microbiota-mediated effects [110–113]. The evidence strength, practical readiness, and principal limitations of these strategies are summarized in Table 3.

Table 3. Evidence strength, practical readiness, and principal limitations of nutritional and microecological nitrogen-management strategies.

Strategy	Primary Nitrogen-Flow Target	Evidence Level	Practical-Readiness Category	Principal Limitation	References
Precision protein and amino acid balance	Nitrogen input, retention, and catabolism	Strong for retention; variable for ammonia excretion	Operationally established for formulation; integrated farm scale validation incomplete	Species and life stage specific targets; few nitrogen budget and pathogen studies	[19–22]
Digestible and fermented ingredients	Digestibility and fecal nitrogen	Moderate; direct fecal-N and TAN data are incomplete	Conditionally applicable; commercial ingredients exist, but processing effects vary	Batch consistency, inclusion level, and intestinal responses	[25–31]
Functional nutrients and N-carbamylglutamate	Ammonia tolerance and host resilience	Direct in selected species; otherwise mainly indirect	Experimental for nitrogen-flow control	Few multi-cycle farm trials or complete nitrogen budgets	[82,106–109]
Biofloc and nitrification management	Inorganic-N transformation and microbial retention	Strong in selected biofloc systems	Operationally established in selected systems	Sensitive to C/N ratio, aeration, solids, stocking density, and system design	[36,37,44,45]

Abbreviations: C/N, carbon-to-nitrogen ratio; N, nitrogen; RAS, recirculating aquaculture system; TAN, total ammonia nitrogen.

7.4. Evaluation Indicators for Feedback Oriented Nutrition

A feedback-oriented nutritional strategy should be evaluated with both host and system indicators. Host indicators include feed intake, digestibility, nitrogen retention, whole body protein deposition, plasma ammonia, branchial transporter expression, antioxidant status, immune function, and pathogen resistance. System indicators include TAN, NH_3 , NH_4^+ , NO_2^- , NO_3^- , total nitrogen, sludge nitrogen, sediment ammonium regeneration, nitrification and denitrification genes, and microbial community stability.

Without this combined indicator set, a diet may appear beneficial for growth while still increasing downstream nitrogen instability.

7.5. Practical Implementation Under Commercial Conditions

Commercial implementation requires adapting integrated nitrogen management to the production system rather than applying a single prescription. Farms must coordinate feed formulation and feeding decisions with aeration, solids removal, biofilter capacity, carbon input, sediment management, and disease surveillance while accounting for rapid variation in stocking biomass, temperature, salinity, and microbial activity. Practical constraints include the cost and frequency of total ammonia nitrogen and nitrogen species monitoring, limited access to process rate measurements, uneven technical capacity across farms, and the need to avoid interventions that transfer nitrogen among pools without achieving removal. Stepwise adoption should therefore prioritize routine mass balance indicators, defined action thresholds, and locally validated combinations of nutritional, water, biofloc, and sediment management, followed by commercial scale trials that assess biological performance, nitrogen discharge, operational cost, and disease outcomes together.

8. Conclusions and Future Perspectives

This review reframes ammonia nitrogen as a reactive node that can be measured across feed input, host retention and excretion, microbial transformation, water quality, and disease risk. Evidence is strongest for dietary control of nitrogen retention, the toxicological effects of ammonia, and microbial conversion or removal of inorganic nitrogen. The new contribution is an evidence-graded framework that connects these established components while explicitly separating measured relationships from proposed pathogen-driven feedbacks.

The framework is not a validated universal model. Most component relationships were studied separately across species, production systems, exposure regimes, and analytical endpoints, and the structured narrative approach did not support a formal meta-analysis. Evidence remains indirect for the complete sequence from infection-driven metabolic reallocation to altered ammonia excretion, organic-nitrogen release, sedimentary ammonium regeneration, and renewed disease susceptibility.

Three experimental priorities would provide the most decisive tests. First, factorial diet $\times$ ammonia $\times$ pathogen studies should quantify full nitrogen budgets together with host and disease endpoints. Second, isotope tracing and process-rate measurements should link branchial and fecal nitrogen release to water and sediment microbial transformations. Third, longitudinal commercial-scale trials across RAS, ponds, biofloc, and IMTA should test whether promising interventions remain effective under variable stocking density, feed input, temperature, salinity, and microbial communities.

Until such studies are available, the reactive node concept should guide integrated measurement and hypothesis generation rather than be interpreted as a universal causal pathway. Its practical value lies in coordinating nutrition, water quality, microbial management, sediment processes, and disease surveillance around measurable nitrogen flows and explicitly defined evidence limits.

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