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REVIEW

Association of hemochromatosis with infectious diseases: expanding spectrum

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Summary Withholding iron from potential pathogens is a host defense strategy. There is evidence that iron overload per se compromises the ability of phagocytes to kill microorganisms. Several hypotheses exist to explain the association of hemochromatosis with infection. A combination of mechanisms likely contributes to the increase in susceptibility to infection in these patients. A review of the current literature delineating various pathogens to which patients with hemochromatosis are potentially susceptible, and recent advances in the understanding of the association of hemochromatosis with infection, are discussed.
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Background

The association of hemochromatosis with certain organisms has been well described. Over the years, several mechanisms have been postulated to explain the association. However, with rapid advances in the understanding of hemochromatosis over the past two years, more data about the complex, iron-dependent host—pathogen interactions are now available. There is no single source in which the various infections seen in hemochromatosis, including viral infections, are described in relation to pathogenesis.

Methods

This review has been formulated after careful scrutiny of the medical literature for the period between 1940 and January 2007, and describes the various infections and the postulated mechanisms of this unique association.

Iron and host defense

A common factor in all infections is the ability of the invading pathogen to propagate in host tissue. Little is known about the alterations that occur in pathogenic bacteria as they adapt to the host environment and multiply in vivo. One of the most notable aspects of the host environment and its effects on bacterial growth concerns the availability of iron. Iron is absorbed in the duodenum by enterocytes and transferred to the plasma. There it is bound by the high-affinity iron-binding glycoproteins — transferrin and structurally related protein lactoferrin.

Liver parenchymal tissue is especially rich in transferrin receptors and stores large quantities of iron. In muscle tissue, iron is used to make myoglobin, and in bone marrow, erythrocytes use it to make hemoglobin. Circulating red blood

cells normally comprise the largest iron storage pool. When they become senescent, red blood cells are engulfed by reticuloendothelial macrophages, which make their iron available for redistribution to other tissues via transferrin. Transferrin has extremely high affinity for iron. This coupled with the fact that two-thirds of the iron binding sites of the protein are normally unoccupied, essentially eliminates free iron from plasma and extracellular tissues. Although there is an abundance of iron present in body fluids, the amount of free iron is very small to sustain bacterial growth.[1] In addition, during infections the host reduces the total amount of iron bound to serum transferrin.[2] Withholding iron from potential pathogens is an important host defense strategy. Moreover both transferrin and lactoferrin are bacteriostatic in vitro for a number of bacteria. Lactoferrin is a prominent component of the granules of polymorphonuclear leukocytes. The protein is released at high concentrations by the cells in areas of infection. However, despite these host mechanisms, pathogenic bacteria manage to multiply successfully in vivo to establish an infection. In contrast, a state of iron excess in hereditary hemochromatosis has different implications, since it involves preferential iron loading of the parenchymal cells and not the reticuloendothelial system, which in turn hinders the growth of many intracellular organisms including *Mycobacterium tuberculosis*, *Salmonella typhi*, and *Chlamydia pneumoniae*.[3,4]

Acquisition of iron by microorganisms

To obtain host iron, successful pathogens with a few exceptions, use one or more of the following strategies to adapt to the iron-restricted environment:[1] (1) proteolytic cleavage of iron-binding glycoprotein, releasing iron; (2) reduction of Fe^{+++} complex to Fe^{++} complex and release of Fe^{++} from the glycoprotein through interaction between receptors on the bacterial cell surface and the Fe^{+++} glycoprotein complex, in a manner analogous to the reaction between transferrin and erythrocyte; or (3) by producing low molecular weight iron-chelating compounds known as siderophores, which are able to remove iron from Fe^{+++} glycoprotein complex and deliver it to the bacterial cell.

The list of infectious disease agents whose virulence is enhanced by iron continues to increase (Table 1).[5] These pathogens include bacteria (Gram-negative and Gram-positive), fungi, and viruses.

Escherichia coli has been extensively studied and found to have the ability to obtain iron via siderophores. *E. coli* specifically is known to secrete enterobactin under conditions of iron restriction.[6,7] Similarly Vibrio has the ability to acquire iron from its host by the production of siderophores and by degradation of heme-containing compounds by proteolytic enzymes.[6,8–11] In contrast, Yersinia species are not able to produce their own siderophores, but possess receptors for iron—siderophore complexes on their surface, which enable them to utilize siderophores synthesized by other bacteria.[12,13] Therefore when patients with iron overload are treated with chelating agents like deferoxamine (a siderophore produced by *Streptomyces pilosus*), Yersinia may use this exogenous siderophore to acquire iron.[14] *Listeria monocytogenes* as a pathogen requires iron for growth within phagocytic cells and virulence expression.[15] Weakened cell-mediated immunity from iron overload[16] is also likely linked to the increased virulence of *L. monocytogenes* in patients with hemochromatosis. Various studies, including experimental studies in mice, have suggested that excess iron may enhance the growth of *M. tuberculosis* and worsen the outcome of human tuberculosis.[17] The association of *Tropheryma whippelii* with iron overload states has also been described.[18] *Plesiomonas shigelloides* has been shown to produce a beta-hemolysin, which is thought to play a role in iron acquisition in vivo via the lysis of erythrocytes.[19] *Gemella haemolysans*, which is a member of the genus Gemella, previously included under Neisseria species, may hypothetically, like certain isolates of Neisseria, use hemin or hemoglobin as an iron source,[20] or produce siderophores.[21]

Data on the ability of fungal pathogens to sequester iron in vivo are not as well described and neither is this aspect well researched. From what we do know, Rhizopus species have been recognized in patients who have undergone treatment of iron overload with deferoxamine,[22] and iron overload in the absence of deferoxamine therapy has also been linked with zygomycosis.[23] Interestingly diabetic ketoacidosis and zygomycosis have been associated with iron metabolism; acidosis may lead to decreased binding of iron by transferrin and hence release of iron to be used by Rhizopus species.[24] Hissen et al. have recently shown that *Aspergillus fumigatus* survival in human serum in vitro involves proteolytic degradation and siderophore-mediated removal of iron from transferrin.[25]

Evidence confirming the persistence and resistance to treatment of viral hepatitis in the presence of excess iron is rapidly mounting.[26] It is now apparent that excess iron enhances fibrogenic pathways and may act as a co-carcinogen or promoter of hepatocellular carcinoma, may worsen the clinical course of HCV infection by causing oxidant stress in nonparenchymal cells, and lead to the irreversible

Table 1	Organisms whose growth in body fluids, cells, tissues, and intact vertebrate hosts is known to be stimulated by excess iron
Fungi	Candida, Cryptococcus, Histoplasma, Paracoccidioides, Rhizopus, Trichosporon, Aspergillus, Pneumocystis
Protozoa	Entamoeba, Leishmania, Naegleria, Plasmodium, Toxoplasma, Trypanosoma
Gram-positive and acid-fast bacteria	Bacillus, clostridia, corynebacteria, Erysipelothrix, Listeria, mycobacteria, staphylococci, streptococci, Gemella
Gram-negative bacteria	Acinetobacter, Aeromonas, Alcaligenes, Capnocytophaga, Campylobacter, Chlamydia, Ehrlichia, Enterobacter, Escherichia, Klebsiella, Legionella, Moraxella, Neisseria, Pasteurella, Proteus, Pseudomonas, Plesiomonas, Shigella, Vibrio, Yersinia
Viruses	Hepatitis B and C, cytomegalovirus, parvovirus, HIV

Modified, with permission, from Weinberg ED. Iron loading and disease surveillance. *Emerg Infect Dis* 1999;**5**:346–52.

mitochondrial derangement associated with the onset of hepatic fibrosis.[27,28] Human cytomegalovirus protein US2 interferes with the expression of the hemochromatosis gene, *HFE*.[29] An increase in the cellular iron pool by downregulating HFE expression may promote the persistence of viruses in general. It has also been shown that excess iron decreases the viability of HIV-infected cells, increases p24 levels, and elevates the activity of reverse transcriptase, indicating that iron overload associated with HIV infection is detrimental to host cell responses against viral infection.[30] Blumberg et al. were the pioneers in describing a role for iron in the modulation of hepatitis B virus. They found that patients with higher levels of serum iron or ferritin were less likely to achieve spontaneous recovery after acute HBV infection.[31]

Hemochromatosis

Hemochromatosis exists both in primary and secondary forms. Primary or hereditary hemochromatosis (HH) is the most common inherited disease in Caucasians. It results from inheritance of an abnormal gene at a locus on the short arm of chromosome 6 near the HLA locus (6p21). There is increased absorption of iron across the gastrointestinal tract, which leads to absorption of 3—4 mg/day of iron as opposed to 1—2 mg/day in normal individuals. The gene (*HFE*) is a class I major histocompatibility complex (MHC) molecule that is mutated in hereditary hemochromatosis. Patients who have a chronic hematologic condition requiring multiple transfusions of red blood cells develop a secondary form of hemochromatosis.[3,11,31—33]

Hemochromatosis and infections

A review of medical literature on Medline for the period January 1940 to January 2007, confirms McClatchie et al. as being some of the first authors to describe the association of sudden release of ferritin, previously shown to be a vasodepressor substance,[34] into the circulation and shock in a patient with hemochromatosis.[35] Jones suggested a possible link between infection and shock in hemochromatosis as one patient was found to have *E. coli* bacteremia.[36] Since that time there have been numerous reports of patients with hemochromatosis having increased susceptibility to infections.

Various infections caused by organisms including *Vibrio vulnificus*,[8,37] non-01 *Vibrio cholerae*,[38] *E. coli*,[36,39,40] *Yersinia enterocolitica*[13,41—43] and *pseudotuberculosis*,[44] *L. monocytogenes*,[45,46] *P. shigelloides*,[47] *G. haemolysans*,[48] cytomegalovirus,[49] hepatitis B,[50] C,[51] and G virus,[52] and HIV[53] have been reported in association with hemochromatosis. Fungi including *A. fumigatus*[54] and Rhizopus species[23,55] have also been described (Table 2). There is an article in German that describes parvovirus in association with hemochromatosis.[56]

A multitude of problems likely contribute to the increased susceptibility to infection in these patients. The very high transferrin saturations attained in patients with iron overload states compromise bacteriostatic properties. In the presence of excessive iron, pathogens can much more readily procure iron from molecules of transferrin. In such cases, even microbial strains that are not ordinarily virulent can cause

illness. In addition, iron overload compromises the ability of phagocytic cells. Excess iron decreases chemotactic response and enhances the ability of ingested microorganisms to proliferate within the polymorphonuclear leukocytes (PMN) by lowering bactericidal capacity.[57,58] The toxicity of iron for neutrophils may be due to the formation of excess oxygen radicals, which alter phagocytosis through peroxidation of neutrophil membrane lipids.[59]

Iron is a central regulator of immune cell proliferation and function. All lymphocyte subsets, including B and T lymphocytes and natural killer (NK) cells, depend on iron uptake, the blockade of which leads to diminished proliferation and differentiation of these cells. It is well established that three subsets of CD4+ T-helper cells exist in man, i.e., Th1, Th2 and Th3, each of which produces a set of cytokines involved in immune regulation; for example, Th1 cytokines such as interferon-γ (IFN-γ) or tumor necrosis factor-β (TNF-β) activate macrophages and contribute to the formation of pro-inflammatory cytokines —TNF-α, interleukin (IL)-1 or IL-6 — and the induction of the cytotoxic immune effector mechanism of macrophages. Iron loading of macrophages results in the inhibition of IFN-γ-mediated pathways and hence they lose their ability to kill intracellular pathogens, e.g., Legionella, Listeria, Ehrlichia. This can partly be attributed to diminished production of nitric oxide (NO) in the presence of iron.[5,16,60]

Hepcidin is a recently described cysteine-rich cationic antimicrobial peptide secreted by the liver, with broad antibacterial and antifungal actions,[61,62] and is central to regulation of iron metabolism corresponding to the body's iron levels, i.e., increasing as they increase, e.g., in hemochromatosis, and vice versa. Specifically hepcidin levels rise with infection or inflammation and fall with hypoxia or anemia.[63] Decreased hepcidin leads to tissue iron overload, whereas hepcidin overproduction leads to hypoferremia. In addition to disrupting bacterial membranes, hepcidin provides an inhospitable internal milieu for microbes that successfully enter the bloodstream.[64,65] It has recently been demonstrated that inadequate expression of hepcidin in patients with liver disease and functional impairment due to high iron concentrations, may be associated with the increased susceptibility for infections in these patients.[66] There is evidence linking HFE with reduced iron uptake by the transferrin receptor (TfR).

It is generally accepted that iron increases the formation of hydroxyl radicals and other highly reactive oxidizing molecules in biological systems. Experimental iron overload in the rat model has been linked to lipid peroxidation in mitochondria and microsomes, with deleterious effects on the electron transport chain. Data suggest that iron causes or enhances the hepatotoxicity and hepatocarcinogenecity caused by chronic viral hepatitis.[67] Enhanced hepatitis C virus replication with iron overload has also been demonstrated.[68,69] Recent studies have indicated that, among patients with chronic hepatitis C, there is an increased prevalence of the C282Y mutation, the major mutation of the *HFE* associated with hereditary hemochromatosis.[26,67,70—72] This is responsible for downregulation of the HFE expression and increasing the cellular iron pool. A similar link between C282Y mutation and hepatitis B has also been suggested by Sendi et al.[50] Further confirmation of these results is ongoing.

Table 2 Various organisms and associated clinical diagnoses in patients with hemochromatosis

Organism	Clinical scenario/infection [reference]	Course/outcome
Plesiomonas shigelloides	Septicemia [47]	Twelve weeks of ofloxacin therapy instituted due to intolerance to other antimicrobials
Gemella haemolysans	Endocarditis [48]	Two weeks of penicillin G/tobramycin with sterilization of blood cultures
Escherichia coli	Septic shock [36,39,40]	Death after 24 hours of onset, despite inotropic support
	Meningitis [40]	Meningitis responded to a 3 week/5 day course of IV/IT moxalactam and gentamicin, respectively
Listeria monocytogenes	Meningitis/endocarditis and pericarditis [45]	Death
Vibrio vulnificus	Fever, emesis diarrhea with shock. There was history of ingestion of raw oysters [37]	Death 7 hours after admission, despite aggressive medical support
Non-O1 *Vibrio cholerae* (NOVC)	Painful edema/erythema left leg with bacteremia [38]	Forty-five day therapy with oral doxycycline until resolution of cellulitis
Yersinia pseudotuberculosis	Bacteremia with aldosterone deficiency [44]	Multiple antimicrobials including erythromycin
Yersinia enterocolitica	Septic yersinosis [14]	Oral ciprofloxacin 750 mg bid for 6 months
	Liver abscess [13,41,43]	Oral ciprofloxacin 500 mg every 8 hours for 23 days
	Peritonitis [42]	Oral doxycycline 400 mg every day for 8 weeks
	Skin infection [43]	Oral trimethoprim—sulfamethoxazole for 2 weeks after initial 9-day course of IV chloramphenicol in case 1. Oral doxycycline for 7 weeks in case 2. Oral trimethoprim—sulfamethoxazole for 6 weeks
Mucor species, including	Periorbital cellulitis [23]	Patient in case with '*Mucor spp*' underwent right orbital exenteration. On postoperative day 5, patient expired after a hemorrhagic stroke
Cunninghamella bertholletiae	Rhinocerebral mucormycosis [55]	Patient died
Aspergillus fumigatus	Peritonitis in patient who underwent orthotopic liver transplant [54]	Death secondary to liver failure
Hepatitis B, C and G	HBV carrier [50]	Severity of chronic hepatitis is linked with degree of iron deposition. Patients with chronic HBV and HCV have greater prevalence of C282Y and C2824 hemochromatosis gene mutations, respectively.
	Chronic HCV [51]	High prevalence of hepatitis G found
	Cryptogenic hepatitis [52]	virus in hemochromatosis
Cytomegalovirus (CMV)	Intrauterine CMV infection; inclusions in hepatocytes, biliary epithelial cells, renal tubular epithelium. Concomitant intracellular iron seen in viscera [49]	1500 g cyanotic neonate died 1.5 hours after birth
Parvovirus	Refractory anemia [56]	69-year-old woman with hemochromatosis and myelodysplastic syndrome

Conclusions

The retrieval of iron is essential to bacterial survival and represents a factor for which both host and pathogen compete. Conditions including hemochromatosis, in which the level of iron in serum is increased, compromise host defenses and increase predisposition to various bacterial and non-bacterial infectious diseases. This excess iron burden does not only help the propagation of pathogens, but also plays a sentinel role in modifying the host immune mechanism, specifically by impairment of cell-mediated immune responses. Hepcidin has recently emerged as an important bridge between innate immunity and iron metabolism and is thought to be responsible for augmentation of the host

response to pathogens. Functional impairment of hepcidin due to high iron concentrations has therefore been associated with the increased susceptibility for infections in these patients. It must be noted that most of the cases reported in this review are based on case reports, but nonetheless may be helpful to physicians in expanding differential diagnoses when faced with similar situations.

Often the diagnosis of hemochromatosis in these patients is an incidental finding and physicians should therefore consider evaluation for the diagnosis of hemochromatosis when faced with infections caused by certain organisms as described. Alternatively clinicians should consider various pathogens in patients with hemochromatosis who present with a febrile illness. Modulation of iron metabolism, including use of recombinant hepcidin in patients with hemochromatosis and infectious diseases, is an area that warrants further research.

Conflict of interest: No conflict of interest to declare.

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