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Using ecological stoichiometry to understand and predict infectious diseases

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A key characteristic of host–parasite interactions is the theft of host nutrients by the parasite, yet we lack a general framework for understanding and predicting the interplay of host and parasite nutrition that applies across biological levels of organization. The elemental nutrients (C, N, P, Fe, etc.), and ecological stoichiometry provide a framework for understanding host–parasite interactions and their relation to ecosystem functioning. Here we use the ecological stoichiometry framework to develop hypotheses and predictions regarding the relationship between elemental nutrients and host–parasite interactions. We predict that a suite of host and parasite traits, stoichiometric homeostasis, host diet stoichiometry, and biogeochemical cycling are related to disease dynamics, host immunity and resistance, and bacterial growth form determination. We show that ecological stoichiometry is capable of expanding our understanding of host–parasite interactions, and complementing other approaches such as population and community ecology, and molecular biology, for studying infectious diseases.

Keywords: stoichiometry, parasitism, infectious disease

Parasites, resource theft and elemental nutrition

Parasites rely on their hosts to supply the resources necessary for growth and reproduction. As resource theft is a core characteristic of host–parasite interactions, an understanding of the flow of resources from host to parasite is central to understanding parasitic relationships (Smith et al. 2005). The availability of host nutrients to a parasite depends on two basic factors: the quantities of nutrients the host possesses in the parasitized tissues or organs (Fig. 1A), and the degree to which the host's nutrients are protected from parasites (Fig. 1B). Both factors are directly or indirectly related to nutrients the host obtains from its environment (Fig. 1C), or what may be referred to as host nutrition (Smith 2007). Thus, parasite nutrition is a function of host nutrition.

Although there are many studies exploring the role of host nutrition in infectious diseases, relatively few describe the relationships and feedbacks between specific nutrients and infection dynamics (Aalto et al. 2015). Past studies have used a variety of currencies for nutrition, from nutritional indices based on growth data (Hall et al.

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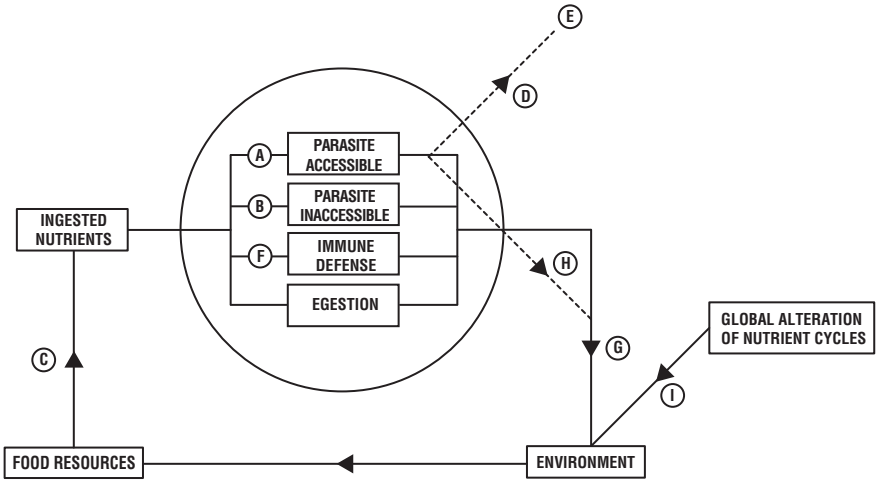

Figure 1. Hypothesized linkages among host–parasite interactions and ecological stoichiometry are represented by a generic host (large circle). (A) Ingested or assimilated host nutrients that are accessible to the parasite. (B) The portion of a host's dietary nutrients that are ingested or assimilated and not accessible to the parasite. (C) Elemental nutrients ingested by the host, or host diet. (D) Parasite growth, reproductive rate, and the number of infectious propagules emitted by the host. (E) Variability in parasite virulence. (F) Host immune function. (G) Host nutrient excretion rates and stoichiometry. (H) Parasite-induced changes in host excretion rates and stoichiometry. (I) Global alteration of nutrient cycling affects nutrient stoichiometry of food resources available to the host.

2009), to macromolecules (Akpom and Warren 1975, Peck et al. 1992), to the chemical elements necessary for life (Pulkkinen et al. 2014). The last of these, the elemental nutrients (e.g. C, N, P, Fe ...), have two major advantages over other currencies: 1) they are universally necessary for all organisms, and 2) they cannot be chemically transformed from one element to another. Thus, elemental nutrients are relevant to both host and parasite, and can be traced from the environment to the host, from host to parasite, and back to the environment (Fig. 1).

Early reviews of the effects of nutrition on infectious disease focused on macromolecules. They concluded that parasites, like their hosts, could be limited by nutrients, and that the supply of nutrients available to the parasite from the host could influence disease dynamics and pathology (Smith et al. 2005, Smith 2007). More recent studies have begun to apply the stoichiometric framework to these questions. Recent reviews have focused on these stoichiometric studies (Aalto et al. 2015), and have reviewed the impact of infectious disease and parasitism on biogeochemical cycles, noting that the majority of studies have tested for effects of host density rather than trait mediated effects (Preston et al. 2016). These past reviews represent milestones toward understanding the interactions between nutrients and infectious disease, each outlining current knowledge to direct future research questions as well as integrate ecosystem and disease ecology. We intend to further develop these ideas and generate more explicit hypotheses by not only reviewing studies that have applied ecological stoichiometry, but also by applying the stoichiometric framework to studies that have used other currencies, and by incorporating first principles.

Here, our goal is to review host–parasite interactions within the stoichiometric framework, and to use the framework to develop hypotheses and predictions, without restriction to particular systems or taxa. The stoichiometric framework takes advantage of the properties of elemental nutrients to offer mechanistic understanding and explanatory predictions for host–parasite interactions that are generalizable across organisms and ecosystems. Our goal is to integrate disparate concepts from ecological stoichiometry and disease ecology to develop hypotheses and predictions that are explicitly mechanistic and that include stoichiometrically mediated changes in parasite and host traits.

Ecological stoichiometry

Ecological stoichiometry is a theoretical framework that describes balances and fluxes of chemical elements among organisms and between organisms and the environment (Sterner and Elser 2002). Because ecological stoichiometry focuses on the chemical elements necessary for all life, it is easily generalizable across systems and taxa. This is particularly useful in studying multi-trophic interactions such as infectious disease, where participants in the interaction require the same elemental nutrients but in different forms (e.g. organic versus inorganic). It also allows us to make generalizable predictions about the roles of specific elements in infectious diseases, and about linkages between infectious diseases and nutrient cycles, by uniting them with a common, multimetric currency. Further, the quantitative nature and simple assumptions (e.g. Liebig's law of the minimum; conservation of matter) of the stoichiometric approach lend it to mathematical modeling, which can then be integrated with mathematical disease models (Vannatta and Minchella 2018).

A major advantage of ecological stoichiometry is that physiological and life-history traits of host and parasite can be explicitly linked to predictions about the influence of

elements on host–parasite interactions. In this regard, ecological stoichiometry complements other approaches (e.g. population modeling) to studying host–parasite interactions. Knowledge of the host's and parasite's physiology and life history can be used to make inferences about its chemical make-up and nutritional demands based on the principles of ecological stoichiometry (Reiners 1986). The "growth rate hypothesis" (Elser et al. 1996) is a classic example: organisms with higher growth rates require a greater cellular concentration of ribosomes, and thus have greater tissue rRNA content. Hence, these organism's stoichiometric signature (tissue carbon:phosphorus) should be closer to that of phosphorus (P) rich RNA. As a consequence, organisms with higher growth rates have lower tissue carbon (C) to P and nitrogen (N) to P ratios, and higher P demand; hence, of the P that is consumed by faster growing organisms, less is egested or excreted as waste products (Elser et al. 1996, however, see Sardans et al. 2012). Thus, growth rate can be useful in predicting the P demands of both parasite and host even when direct measures of tissue chemistry are unknown. Similarly, body size, photosynthetic rate, cellular organelles, structural tissues (such as bone, chitin and cellulose), behavior, method of nutrient acquisition, and various other traits can all be used to help predict an organism's nutritional demands and fluxes (Allen and Gillooly 2009, Meunier et al. 2017). Thus, considering traits of both the host and parasite within an elemental stoichiometry framework offers an approach to making predictions and improving our understanding of the outcome of host–parasite interactions.

Elemental physiology of host and parasite

Ecological stoichiometry can be used to explicitly link the elemental physiology of host and parasite to predict host–parasite interactions. Clasen and Elser's (2007) study on Chlorella Virus is one of the few explicitly stoichiometric studies on the effects of host nutrition on infectious disease. A physiological trait germane to all viruses is that they have a lower C:P ratio than their hosts' cells due to their smaller size, high growth rate, and more simple cellular and mechanical structure (Jover et al. 2014). Thus, Clasen and Elser (2007) hypothesized that because the C:P ratio of Chlorella Virus is much lower than that of its host, the alga *Chlorella NC64A*, viral production would be suppressed when the alga was grown in low P versus high P media. This prediction was supported by experimental data showing that the number of viral particles produced per host cell was significantly higher for cells cultured in P rich media (Clasen and Elser 2007). Thus the stoichiometry of host resources was shown to influence the production of infectious propagules, which in turn would be expected to increase transmission pressure (Fig. 1D). Interestingly, the alga's growth and reproduction were similar in both media, suggesting that changes in nutrient availability that do not affect host growth and reproduction can still be relevant for host–parasite interactions. Phosphorus specific effects on viral disease are also supported by evidence that prevalence of barley and cereal yellow dwarf viruses in a grassland plant community increased in response to P fertilization but not N (Borer et al. 2010). The consistent enhancement of viruses by P more than N agrees with our biological understanding of viruses, which are essentially packages of nucleic acid contained within a protein envelope, and are extremely P rich compared to most host organisms (Elser et al. 1996, Clasen and Elser 2007, Jover et al. 2014). Thus, knowledge of parasite and host physiology in conjunction with a stoichiometric framework can generate explanatory hypotheses and predictions of host–parasite interactions in the natural environment.

Bacterial parasites, like viruses, are much smaller than their hosts, or their hosts' cells, and have much higher rates of growth and reproduction. Accordingly, they have relatively low C:P and N:P ratios by virtue of their high P content (Fagerbakke et al. 1996, Elser et al. 2003, Makino et al. 2003). Thus, bacteria are expected to be generally P limited, especially if their host is itself subsisting on P deplete resources. Published results demonstrate that bacterial production can be strongly influenced by the C:P of their host's diet, and that decreases in bacterial production related to high host diet C:P can lead to lower transmission and infection prevalence (Frost et al. 2008b).

Studies of fungal parasites of plants have shown that fungal sporulation and biomass are more strongly influenced by N than P (Jensen and Munk 1997), an outcome that is predicted based on the lower C:N ratio of fungi versus their plant hosts and is consistent with ecological stoichiometry. *Rhizophydium megarrhizum*, a chytrid parasite of Cyanobacteria, has been shown to increase zoospore production under elevated N:P conditions, and decrease under low N:P conditions (Frenken et al. 2017). Similar to the results of Clasen and Elser (2007) in their Chlorella Virus study, experimental N:P conditions had a much stronger effect on zoospore production than host growth rate. Fungal parasites of animals are also sensitive to N; *Batrachochytrium dendrobatidis* (Chytrid) growth is known to be influenced by media C:N (Piotrowski et al. 2004). Conversely, P limitation was shown to have no significant effect on spore production by a microsporidian parasite of *Daphnia* (Aalto and Pulkkinen 2013). P deplete media was shown to decrease spore production by a chytrid parasite of the alga *Astrionella*, relative to standard media, but the effect of P limitation on *Astrionella*'s growth was substantially more severe, suggesting that the pathogen was less sensitive to P availability than its host (Bruning and Ringelberg 1987). Shifts from N to P limitation are also associated with shifts from bacterial decomposition of cellulose to fungal decomposition, further suggesting that fungi are more sensitive to variation in N availability than P (Güsewell and Gessner 2009). Studies of soil communities have shown that P fertilization increases the flow of energy through bacterial pathways relative to fungal (Parfitt et al. 2010), and that increases in soil C:N, C:P and N:P over forest chronosequences were related to shifts in energy flow from bacterial pathways to fungal pathways (Williamson et al.

2005). Moreover, fungi usually have slower growth rates than bacteria. Hence, the finding that fungi dominate or perform well under low P conditions, or P limitation, is consistent with the growth rate hypothesis. Taken together, applying a stoichiometric approach to fungal diseases may open new discoveries linking variation in host or environmental nutrients to patterns in the emergence and distribution of fungal parasites, and better understanding and prediction of host–fungal interactions.

Helminths, which are much larger and slower growing than either bacteria or fungi, are expected to be even more sensitive to dietary N. Helminth fecundity has been shown to be density dependent (i.e. helminth fecundity is inversely related to worm burden) (Anderson and May 1985), suggesting intra-specific competition between individual co-infecting worms, potentially for nutrients. Evidence suggests that reducing carbohydrate in the host's diet (decreasing diet C:N) can alleviate the density-dependent constraints on helminth fecundity (Bundy and Golden 1987), and that increases in host diet % protein can increase the percentage of eggs released by an infected host which are viable (Akpom and Warren 1975). Increases in detrital %N have been shown to be related to increases in the number of cercaria produced by trematode infected amphibians (Stephens et al. 2016). Together, these results suggest that helminth transmission is sensitive to host diet C:N. There is evidence that trematode cercaria production can be influenced by host diet P content, but cercaria production was higher in both low and high P treatments relative to an intermediate control, suggesting that nutrient limitation of the parasite was not the causal mechanism (Narr and Krist 2015).

From viruses to microbes and metazoans, parasites respond to the stoichiometry of their hosts' diets. With this core principle in mind, we now look more closely at key concepts from ecological stoichiometry in the context of host–parasite interactions, hypotheses regarding interactions between stoichiometry and specific facets of host–parasite relationships, and broader ideas regarding the stoichiometric impacts of parasites on the ecological matrices they are imbedded within.

Stoichiometric homeostasis and host–parasite interactions: predictions

Homeostasis, the ability of an organism to maintain constant internal conditions, is a defining characteristic of life, and a key concept of ecological stoichiometry. Stoichiometric homeostasis is the ability of an organism to maintain constant body chemistry in the face of variable diet chemistry. There is substantial variation in the strength of stoichiometric homeostasis across taxa (Persson et al. 2010).

Weak stoichiometric homeostasis is the result of an organism's ability to store excess nutrients that have been consumed, or decrease their stores of nutrients that are in short supply (Meunier et al. 2014). Aalto et al. (2015) propose that weakly-homeostatic hosts may suffer less fitness impacts from elemental exploitation by parasites than strictly homeostatic hosts, because they may be more tolerant of parasite driven nutrient depletion. We expand on this hypothesis and suggest that the relationship between stoichiometric homeostasis and parasitism is more complex, and depends on the underlying homeostatic physiology of the host (Table 1). We pose two related hypotheses concerning the effect of weak stoichiometric homeostasis on host–parasite interactions (Fig. 2): 1) hosts that have weak stoichiometric homeostasis, and have readily accessible nutrient stores, become better or worse resources for the parasites depending on whether the host's stoichiometry shifts closer to, or farther from, the parasite's nutritional demand (Fig. 2 – solid line). For example, viruses have high P demand and thus a weakly homeostatic host consuming P rich food becomes more P rich in its body stoichiometry and, therefore, a more suitable host for replication of the virus. Conversely, if the host is feeding on P deplete food, the virus will experience exacerbated P limitation. Alternatively, 2) if stoichiometrically weak hosts store excess nutrients in an organ, organelle, or chemical form that is inaccessible to parasites, their diet stoichiometry should have less influence on their parasites (Fig. 2 – dashed line), and their parasites should be more host specific and specialized to access those stores.

Further, maintaining stoichiometric homeostasis, requires energy expenditure in accordance with the 1st law of thermodynamics (Sterner and Elser 2002). Therefore, parasites are predicted to negatively impact their hosts' ability to invest energy into regulating body chemistry, weakening host homeostasis (Table 1). Indeed, Frost et al. (2008a) showed that not only did bacterial infection alter the stoichiometry of *Daphnia* tissue, but that it interacted with food stoichiometry, suggesting that the tissue stoichiometry of infected *Daphnia* responds to changes in diet stoichiometry different than uninfected *Daphnia*. More specifically, Frost et al. (2008a) found that increases in diet C:P resulted in a stronger reduction in tissue %P for infected *Daphnia* feeding on low C:P diets. We predict that a host's stoichiometric homeostasis is related to the diversity of parasites it may support and variation in competence within and among host species. Further, we predict that infected hosts will display greater stoichiometric homeostatic variability than uninfected hosts, and thus that some of the variation in field measurements of stoichiometric homeostasis (Halvorson and Small 2016) is due to parasitism.

Threshold elemental ratios and host–parasite interactions: a prediction

Another ecological stoichiometry concept that is relevant to host–parasite interactions, but has been overlooked to our knowledge, is the "threshold elemental ratio" (TER) hypothesis (Boersma and Elser 2006). The TER hypothesis proposes that disposing of excess dietary nutrients imposes a growth cost on organisms, so that growth exhibits a hump-shaped relationship with diet stoichiometry, whereby growth is maximized on a diet with a particular stoichiometry, and reduced as diet stoichiometry departs from this optimum in either direction (Sterner 1997, Boersma and Elser 2006).

Table 1. Selected hypotheses, predictions, and approaches for testing the linkages between ecological stoichiometry and infectious disease.

Hypothesis	Predictions	Approach to test
Host metabolic pathways direct the flow of excess nutrients toward or away from parasites (Fig. 2)	There will be a stronger relationship between host diet and parasite performance if nutrients are routed through tissues accessible to the parasite	Compare the effects of host diet on the performance of parasites infecting plastic and homeostatic tissues or hosts. Do parasites of homeostatic and plastic tissues or hosts respond differently to changes in host diet stoichiometry?
Parasites alter the relationship between host diet and host tissue stoichiometry	Parasites will decrease the energy available to maintaining elemental homeostasis resulting in greater plasticity among infected hosts	Compare the stoichiometric plasticity of infected and uninfected hosts. Are infected hosts less homeostatic than uninfected hosts?
Parasites exhibit TERs (Fig. 3)	Parasite growth or reproduction/replication will display a hump shaped relationship with host diet stoichiometry	Quantify parasite performance over a range of host diet stoichiometries. Is there a single host diet stoichiometry that results in maximum parasite performance and what is the shape of this relationship?
Epidemiological outcomes depend on the degree of overlap between host and parasite TERs (Fig. 3)	The less overlap between host and parasite TER the stronger the impact host diet stoichiometry has on the parasite's production	Quantify parasite performance over a range of host diet stoichiometries of at least two parasites that may have different TERs (e.g. virus and fungi). Do endemic and epidemic parasites have TERs that are closer and farther from host TERs respectively?
Host diet influences parasite virulence (Fig. 1E)	High C:nutrient ratios will shift pathogenic bacteria toward biofilm associated growth forms	Quantify biofilm formation over a range of host diet C:P stoichiometry. Can pathogenic bacteria be induced to form biofilms by feeding their hosts a C rich diet?
Host diet influences host immunity (Fig. 1F)	Decreasing N:Fe availability will decrease mammal immune function by limiting the host's ability to protect Fe stores and produced immune cells	Quantify immune function and parasite virulence across a range of diet N:Fe ratios. Do low N:Fe diets result in more severe disease symptoms, transmission risk, and thus epidemics?
	1. High C:P and C:N diets will decrease immune function by limiting the host's ability to produce immune cells and proteins	1. Quantify immune function over a range of diet C:P and N:P ratios. Do hosts fed C rich diets have poor immune function?
	2. Hosts feeding on extreme diet stoichiometries (i.e. very high or very low) will have increased susceptibility to infection, especially by gut parasites	2. Analyze gut microbiome and ability to resist infection over a range of diet stoichiometries Are hosts fed extreme diets more likely to become infected?
Parasites alter the ratios and rates of nutrient recycling by hosts (Fig. 1G)	Parasites will decrease excretion rates of nutrients that comprise a greater proportion of parasite biomass than host biomass, relative to other nutrients	Compare nutrient excretion rates of parasitized and unparasitized hosts. Do parasites predictably alter host excretion stoichiometry?
Global changes in nutrient cycling affect host–parasite interactions (Fig. 1G,C)	Increasing N:P in the environment will favor helminth and fungal parasites and reduce prevalence of bacterial and viral parasites	Compare parasite community composition and taxon-specific performance under different nutrient regimes. Do exogenous changes in nutrients have predictable impacts on host-parasite interactions?

We hypothesize that parasites are subject to TERs (Table 1). Given the life history of most parasites: sessile, small size compared to host, continuous feeding, and r selected reproduction, we hypothesize that food quantity is not limiting for parasites, and so parasite TERs are expected to be consistent for a given host–parasite pair.

There is evidence of TERs for pest population growth. For example, aphid performance and population growth is maximal when foliar nitrogen content is intermediate (Zehnder and Hunter 2009). We predict that over a wide range of host diet stoichiometries, parasite performance (measured as either growth rate, reproduction, or propagules emitted by the host) will display a unimodal relationship similar to growth rate TERs (Fig. 3).

Aalto et al. (2015) hypothesize that the outcome of infection can be expected to depend on the overlap of stoichiometric demands of host and parasite. We propose that more specifically, the juxtaposition of host and parasite TERs determine the outcome of infection (Table 1). For instance, if the TER optima of host growth and parasite reproduction are similar (Fig. 3 – solid and dotted line, respectively), then disease risk is predicted to be low to moderate because high parasite growth or reproduction can be counteracted by high host resistance or tolerance if the host is feeding at its TER optimum (diet A). Alternatively, if the TER optima of host growth and parasite reproduction are different (Fig. 3 – solid and dashed line, respectively) and the host is feeding on a diet that is closer to the optimum for parasite reproduction

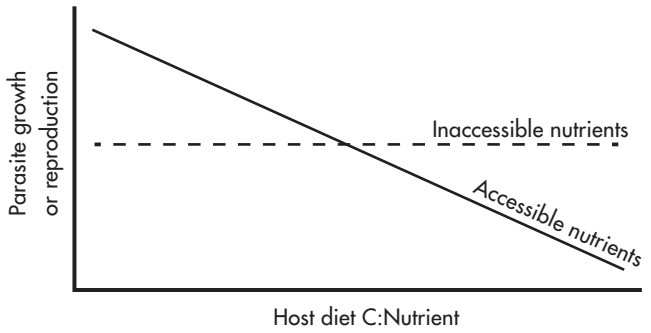

Figure 2. Hypothesized effects of homeostasis on the relationship between diet stoichiometry and parasite performance. Two alternative hypotheses for the relationship between host stoichiometric homeostasis and parasite production are presented. Solid and dashed lines represent two hosts both with weak stoichiometric homeostasis but that differ in how accessible their nutrients are to parasites. A host with weak stoichiometric homeostasis infected with a parasite that can readily access the host's nutrients becomes better or worse for a parasite depending on the stoichiometry of the host's diet (solid line). In contrast, parasite performance will be invariant if its host has weak stoichiometric homeostasis and the host's excess nutrients inaccessible to the parasite. For strongly homeostatic hosts, the same logic applies. If excess nutrients are processed in a way that makes them accessible to a parasite, then parasite performance should vary with host diet.

(diet B) than to the host's TER optimum, then disease risk is predicted to be at its highest, either because parasite production is high, the host cannot mount strong immune responses, or both. However, if the host is feeding at its TER optimum (diet A), then disease risk is predicted to be low. To our knowledge, no studies have tested for a TER in parasite growth rate or reproduction, or for interactions between parasite and host TERs.

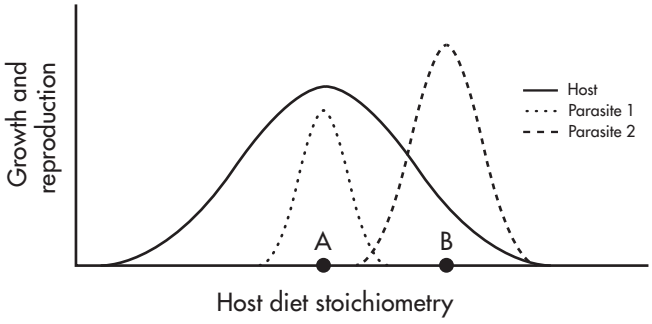

Figure 3. Some hypothesized associations between threshold elemental ratios (TERs) of a host and parasite. For instance, a host population feeding on diet A is predicted to have moderate risk to parasite 1 because diet A should be the optimum diet for host performance and thus immune function, which should reduce parasite performance. In contrast, a host population feeding on diet A is predicted to have low disease risk to parasite 2 because diet A is the optimum for host performance but very low quality for parasite 2. However, hosts feeding on diet B are predicted to have high disease risk to parasite 2 but not parasite 1 because diet B is the optimum diet for parasite 2 performance and very low quality for parasite 1.

Results have shown that snails infected with trematodes produce few infectious propagules on diets at the snail's $TER_{C:P}$, whereas they produce the most propagules on diets with high P, and intermediate numbers of propagules on low P diets (Narr and Krist 2015), suggesting that the parasite optimum is not the same as the host's diet stoichiometry optimum, supporting our prediction in Fig. 3. Additionally, in laboratory culture the maximum production of zoospores by the fungal parasite *B. dendrobatidis* occurs on diets with intermediate C:N ratios (Piotrowski et al. 2004). Mice infected with Schistosomiasis showed a hump shaped relationship in egg production with diet C:N, but the percentage of viable eggs decreased with increasing C:N (Akpom and Warren 1975). Thus, TERs are probably important to host–parasite interactions by affecting host and parasite performance differentially. We propose that non-linear relationships between host diet and parasite production can be explained by the relative TERs of host and parasite.

Stoichiometric effects on pathogenicity and virulence

Many organisms display changes in their phenotype or ontogeny when confronted with nutrient limitation. We hypothesize that parasites exposed to elevated nutrient availability will invest more heavily in pathogenic machinery or in outfitting propagules/offspring with greater stores of nutrients (Table 1). For example, many pathogenic bacteria have two distinct modes of growth: planktonic and biofilm associated. These two growth modes can depend on the relative amounts of different nutrients available to the bacteria (Cowan et al. 1991, Danhorn et al. 2004, Thompson et al. 2006, Monds et al. 2007), and differ in their pathogenicity (Parsek and Singh 2003). In the biofilm associated growth form, invasion and motility machinery are not expressed, and bacteria that can cause severe and acutely pathogenic infections in their planktonic form may persist avirulently in a host, or the environment, for decades in the biofilm associated form (Parsek and Singh 2003).

Biofilms confer numerous advantages to bacteria, including protecting them from immune system detection and attack, and from antibiotics (Fux et al. 2005). Because of their high sugar content, we predict that biofilms have high C:N and C:P relative to bacterial cells and host tissue, and thus biofilm production requires high C availability to the bacteria. When N, P, Fe or other non-carbon elements are limiting, the nutritional advantage of producing a biofilm matrix is twofold: It aligns demand with excess C availability, and it creates a complex organic structure that increases local nutrient availability by capturing materials that can then be degraded with extracellular bacterial enzymes (Wingender et al. 1999, Battin et al. 2003). Thus, shifting between growth forms enables bacteria to balance nutrient demand and availability.

The hypothesis that the availability of dissolved nutrients is related to bacterial growth form determination is not new, however, we propose that ecological stoichiometry represents a framework for understanding this interaction. Further, we predict that biofilms are the preferred growth form of pathogenic bacteria when sugars and other forms of carbon are

available in great excess relative to other potentially limiting nutrients, and published results support this prediction (Cowan et al. 1991, Danhorn et al. 2004, Thompson et al. 2006). For both pathogenic and non-pathogenic bacteria, expression of the Pho regulon, which is activated in response to P limitation, is related to biofilm formation (Danhorn et al. 2004, Monds et al. 2007). Thus, we hypothesize that nutrient effects on biofilm formation can be better understood using the ecological stoichiometric framework.

Fungal parasites have also shown phenotypic plasticity in the face of nutrient limitation. Chytrid parasites of cyanobacteria have been shown to produce fewer and larger zoospores under low N:P conditions, and many, smaller zoospores under high N:P conditions (Frenken et al. 2017). It is presumed that larger zoospores are outfitted with larger stores of lipid and fatty acid, allowing them to survive longer in the environment. It is also presumed that larger, more C rich zoospores take longer to produce. Thus, we hypothesize that these results are more indicative of C:N availability to the pathogen than N:P; as N limitation and C availability increases, the fungus balances demand, and slow growth rate under N limitation, by producing fewer zoospores of higher quality. Indeed, the authors note relatively higher light availability in the low N:P treatment that would be expected to increase photosynthetic rates and therefore cyanobacteria %C.

For parasites with more complex life cycles, we predict that host diet mediated nutrient availability will impact provisioning of infectious propagules. We predict that parasites metamorphosing from a parasitic larval stage to a free-living (non-parasitic) adult stage will display sensitivity to host diet %N in size at emergence and development time to adult emergence. In contrast, we predict that parasites with parasitic adults will show sensitivity to host diet %N and %P in egg viability and larval survival. For instance, increased % protein (assumed to reduce diet C:N), in bovine diets has been shown to result in female ticks that were larger at time of detachment, and somewhat shorter development time (time until detachment) (Gladney et al. 1973). Foliar %N has been shown to be positively related to the adult body weight of ichneumonid wasps that emerge from their herbivorous caterpillar host, and the ratio of emerging females to male wasps (Fox et al. 1990). Studies on the impacts of carbohydrate and protein on helminth parasites in the mouse model system suggest that the viability of worm eggs is negatively correlated with host diet C:N (Akpom and Warren 1975). These results mirror those of Urabe and Sterner (2001), who found that *Daphnia* reared on high C:P and C:N diets produced a substantially higher fraction of eggs that were non-viable than *Daphnia* reared on P and N replete media.

Effects of elemental stoichiometry on host immune function

In addition to the benefits afforded to parasite growth and virulence, a host diet rich in particular nutrients may benefit host immune function (Table 1), thereby circumventing the positive effects of nutrients on parasites, especially if the host can allocate nutrients to immune defense before they are stolen by its parasite (Fig. 1F, 1B). For example, iron (Fe) is a critical nutrient to all life as it plays an important role in respiration. Biologically available reduced Fe is scarce, and hosts protect their stores by binding it to large proteins such as transferrin and ferritin. Therefore, we predict that host diets with high N:Fe ratios support greater immune function because N-rich diets support the production of Fe binding proteins and their upregulation in response to immune challenge. This prediction is supported by evidence that humans suffering from kwashiorkor (protein deficiency) and hemochromatosis (a hereditary disease causing elevated serum Fe levels) have increased susceptibility to infectious disease (McFarlan et al. 1970, Muench 1989, Doherty 2007).

Dietary P has also been shown to influence host immunity. Evidence suggests that high P diets support cell mediated immunity, but the underlying mechanisms are unclear (Kegley et al. 2001, Heyer et al. 2015). It has also been shown that low dietary P can fail to support a stable intestinal microbiome, increasing the chance of invasion by pathogenic microbes (Heyer et al. 2015). Therefore, we predict that there is probably an ideal stoichiometric ratio of dietary nutrients (a TER) that supports a robust internal microbe community, and that diets imbalanced in nutrients for a healthy microbe community will predispose the host to invasion by gut microparasites that are better competitors for limiting nutrients. Taken together, we can use ecological stoichiometry to predict that hosts with diet C:N and C:P ratios higher than optimal should be at greater risk of infection because of the decrease in magnitude and rate at which immunological cells and proteins are produced, and that hosts with extreme diet nutrient ratios in general should be at greater risk of infection due to their microbiome's greater susceptibility to invasion.

Parasite effects on the stoichiometry of consumer-driven nutrient recycling

Consumer-driven nutrient recycling (CDNR, Fig. 1G), the re-mineralization of nutrients by living organisms, can be a major driver of local nutrient cycles (Vanni 2002, Small et al. 2011) and nutrient limitation (Elser et al. 1988). CDNR follows directly from ecological stoichiometry: if a consumer is stoichiometrically homeostatic to any degree, and their diet is variable and stoichiometrically unbalanced, then their waste products must vary with their diet to satisfy the law of conservation of mass (Olsen et al. 1986, Moody et al. 2015). Alternatively, if an organism undergoes physiological changes in response to ontogenetic or environmental shifts, but its diet remains relatively constant, a commensurate change in waste stoichiometry is expected (Dalton and Flecker 2014). Together, host and parasite are expected to have different nutritional requirements than the host alone. For one reason, parasites can cause physiological changes within the host (e.g. immune response) that affect nutrient retention by the host. Further, the parasite itself may have substantially different tissue chemistry from the host, and may constitute a

large proportion of the total biomass of the host and parasite combined, or may have much higher metabolic rates, or very high turnover rates. Thus parasites are predicted to alter the absolute rates of nutrient excretion, and often the relative rates (i.e. stoichiometric ratios; Fig. 1H, Table 1). The effects of parasites on CDNR have important implications for understanding and predicting the direct effects of consumers on nutrient cycling, yet studies of disease-induced changes in consumer functional roles, such as nutrient recycling, are rare.

Parasites should have higher P demand than their hosts, because parasites are usually smaller than their hosts and P demand increases as body size decreases (Elser et al. 1996, Woods et al. 2004, Allen and Gillooly 2009, Back and King 2013). Thus, parasites should decrease P in host excretion relative to N, as the P demand of the host and parasite combined should be greater than the P demand of the host alone, assuming parasitism does not disproportionately reduce growth demand for P of the parasitzed host. Indeed, snails infected with trematodes had higher N:P in their excretion than uninfected snails (Bernot 2013), supporting the hypothesis that parasites alter the stoichiometry of CDNR, and models suggest parasite-induced changes in excretion can alter N cycling at the ecocsystem level (Mischler et al. 2016). Further, *Daphnia* infected with bacteria and fungi excreted more N and P, and higher N:P (Narr and Frost 2016). This finding combined with our knowledge of how CDNR can affect nutrient limitation (Sterner 1986, Hall et al. 2003, Small et al. 2011, Munshaw et al. 2013) and shift the limiting nutrient (Sterner et al. 1992), leads to the hypothesis that parasites could shift ecosystem nutrient limitation by changing CDNR as has been shown for top predators (Elser and Carpenter 1988, Elser et al. 1988, Munshaw et al. 2013). Moreover, if parasites are capable of shifting nutrient limitation via CDNR by their host, then we predict that there will be feedbacks whereby a parasite-mediated shift in the identity of the limiting element (e.g. N to P or Fe) leads to repression of the parasite as that element becomes limited within their hosts (Fig. 1H, C). For examples, if an extremely P hungry parasite causes a severe reduction in its host's P remineralization resulting in exacerbated P limitation in the local environment, then the parasite will eventually experience increased P limitation itself.

Effects of global alterations in nutrient cycles on the relationship between stoichiometry and infectious disease

One of the primary strengths of ecological stoichiometry is the ability to apply it across biological levels from cells to ecosystems to understand the impacts of elements (Elser et al. 2000). Hence, ecological stoichiometry can be used for predicting and investigating how anthropogenic alterations to global nutrient cycles affect infectious disease through host–parasite stoichiometry (Fig. 1I). While P enrichment generally originates from relatively local sources (Ansari et al. 2011), human activities are increasing the availability of N at a global scale through atmospheric deposition, fertilizer runoff, and other pathways (Vitousek et al. 1997, Bergstrom and Jansson 2006). Further, efforts to mitigate nutrient pollution in lakes and coastal waters have generally resulted in greater decreases in P loading than N loading (Paerl 2009).

Increases in global N availability relative to P have been shown to shift a diversity of ecosystems to P limitation (Elser et al. 2009), or increase the strength of existing P limitation of primary producers and consumers (Bergstrom and Jansson 2006, Elser et al. 2010, Crowley et al. 2012, Penuelas et al. 2012). N pollution can also alter community structure by shifting the relative abundance and density of primary and secondary host taxa (Johnson and Chase 2004, Johnson et al. 2007, Bobbink et al. 2010, Aalto et al. 2015). Eutrophication by either N or P can also have a negative effect on biodiversity by altering species richness and evenness, which are known to modulate disease risk (Tilman et al. 2001, Johnson et al. 2013). The ability to trace the effects of changes in nutrient cycling from the base of food webs (i.e. plants, bacteria, fungi and algae) to higher consumers and their parasites is a powerful application of ecological stoichiometry for predicting and managing infectious diseases.

Using the principles of ecological stoichiometry, we can predict that increasing global N availability relative to P should shift nutrient limitation to P, or increase existing P limitation, for both hosts and their parasites (Table 1). Thus one potential consequence of N enrichment for parasites limited by P, such as bacteria and viruses, is that they should have lower performance or prevalence in P limited hosts, whereas parasites more sensitive to N, such as fungi and helminths, should have higher performance and prevalence, all else being equal. For example, *B. dendrobatidis*, the fungal agent that causes chytridiomycosis in amphibians, lives in the keratinized layers of the epidermis and feeds on keratin. If infected amphibians are feeding on N enriched food resources and are capable of investing greater N to replenish keratin, we predict that this will lead to faster growth and increased zoospore production by the fungal parasite, and higher prevalence and mortality within the host population. P limitation can also affect competition between co-infecting parasites (Lacroix et al. 2014) potentially leading to proliferation of previously rare parasites that are poor competitors under historical nutrient limitation scenarios. Further, evidence suggests that consumers evolving under eutrophic conditions can become increasingly sensitive to poor diet quality, and show stronger relationships between host diet quality and parasite virulence (Reyserhove et al. 2017). This suggests that anthropogenic changes in resource stoichiometry over evolutionary timescales will feedback, with eutrophication causing increasingly severe responses of infectious diseases to nutrient pollution. We hypothesize that because eutrophication decreases selection pressure on nutrient use efficiency, these results are likely generalizable, however further research is needed. For example, it is unknown if the results of Reyserhove et al.'s (2017) study were due to a decrease in the host's ability to compete for limiting nutrients, or the host's inability to meet immune system demand. We suspect the former, and that it

would be detectible as an increase in the parasite's production efficiency (production of infectious propagules relative to production of host tissue) as host diet C:P or N:P increased. In other words, if increased nutrient limitation reduced host growth more than it reduced parasite production, than that would suggest that the observed increase in virulence was due to the parasite outcompeting the host for nutrients, whereas an equal or lesser reduction in host growth compared to parasite production would suggest that the hosts diet is of too poor of quality to support immune function. We also suggest performing similar feeding experiments on a variety of other host–parasite pairings to better understand how host resistance and parasite virulence may evolve under different nutrient regimes. For example, by taking hosts (or parasite strains) from distinctly separate populations that have experienced widely divergent nutrient regimes for many generations and exposing them to a parasite strain (or host) isolated from a population that has been evolving under an intermediate nutrient regime.

We predict that shifts in the availability of different nutrients, and differential responses of various parasites to those shifts, should change the composition and relative abundance of the parasite community (Table 1). We also predict that bottom up effects on parasites will strengthen as anthropogenic eutrophication continues. Altogether, our current understanding suggests that the effects of eutrophication on host-pathogen interactions are the result of complex interactions between effects on the density of hosts, competition for nutrients between hosts and parasites, and competition for nutrients between co-infecting parasites. We predict that anthropogenic changes to biogeochemical cycling will promote global increases in fungal infection, such as chytrid, and lead to the emergence of previously rare infectious diseases. We also predict that global N enrichment will favor biofilm formation by pathogenic bacteria due to increased strength of P limitation. Most importantly, we suggest that ecological stoichiometry presents a powerful framework for understanding and predicting the impacts of human alterations to global biogeochemical cycling on emerging infectious diseases.

Conclusions

The theft of resources, principally nutrients, is an integral facet of host–parasite interactions. Ecological stoichiometry provides a framework for understanding fluxes of nutrients among organisms and between organisms and their environments, and thus offers substantial utility for studying infectious diseases. Here, one of our goals was to describe the application of ecological stoichiometry to infectious disease by presenting specific hypotheses and predictions.

Although focusing on the stoichiometry of chemical elements may be viewed as overly reductionist, we contend that ecological stoichiometry is a complement to, not a replacement for, other theoretical and empirical lines of inquiry. For example, macromolecules as a nutritional currency may provide precise predictions for specific host–parasite interactions because a given host or parasite's physiological requirements for them are often highly specific and well understood, however, they cannot be traced through food webs and the environment like the chemical elements. The stoichiometric approach offers greater generality and the inclusion of food webs and biogeochemical cycles into predictions of host–parasite interactions. Importantly, it provides a framework for uncovering general patterns occurring among the myriad of host-parasite interactions, and for integrating disease and ecosystem ecology (Aalto et al. 2015, Preston et al. 2016). However, a stoichiometric approach cannot address emergent properties of compounds, such as pheromones, medicinal secondary chemicals, or digestibility that are not readily apparent from their stoichiometry. Further, many aspects of host–parasite interactions cannot be addressed by nutritional studies alone – genetics, population ecology, and community ecology are all needed. Ecological stoichiometry is thus no panacea, but a potentially underutilized tool in the study of host–parasite interactions that can complement other approaches and explain additional variation. As a tool for simplifying the role of nutrition in biological processes, deviations between observations and predictions from ecological stoichiometry can highlight opportunities for discovery (Urabe et al. 2018). In many cases, ecological stoichiometry can be easily integrated into studies by taking some additional measurements of host, diet and parasite elemental content, as opposed to radically altering the scientific approach or study design. Thus we urge investigators to consider adding a stoichiometric dimension to studies of infectious diseases.

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References

Aalto, S. L. and Pulkkinen, K. 2013. Food stoichiometry affects the outcome of *Daphnia*–parasite interaction. – Ecol. Evol. 3: 1266–1275.

Aalto S. L. et al. 2015. A three-way perspective of stoichiometric changes on host–parasite interactions. – Trends Parasitol. 31: 333–340.

Akpom, C. A. and Warren, K. S. 1975. Calorie and protein malnutrition in chronic murine schistosomiasis mansoniI: effect on the parasite and the host. – J. Infectious Dis. 132: 6–14.

Allen, A. P. and Gillooly, J. F. 2009. Towards an integration of ecological stoichiometry and the metabolic theory of ecology to better understand nutrient cycling. – Ecol. Lett. 12: 369–384.
Anderson, R. M. and May, R. M. 1985. Helminth infections of humans: mathematical models, population dynamics and control. – Adv. Parasitol. 24: 1–101.
Ansari, A. A. et al. (eds) 2011. Eutrophication: causes, consequences and control. – Springer.
Back, J. A. and King, R. S. 2013. Sex and size matter: ontogenetic patterns of nutrient content of aquatic insects. – Freshwater Sci. 32: 837–848.
Battin, T. J. et al. 2003. Contributions of microbial biofilms to ecosystem processes in stream mesocosms. – Nature 426: 439–442.
Bergstrom, A. K. and Jansson, M. 2006. Atmospheric nitrogen deposition has caused nitrogen enrichment and eutrophication of lakes in the northern hemisphere. – Global Change Biol. 12: 635–643.
Bernot, R. J. 2013. Parasite–host elemental content and the effects of a parasite on host-consumer-driven nutrient recycling. – Freshwater Sci. 32: 299–308.
Bobbink, R. et al. 2010. Global assessment of nitrogen deposition effects on terrestrial plant diversity: a synthesis. – Ecol. Appl. 20: 30–59.
Boersma, M. and Elser, J. J. 2006. Too much of a good thing: on stoichiometrically balanced diets and maximal growth. – Ecology 87: 1325–1330.
Borer, E. T. et al. 2010. Local context drives infection of grasses by vector-borne generalist viruses. – Ecol. Lett. 13: 810–818.
Bruning, K. and Ringelberg, J. 1987. The influence of phosphorus limitation of the diatom *Asterionella formosa* on the zoospore production of its fungal parasite *Rhizophydium planktonicum*. – Hydrobiol. Bull. 21: 49–54.
Bundy, D. A. P. and Golden, M. H. N. 1987. The impact of host nutrition on gastrointestinal helminth populations. – Parasitology 95: 623–635.
Clasen, J. L. and Elser, J. J. 2007. The effect of host *Chlorella NC64A* carbon : phosphorus ratio on the production of *Paramecium bursaria Chlorella Virus-1*. – Freshwater Biol. 52: 112–122.
Cowan, M. M. et al. 1991. Mixed-species colonization of solid surfaces in laboratory biofilms. – Biofouling 3: 23–34.
Crowley, K. F. et al. 2012. Do nutrient limitation patterns shift from nitrogen toward phosphorus with increasing nitrogen deposition across the northeastern United States? – Ecosystems 15: 940–957.
Dalton, C. M. and Flecker, A. S. 2014. Metabolic stoichiometry and the ecology of fear in Trinidadian guppies: consequences for life histories and stream ecosystems. – Oecologia 176: 691–701.
Danhorn, T. et al. 2004. Phosphorus limitation enhances biofilm formation of the plant pathogen *Agrobacterium tumefaciens* through the PhoR-PhoB regulatory system. – J. Bacteriol. 186: 4492–4501.
Doherty, C. P. 2007. Host–pathogen interactions: the role of iron. – J. Nutr. 137: 1341–1344.
Elser, J. J. and Carpenter, S. R. 1988. Predation-driven dynamics of zooplankton and phytoplankton communities in a whole-lake experiment. – Oecologia 76: 148–154.
Elser, J. J. et al. 1988. Zooplankton-mediated transitions between N-Limited and P-Limited algal growth. – Limnol. Oceanogr. 33: 1–14.
Elser, J. J. et al. 1996. Organism size, life history and N:P stoichiometry. – Bioscience 46: 674–684.
Elser, J. J. et al. 2000. Biological stoichiometry from genes to ecosystems. – Ecol. Lett. 3: 540–550.
Elser, J. J. et al. 2003. Growth rate–stoichiometry couplings in diverse taxa. – Ecol. Lett. 6: 936–943.
Elser, J. J. et al. 2009. Shifts in lake N:P stoichiometry and nutrient limitation driven by atmospheric nitrogen deposition. – Science 326: 835–837.
Elser, J. J. et al. 2010. Atmospheric nitrogen deposition is associated with elevated phosphorus limitation of lake zooplankton. – Ecol. Lett. 13: 1256–1261.
Fagerbakke, K. M. et al. 1996. Content of carbon, nitrogen, oxygen, sulfur and phosphorus in native aquatic and cultured bacteria. – Aquat. Microbial Ecol. 10: 15–27.
Fox, L. R. et al. 1990. Parasitism rates and sex ratios of a parasitoid wasp: effects of herbivore and plant quality. – Oecologia 83: 414–419.
Frenken, T. et al. 2017. Changes in N:P supply ratios affect the ecological stoichiometry of a toxic cyanobacterium and its fungal parasite. – Front. Microbiol. 8: 1015.
Frost, P. C. et al. 2008a. Bacterial infection changes the elemental composition of *Daphnia magna*. – J. Anim. Ecol. 77: 1265–1272.
Frost, P. C. et al. 2008b. Responses of a bacterial pathogen to phosphorus limitation of its aquatic invertebrate host. – Ecology 89: 313–318.
Fux, C. A. et al. 2005. Survival strategies of infectious biofilms. – Trends Microbiol. 13: 34–40.
Gladney, W. J. et al. 1973. *Boophilus annulatus*: effect of host nutrition on development of female ticks. – J. Med. Entomol. 10: 123–130.
Güsewell, S. and Gessner, M. O. 2009. N : P ratios influence litter decomposition and colonization by fungi and bacteria in microcosms. – Funct. Ecol. 23: 211–219.
Hall, R. et al. 2003. Exotic snails dominate nitrogen and carbon cycling in a highly productive stream. – Front. Ecol. Environ. 1: 407–411.
Hall, S. R. et al. 2009. Quality matters: resource quality for hosts and the timing of epidemics. – Ecol. Lett. 12: 118–128.
Halvorson, H. M. and Small, G. E. 2016. Observational field studies are not appropriate tests of consumer stoichiometric homeostasis. – Freshwater Sci. 35: 1103–1116.
Heyer, C. M. et al. 2015. The impact of phosphorus on the immune system and the intestinal microbiota with special focus on the pig. – Nutr. Res. Rev. 28: 67–82.
Jensen, B. and Munk, L. 1997. Nitrogen-induced changes in colony density and spore production of *Erysiphe graminis* f.sp. *hordei* on seedlings of six spring barley cultivars. – Plant Pathol. 46: 191–202.
Johnson, P. T. J. and Chase, J. M. 2004. Parasites in the food web: linking amphibian malformations and aquatic eutrophication. – Ecol. Lett. 7: 521–526.
Johnson, P. T. et al. 2007. Aquatic eutrophication promotes pathogenic infection in amphibians. – Proc. Natl Acad. Sci. USA 104: 15781–15786.
Johnson, P. T. et al. 2013. Biodiversity decreases disease through predictable changes in host community competence. – Nature 494: 230–233.
Jover, L. F. et al. 2014. The elemental composition of virus particles: implications for marine biogeochemical cycles. – Nat. Rev. Microbiol. 12: 519–528.

Kegley, E. B. et al. 2001. Dietary phosphorus and an inflammatory challenge affect performance and immune function of weanling pigs. – J. Anim. Sci. 79: 413–419.
Lacroix, C. et al. 2014. Environmental nutrient supply alters prevalence and weakens competitive interactions among coinfecting viruses. – New Phytol. 204: 424–433.
Makino, W. et al. 2003. Are bacteria more like plants or animals? Growth rate and resource dependence of bacterial C : N : P stoichiometry. – Funct. Ecol. 17: 121–130.
McFarlan, H. et al. 1970. Immunity, transferrin, and survival in kwashiorkor. – Br. Med. J. 4: 268–270.
Meunier, C. L. et al. 2014. A new approach to homeostatic regulation: towards a unified view of physiological and ecological concepts. – PloS One 9: 7.
Meunier, C. L. et al. 2017. From elements to function: toward unifying ecological stoichiometry and trait-based ecology. – Front. Environ. Sci. 5: 18.
Mischler, J. et al. 2016. Parasite infection alters nitrogen cycling at the ecosystem scale. – J. Anim. Ecol. 85: 817–828.
Monds, R. D. et al. 2007. Phosphate-dependent modulation of c-di-GMP levels regulates *Pseudomonas fluorescens* Pf0-1 biofilm formation by controlling secretion of the adhesin LapA. – Mol. Microbiol. 63: 656–679.
Moody, E. K. et al. 2015. Diet composition affects the rate and N:P ratio of fish excretion. – Freshwater Biol. 60: 456–465.
Muench, K. H. 1989. Hemochromatosis and infection: alcohol and iron, oysters and sepsis. – Am. J. Med. 87: 40N–43N.
Munshaw, R. G. et al. 2013. Predator-driven nutrient recycling in California stream ecosystems. – PLoS One 8: e58542.
Narr, C. F. and Krist, A. C. 2015. Host diet alters trematode replication and elemental composition. – Freshwater Sci. 34: 81–91.
Narr, C. F. and Frost, P. C. 2016. Exploited and excreting: parasite type affects host nutrient recycling. – Ecology 97: 2012–2020.
Olsen, Y. et al. 1986. Dependence of the rate of release of phosphorus by zooplankton on the P-C ratio in the food-supply, as calculated by a recycling model. – Limnol. Oceanogr. 31: 34–44.
Paerl, H. W. 2009. Controlling eutrophication along the freshwater–marine continuum: dual nutrient (N and P) reductions are eEssential. – Estuaries Coasts 32: 593–601.
Parfitt, R. L. et al. 2010. Effect of fertilizer, herbicide and grazing management of pastures on plant and soil communities. – Appl. Soil Ecol. 45: 175–186.
Parsek, M. R. and Singh, P. K. 2003. Bacterial biofilms: an emerging link to disease pathogenesis. – Annu. Rev. Microbiol. 57: 677–701.
Peck, M. et al. 1992. The role of protein and calorie restriction in outcome from *Salmonella* infection in mice. – J. Parenteral Enteral Nutr. 16: 561–565.
Penuelas, J. et al. 2012. The human-induced imbalance between C, N and P in Earth's life system. – Global Change Biol. 18: 3–6.
Persson, J. et al. 2010. To be or not to be what you eat: regulation of stoichiometric homeostasis among autotrophs and heterotrophs. – Oikos 119: 741–751.
Piotrowski, J. S. et al. 2004. Physiology of *Batrachochytrium dendrobatidis*, a chytrid pathogen of amphibians. – Mycologia 96: 9–15.
Preston, D. L. et al. 2016. Disease ecology meets ecosystem science. – Ecosystems 19: 737–748.
Pulkkinen, K. et al. 2014. Phosphorus limitation enhances parasite impact: feedback effects at the population level. – BMC Ecol. 14: 11.
Reiners, W. A. 1986. Complementary models for ecosystems. – Am. Nat. 127: 59–73.
Reyserhove, L. et al. 2017. A historical perspective of nutrient change impact on an infectious disease in *Daphnia*. – Ecology 98: 2784–2798.
Sardans, J. et al. 2012. The elemental stoichiometry of aquatic and terrestrial ecosystems and its relationships with organismic lifestyle and ecosystem structure and function: a review and perspectives. – Biogeochemistry 111: 1–39.
Small, G. E. et al. 2011. Role of the fish *Astyanax aeneus* (Characidae) as a keystone nutrient recycler in low-nutrient Neotropical streams. – Ecology 92: 386–397.
Smith, V. 2007. Host resource supplies influence the dynamics and outcome of infectious disease. – Integr. Compar. Biol. 47: 310–316.
Smith, V. H. et al. 2005. Host nutrition and infectious disease: an ecological view. – Front. Ecol. Environ. 3: 268–274.
Stephens, J. P. et al. 2016. Bottom–up and trait-mediated effects of resource quality on amphibian parasitism. – J. Anim. Ecol. 86: 3015–315.
Sterner, R. W. 1986. Herbivores direct and indirect effects on algal populations. – Science 231: 605–607.
Sterner, R. W. 1997. Modelling interactions of food quality and quantity in homeostatic consumers. – Freshwater Biol. 38: 473–481.
Sterner, R. W. and Elser, J. J. 2002. Ecological stoichiometry: the biology of elements from molecules to the biosphere. – Princeton Univ. Press.
Sterner, R. W. et al. 1992. Stoichiometric relationships among producers, consumers and nutrient cycling in pelagic ecosystems. – Biogeochemistry 17: 49–67.
Thompson, L. J. et al. 2006. Carbon : nitrogen : phosphorus ratios influence biofilm formation by *Enterobacter cloacae* and *Citrobacter freundii*. – J. Appl. Microbiol. 101: 1105–1113.
Tilman, D. et al. 2001. Forecasting agriculturally driven global environmental change. – Science 292: 281–284.
Urabe, J. and Sterner, R. W. 2001. Contrasting effects of different types of resource depletion on life-history traits in *Daphnia*. – Funct. Ecol. 15: 165–174.
Urabe, J. et al. 2018. Understanding the stoichiometric limitation of herbivore growth: the importance of feeding and assimilation flexibilities. – Ecol. Lett. 21: 197–206.
Vannatta, J. T. and Minchella, D. J. 2018. Parasites and their impact on ecosystem nutrient cycling. – Trends Parasitol. 10.1016/j.pt.2018.02.007.
Vanni, M. J. 2002. Nutrient cycling by animals in freshwater ecosystems. – Annu. Rev. Ecol. Syst. 33: 341–370.
Vitousek, P. M. et al. 1997. Human alteration of the global nitrogen cycle: sources and consequences. – Ecol. Appl. 7: 737–750.
Williamson, W. M. et al. 2005. Changes in soil microbial and nematode communities during ecosystem decline across a long-term chronosequence. – Soil Biol. Biochem. 37: 1289–1301.
Wingender, J. et al. (eds) 1999. Microbial extracellular polymeric substances: characterization, structure and function. – Springer.
Woods, H. A. et al. 2004. Allometric and phylogenetic variation in insect phosphorus content. – Funct. Ecol. 18: 103–109.
Zehnder, C. B. and Hunter, M. D. 2009. More is not necessarily better: the impact of limiting and excessive nutrients on herbivore population growth rates. – Ecol. Entomol. 34: 535–543.