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REVIEW ARTICLE

The Battle for Iron between Humans and Microbes

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Abstract: ***Background:*** Iron is an essential micronutrient for bacteria, fungi, and humans; as such, each has evolved specialized iron uptake systems to acquire iron from the extracellular environment.

Objective: To describe complex 'tug of war' for iron that has evolved between human hosts and pathogenic microorganisms in the battle for this vital nutrient.

Methods: A review of current literature was performed, to assess current approaches and controversies in iron therapy and chelation in humans.

Results: In humans, sequestration (hiding) of iron from invading pathogens is often successful; however, many pathogens have evolved mechanisms to circumvent this approach.

Conclusion: Clinically, controversy continues whether iron overload or administration of iron results in an increased risk of infection. The administration of iron chelating agents and siderophore-conjugate drugs to infected hosts seems a biologically plausible approach as adjunctive therapy in the treatment of infections caused by pathogens dependent on host iron supply (*e.g.* tuberculosis, malaria, and many bacterial and fungal pathogens); however, thus far, studies in humans have proved unsuccessful.

Keywords: Infection, iron, nutritional immunity, siderophore, iron overload, iron chelation.

1. INTRODUCTION

Iron is an essential micronutrient for bacteria, fungi, and humans. Although certain species of streptococci can utilize manganese as an alternative to iron, during iron limitation, with rare exceptions, bacteria depend upon iron for their growth. Microbes that possess multiple mechanisms for iron uptake, or that can utilize alternative metal ions (*e.g.,* zinc or manganese) have an advantage when iron sources are limited. The human body contains 3-5 gm of iron, most of which is intracellular; 65-75% of the body's iron is bound to the porphyrin heme (as hemoglobin) in erythrocytes. A complex system of transporters regulates iron homeostasis in humans, which is maintained through careful coordination of duodenal absorption and recycling of iron stores. Extracellular iron is rapidly removed by the high-affinity iron binding proteins transferrin, ferritin, and lactoferrin, and hemoglobin is complexed by haptoglobin and removed by the liver. During inflammation and febrile conditions, humans increase synthesis of ferritin and lactoferrin; as a result, iron starvation of microbes limits their growth, allowing the host time to eradicate the infection *via* immune-related mechanisms [1, 2].

2. KEY PLAYERS IN THE TUG OF WAR-FOR - IRON

In infected patients, sequestration (hiding) of Fe, Zn, and Se from the pathogen provides "nutritional immunity" to the host. Pathogenic (disease-causing) bacteria have developed mechanisms to circumvent nutritional immunity, but in turn, complex host defense mechanisms have evolved to counteract these defense mechanisms [3, 4]. In the host versus pathogen tug-of-war over iron acquisition, there are key players on each side [5, 6].

Microorganisms have evolved or acquired a variety of specialized iron uptake systems to overcome environmental iron limitation, and to take up iron from the extracellular environment, including during infection, when the host limits access to iron. High-affinity iron

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uptake systems, active under low iron environments, include assimilation from transferrin, ferritin, lactoferrin, or other proteins, reductive iron assimilation, siderophore-mediated uptake, and heme acquisition (uptake and degradation) systems. Under conditions of iron abundance, a low affinity Fe^{+2} system can also be utilized [7].

Pathogens obtain iron from the environment using the iron scavenging systems known as *siderophores,* which are low molecular weight, high affinity iron chelators secreted by bacteria and many fungi. Iron can be internalized as a whole Fe-siderophore complex, or solely as the reduced Fe^{+2} form [7]. Siderophores compete with transferrin for Fe, and bind Fe^{+3} with an affinity stronger than that of transferrin or lactoferrin. The 3 main structural families of siderophores include catecholate, hydroxamate, carboxylate; there are also 'mixed-type' siderophores containing structural elements of two or more siderophore families. More than 500 different siderophores have been identified, and some pathogens secrete several, structurally different siderophores. In addition, some pathogens can accept xenosiderophores (siderophores produced by other organisms), allowing iron scavenging even if the pathogen is unable to produce siderophores [7]. While the ability of a pathogen to secrete more than one type of siderophore may appear redundant, this functional redundancy may allow specialization of function in scavenging iron and perhaps other metal ions, to regulate oxidative stress, as well as evasion of host immune factors [8, 9]. Among siderophores, the catecholate siderophore enterobactin forms the most stable ferric complex, as compared to hydroxamate, carboxylate, or 'mixed-type' siderophores. However, as discussed below, iron uptake by enterobactin can be 'neutralized' by its binding to *siderocalin* (also known as NGAL (neutrophil gelatinase-associated lipocalin) and Lipocalin-2), an endogenous antimicrobial protein produced by the human immune system, that binds many catecholate siderophores.

For many common gram negative (including uropathogenic *E. coli, Pseudomonas aeruginosa, Hemophilus influenzae, Neisseria meningitides*, and *Acinetobacter baumannii*), gram-positive (including *Staphylococcus aureus* (but not *S. epidermidis*), and fungal pathogens (including *Candida albicans, Cryptococcus neoformans,* but not *Aspergillus* species), heme provides the potential for a rich source of iron [2, 7, 10]. Bacteria secrete hemolysins that lyse erythrocytes, releasing hemoglobin [11]. In gram negative bacteria, hemoglobin binds to an outer membrane surface receptor on the bacteria, and the iron is transported as heme across the outer membrane to the periplasm via an energy-coupled process thru 'beta-barrel' pores. After transiting the periplasm, heme is bound to a periplasmic heme binding protein, which delivers the heme to ABC (ATP-binding cassette) transporters found in the cytoplasmic membrane, which translocate heme (and iron-containing siderophores) across the cytoplasmic membrane. Gram positive bacteria lack the outer membrane found in gram negative bacteria; heme transport occurs across the cytoplasmic membrane via ABC transporters, similar to the system used by gram-negative bacteria. This ability to bind hemoglobin appears to translate into increased virulence of these pathogens [11].

In humans, iron is removed from serum in response to infection by upregulation of the iron regulatory hormone hepcidin, which is produced by the liver and serves to regulate levels of ferroportin, a cellular iron exporter. As ferroportin is degraded, there is a decreased transfer of cellular iron to plasma, resulting in hypoferremia [12]. Humans also produce *siderocalin,* which binds siderophores to sequester iron, providing human defense against pathogens. First identified as a neutrophil granule component, siderocalin is a member of the lipocalin family of binding proteins. Siderocalin is unable to bind directly to Fe^{+3}; rather, it binds bacterial catecholate-type ferric siderophores such as enterobactin and exerts an antibacterial effect by blocking siderophore delivery of iron to the pathogen [13]. In animal models, siderocalin is highly upregulated during inflammation and infection. Additional metal ion sequestering is provided by the S100 proteins, including *calprotectin*, which bind Zn^{+2}, Cu^{+2}, and Mn^{+2} to 'starve' pathogens of these essential nutrients and by bacterial metal ion transport systems such as the natural resistance-associated macrophage protein (NRAMP), which transports Fe (and Mn) into the cytosol [14, 15]. The depletion of iron and manganese (combined with an acidic pH, and the presence of reactive oxygen species), create inhibitory or even bactericidal conditions for pathogens residing in NRAMP-containing vesicles. *In vitro*, calprotectin has demonstrated the ability to inhibit the growth of several medically relevant bacteria and fungi, including *E. coli*, *Klebsiella pneumoniae*, *Candida albicans, Staphylococcus aureus, Acinetobacter baumannii, Aspergillus fumigatus, Cryptococcus neoformans,* and *Helicobacter pylori*, *via* sequestration of Zn^{+2} and (in particular) Mn^{+2} [16]. However, pathogenic strains of *E. coli, Salmonella,* and *Bacillus anthracis* are able to synthesize the 'stealth siderophores' salmochelin and petrobactin, which are modified forms of enterobactin that are able to evade siderocalin, restoring the pathogen's iron scavenging ability [13, 16-19]. Never-

theless, some pathogens are able to elude the nutritional immunity system in select body sites in the host. For example, invasion of the kidney by *Candida albicans* stimulates a decrease in kidney tissue levels of iron (and copper). However, despite limiting the local availability of iron and copper, the pathogen thrives, due to its ability to change expression of copper-zinc superoxide dismutase (SOD) to manganese-SOD [20, 21].

3. FE DEFICIENCY – SHOULD WE SUPPLEMENT IRON? IRON ADMINISTRATION AS A RISK FACTOR FOR THE DEVELOPMENT OF INFECTION

The growth of bacteria, viruses, parasites, helminths, and fungi are dependent on the availability of iron. Once transferrin saturation in the host exceeds a critical threshold, free iron becomes available for bacterial utilization [2]. The relationship between iron stores (as measured by serum iron biomarkers) and infection is complex, and currently under debate. However, iron administration alone does not appear to cause bacterial growth, and whether iron administration in infected patients or in those at high risk of infection results in an increased risk of infection, or the re-emergence of chronic infections, such as latent *M. tuberculosis,* remains controversial [22-24].

The administration of red blood cell transfusions adds exogenous iron, at a rate of 200–250 mg of iron per unit of red blood cells [25]. Not surprisingly, blood transfusions have been linked to excess iron and an increased risk of infections. Rachoin *et al.* [26] evaluated medical-surgical intensive care unit (ICU) patients who received packed red blood cell transfusions (N=609 of 2432 patients; 25%). Blood transfusion was an independent risk factor for infection, mortality, hospital and ICU length of stay. Infections caused by methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, and *Acinetobacter* occurred more often in transfused patients.

Although the protective carbohydrate shell of commercially available intravenous (IV) iron compounds (iron dextran, iron sucrose, sodium ferric gluconate, and ferumoxytol) is designed to prevent immediate dissolution of ferric iron, all IV iron products have the potential to release free, non-transferrin-bound iron (NTBI) into plasma, a physicochemical characteristic that appears to be directly related to transferrin levels (which tend to be lower in hemodialysis patients), transferrin saturation, molecular weight, and drug clearance by the reticuloendothelial system [27, 28]. Following administration of small (100 mg) IV doses of iron sucrose, NTBI was observed more commonly in the sera of hemodialysis patients whose baseline transferrin saturation was >30%; *in vitro* bacterial growth was significantly higher in sera containing NTBI [27]. Iron sucrose administration is associated with higher maximum serum NTBI concentrations compared to iron dextran, however, both compounds produce similar levels of reactive oxygen species (ROS) generation and cytokine activation that is more pronounced among end stage renal disease patients [29]. Bolus dosing may be more likely to produce higher NTBI concentrations, as compared to maintenance dosing, and it is associated with a higher risk of infection-related hospitalization [30].

The majority of data evaluating the safety of IV iron have been conducted in patients with chronic kidney disease (CKD) and in those undergoing hemodialysis, who may be vulnerable to infection due to iron-mediated impairment of the innate immune response, or due to dysregulated iron metabolism caused by CKD-mediated inflammation [30-32]. Conflicting results have been reported in several large cohort studies evaluating the association between IV iron administration and the risk of subsequent infections in CKD patients. Teehan *et al.* [33] found that in hemodialysis patients receiving IV iron, patients who are iron-replete (those with an iron saturation ≥20% and a ferritin level ≥100 ng/mL) are at significantly increased risk for bacteremia compared with patients having deficient iron stores.

Many clinicians favor withholding administration of iron (as iron formulations or as transfusions) in patients who are already infected, based upon the biologic plausibility that iron administration poses an increased risk of infection [34]. Indeed, limited animal studies have reported an increased risk of mortality with administration of IV iron during infection. For example, in a murine model of *E. coli* sepsis, administration of IV iron sucrose was associated with a mortality rate of nearly 60% when septic mice were administered iron, as compared to a mortality rate of 0% in mice with sepsis alone, or in those administered iron alone [1, 35].

However, in humans, currently available literature evaluating this practice have provided mixed results [34, 36-42]. In a recent Cochrane analysis of CKD patients who had received intravenous iron in the 14 days preceding their first hospitalization for bacterial infection, continued iron administration during hospitalization was not associated with an increase in 30 day mortality, length of hospital stay, or readmission for infection or death within 30 days of hospital discharge. However, among the subgroup of patients hospitalized

for septicemia or bacteremia, iron administration during hospitalization was associated with higher odds of readmission for infection [23].

Administration of iron is a double-edged sword: world-wide, anemia is a major cause of morbidity and mortality; however, dietary iron supplementation in areas with a high burden of infectious diseases risks increasing morbidity and mortality from infectious diseases, including invasive bacterial infections, gastrointestinal infections, tuberculosis and malaria [43, 44].

3.1. Malaria

In children and pregnant women living in areas of intense malaria transmission, iron deficiency decreases the risk of parasitemia, severe malaria, and malaria-associated mortality [45-47]. Controversy continues over the question of whether the benefits of iron supplementation in iron-deficient patients outweigh its potential risks. In particular, this is an important issue in children and pregnant women, in whom iron deficiency is common, and is linked to higher infant mortality [48, 49].

3.2. Protective Effect of Iron Deficiency and the Use of Iron Supplementation in Areas with a High Incidence of Malaria

3.2.1. Children

The epidemiology of the iron-malaria association in children has been studied since the early 1970s, with frequent associations of iron deficiency with a reduced risk of malaria. However, debate continues regarding the safety and efficacy of iron supplementation in this population [39, 48, 50-57]. In the early 2000s, the World Health Organization (WHO) recommended universal supplementation of young children living in areas where anemia rates are >40 %. It is also important to note that nearly all trials of iron supplementation have been conducted in conjunction with some form of malaria control (*e.g.* bed nets, malaria prophylaxis), and some trials took place in areas of lower malaria transmission [48, 58]. As a result, conflicting data have been reported regarding the potential adverse effects of iron supplementation on the incidence of malaria, sparking intense debate regarding the guidelines. In particular, the conflicting results of two large studies – one in Pemba, Tanzania [54], an area endemic for malaria, and the other [51] in Nepal, a non-endemic region – prompted new WHO guidelines recommending against universal supplementation in malaria endemic regions, and that iron be administered to iron-deficient children only when adequate anti-malaria treatment was available. The Tanzania study demonstrated an increased rate of hospitalizations and deaths in iron-supplemented children, prompting an early halt to the trial, while the Nepalese study demonstrated no net benefit or harm to supplementation in a non-endemic region [48, 51, 54]. Shortly thereafter, a 2006 Cochrane analysis concluded that overall, iron supplementation did not increase the risk of clinical malaria in children who were anemic or non-anemic at baseline, although an increased risk of malaria was observed in trials that did not provide malaria surveillance and treatment, and the risk of malaria parasitemia was higher with iron supplementation. They further concluded that iron supplementation may be safe when appropriate malaria surveillance and treatment were available [39]. However, the outcome measure utilized in the Cochrane analysis was based only upon the 'incidence of clinical malaria', rather than using pooled data which would have included 'severe malaria', de-emphasizing of the finding of the Tanzanian study that iron (with folic acid) supplementation resulted in a significant increase in the risk of cerebral malaria [39, 48, 51, 54]. In a recent randomized trial in an area where protection against malaria was provided by insecticide-treated bed nets, dietary iron supplementation did not result in a higher incidence of malaria [50]. In the most recent (2016) Cochrane review and meta-analysis of 35 trials (31,955 children) in anemic and non anemic children residing in areas with malaria concluded that overall, iron probably does not increase malaria. However, they conceded that in areas where methods to prevent or manage malaria (*e.g.*, bed nets, malaria prophylaxis) are lacking, the incidence of malaria may increase upon iron supplementation [56].

3.2.2. Pregnant Women

Pregnant women, like children, are among the populations in greatest need of iron supplementation while also being at greatest risk of malaria, and the WHO recommends universal supplementation of pregnant women [58, 59]. Iron supplementation reduces the risk of anemia by 70%, and the risk of low birth weight newborns [49]. Although some studies have reported that iron supplementation in pregnant women increases the risk of malaria, these effects are likely diminished by factors such as host immunity, host iron status, the strain of Plasmodium (*vivax vs. falciparum*) and effective malaria surveillance and control [46, 60]. A recent meta-analysis of 23 studies conducted in countries having some risk of malaria concluded that there is no evidence that iron supplementation increases placental

malaria. However, only 2 of the 23 studies reported malaria outcomes, and the authors qualified their findings by noting that there was a significantly increased risk of malaria associated with iron supplementation in areas without adequate malaria surveillance and adherence to treatment programs [49]. However, another meta-analysis reported that iron supplementation was associated with an increased risk of *Plasmodium vivax*, but that data were insufficient to determine whether there was an increased risk of *P. falciparum*; thus, it would be prudent to use malaria prevention measures when iron supplementation is given to pregnant women in malaria-endemic areas [61].

In summary, the interaction between iron level, iron supplementation and susceptibility to maternal and childhood malaria remains a concern, in particular in areas without adequate malaria surveillance and treatment programs [48, 58]. Several ongoing studies are currently comparing the risk of malaria in iron-supplemented versus non-supplemented pregnant women [58].

4. FE OVERLOAD AND THE RISK OF INFECTIONS

Patients with iron overload due to a genetic basis, or as a consequence of receiving multiple blood transfusions in the treatment of hemoglobinopathies or malignancy (*e.g.,* patients with hemochromatosis, thalassemia, and myelodysplastic syndromes), are at a higher risk for infections, as are humans with polymorphisms in NRAMP [34, 42, 62-65]. The growth of a number of pathogens in tissues or cells appears to be stimulated under conditions of excess iron, including *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Streptococcus pneumoniae, Salmonella typhi, Listeria, Yersinia,* fungi (*Candida*, *Cryptococcus, Histoplasma, Mucorales, Aspergillus*), viruses (Hepatitis B and C, cytomegalovirus, HIV), protozoa (*Plasmodium, Toxoplasma, Leishmania*) and mycobacteria [66, 67].

4.1. Thalassemia

Worldwide, thalassemia is associated with the highest morbidity and mortality related to metabolic iron disorders. The disease is found primarily in the Middle East, the Mediterranean, and in Southeast Asian countries; often, the economic burden of treating these patients is enormous and not available to all in need. The need for frequent blood transfusions in these patients often results in iron overload, and mortality from congestive heart failure due to cardiac iron overload [68]. Infections continue to be among the major causes of mortality, even in patients who are non transfusion dependent; the bacteria isolated most frequently include *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Streptococcus pneumoniae, Salmonella typhi, Yersinia enterocolitica* and other Gram-negative bacteria [65, 66, 69-73]. *Klebsiella* species are more common in Asian countries, while *Yersinia* is more commonly observed in western countries [69].

4.2. Hematopoietic Stem Cell and Liver Transplantation

Iron overload is common in patients undergoing hematopoietic stem cell transplantation (HSCT), and increased ferritin or bone marrow iron stores is an independent risk factor for invasive fungal infections, including those caused by *Aspergillus, Candida, Cryptococcus, Histoplasma, Paracoccidioides, Pneumocystis, Pythium, Rhizopus, Trichosporon*, and the Mucorales (*Rhizopus, Mucor, Absidia*) [25, 74-94]. Similarly, in patients undergoing liver transplantation, elevated serum iron and hepatic iron overload is associated with decreased long term survival, regardless of whether the patient had hereditary hemochromatosis [95-98].

4.3. Hemodialysis

Patients with chronic kidney disease are often anemic. While the treatment is generally to give erythropoiesis-stimulating agents, iron supplementation is often necessary in patients with iron deficiency anemia. However, patients risk becoming iron overloaded, which can increase mortality due to oxidative stress and an increased risk of infection [42]. Higher iron stores, as assessed by ferritin levels or iron saturation, are associated with an increased risk of infection in patients undergoing hemodialysis [62, 99] and serum ferritin > 500-1000 ng/dL is an independent risk factor for infection in hemodialysis patients [99].

5. NOVEL APPROACHES TO THE TREATMENT OF INFECTIONS: CAPITALIZING ON THE NEED FOR IRON BY PATHOGENS

5.1. The Role of Iron Chelators in Infectious Diseases

Given the associations between iron overload or iron administration (as siderophores, or as IV iron products), and infection, it is tempting to consider removal of iron by chelation as a useful adjunct for the treatment of infectious diseases. Interestingly, administration of the iron chelating agent deferoxamine predisposes patients to the development of infections caused by *Mucorales*, *Yersinia*, and *Vibrio vulnificus*.

Following an outbreak of *Mucor* infections in hemodialysis patients following administration of deferoxamine (a hydroxamate chelator), it was established that feroxamine (a deferoxamine-Fe chelate which structurally, is a hydroxamate siderophore) acts to deliver iron to the pathogen. After stripping ferric (Fe^{+3}) iron from transferrin, deferoxamine Fe is transported intracellularly by an active reduction of the ferric form into the more soluble ferrous (Fe^{+2}) form [100-102].

More recently developed hydroxypyridinone iron chelators such as deferiprone do not act as siderophores, leading investigators to theorize that these non-hydroxamate iron chelators might be effective as a means of reducing the availability of iron to pathogens during infections. Iron chelation therapy has been assessed in the treatment of tuberculosis, malaria, and infections caused by Mucorales species, including *Rhizopus* and *Mucor* [103-106]. *In vitro*, use of newer, non-siderophore chelators reduced the growth and virulence of *Mycobacterium avium*, *Yersinia enterocolitica, Vibrio vulnificus, Klebsiella pneumonia,* and *Aeromonas hydrophila* as compared to deferoxamine [107-110]. *In vitro*, the growth of erythrocytic *Plasmodium falciparum* is successfully inhibited by the addition of iron chelators; however, outcomes in animal and human studies of malaria, using deferoxamine and deferiprone, were less successful [53, 111]. More recently, in a murine model of infection caused by methicillin-resistant *S. aureus,* bacteremia was successfully treated with adjunctive iron chelation therapy [112].

As noted above, increased bone marrow iron stores in patients following HSCT are associated with a significantly increased risk for invasive mold infections, which are associated with high morbidity and mortality despite the use of antifungal therapy. The use of non-deferoxamine-based iron chelator-mediated reduction of iron overload was theorized to be beneficial in the treatment of mold infections in these patients. Based upon promising results from *in vitro* studies and case reports in humans, a randomized, double-blind, placebo-controlled trial of adjunctive deferasirox therapy for the treatment of *Mucor* infections was initiated. Unfortunately, the treatment was unsuccessful; imbalances in the study arms make the results of this study difficult to interpret [105, 113, 114].

5.2. Unmet Needs, Novel Therapeutic Strategies, and Future Applications

5.2.1. Defining Iron Status

The criteria used to define iron overload (or deficiency) vary considerably. While the majority of studies have utilized serum ferritin as a biomarker for iron status, others have evaluated the number of red blood cell transfusions, serum levels of ferritin or hepcidin, or staining of bone marrow iron [87, 115]. However, serum ferritin, which is utilized constitutively for iron storage, is an acute-phase protein whose levels are affected by liver disease, malignancy, infection, and inflammation. Newer diagnostic techniques, including the use of magnetic resonance imaging (MRI) may increase our understanding of iron metabolism and homeostasis, improve our ability to diagnose iron overload, and to improve the efficacy of chelation therapies [68].

5.2.2. Siderophore–Antibiotic Conjugates: the 'Trojan Horse' Strategy of Drug Delivery

The iron-siderophore acquisition system in pathogens has been exploited to develop siderophore-based siderophore-antibiotic conjugates which can act in a 'Trojan Horse' strategy to deliver antimicrobials *via* siderophore uptake by pathogens. The majority of antibacterial siderophore conjugates have utilized agents whose target sites of action are located in the pathogen's periplasm. For example, drug conjugates have been developed with beta-lactams, monobactams, and monocarbams, which affect bacterial penicillin-binding proteins in bacteria [116-119]. However, drug conjugates have also been developed with antifungal, antitubercular, and anti-malarial agents [7, 116, 120, 121].

Alternative strategies to inhibit the growth of pathogens include inhibition of siderophore biosynthesis, and the binding of siderophores to siderophore receptors on the microbial cell surface [122].

CONCLUSION

Iron is an essential micronutrient for bacteria, fungi, and humans; as such, they have evolved specialized iron uptake systems to acquire iron from the extracellular environment. A complex 'tug of war' has evolved between human hosts and pathogenic microorganisms in the battle for this vital nutrient. In humans, sequestration (hiding) of iron from invading pathogens is often successful; however, many pathogens have evolved mechanisms to circumvent this approach. Clinically, controversy continues whether the administration of iron for the treatment of anemia results in an increased risk of infection, or the re-emergence of chronic infection. The administration of iron chelating agents to infected hosts may proved useful as adjunctive therapy in the treatment of infections caused by pathogens dependent on host iron supply (*e.g.* tuberculosis, malaria, and many bacterial and fungal pathogens); however, thus far, studies in humans have proved unsuccessful.

Similarly, the use of siderophore-drug conjugates for the treatment of infections remains a potentially viable approach.

LIST OF ABBREVIATIONS

ABC = ATP-binding cassette

CKD = Chronic kidney disease

HSCT = Hematopoietic stem cell transplantation

ICU = Intensive care unit

IV = Intravenous

MRI = Magnetic resonance imaging

NGAL = Neutrophil gelatinase-associated lipocalin

NRAMP = Natural resistance-associated macrophage protein

NTBI = Non-transferrin-bound iron

ROS = Reactive oxygen species

SOD = Superoxide dismutase

WHO = World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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