Editorial Response: Iron and Infection

In this issue, Adamkiewicz and colleagues [1] review the experience with *Yersinia enterocolitica* infection in Canadian patients with β-thalassemia, seen in two large centers in the provinces of Quebec and Ontario over a 15-year period. The estimated annual incidence of severe yersiniosis was 0.6 per 100 patient-years, which they estimate was 5,000-fold greater than in the general population. All patients were receiving transfusions, and most were being treated with the iron chelator deferoxamine; many were splenectomized. The majority of infections were systemic, unlike *Y. enterocolitica* infections in healthy hosts, in whom gastrointestinal syndromes are most common. Serotype 3, the most common serotype in Canada, was responsible for all infections.

This report extends the growing literature related to the dangers of yersiniosis in patients with homozygous thalassemia and raises several questions. Is the association between thalassemia and yersiniosis due to iron-overloading, or were the infections the result of transfusion by contaminated blood? Are thalassemic patients at risk of infection by other bacteria as well? If the risk is specific to *Y. enterocolitica*, is there a plausible explanation? Why does iron-overloading apparently predispose patients with other types of illness other than thalassemia to increased risk of bacterial infection?

The answers to these questions are not entirely clear. The authors speculate that the blood products were not contaminated, because the latent period between transfusion and onset of symptoms often was relatively long (10 days). Blood products used were not available for culture, so a definitive answer is not possible. *Yersinia* is capable of surviving in blood under conditions of cold storage, but it seems unlikely that contaminated blood was responsible for the majority of the infections.

Patients with β-thalassemia often are iron-overloaded because of their need for frequent transfusions. It has been known for years that increased availability of host iron increases virulence of many bacterial species, including various pathogenic *Yersinia* species, certain pathogenic vibrios, some mycobacteria, and other organisms. Because iron-overloading causes damage to multiple organs, due to increased iron-dependent oxidative reactions, patients with β-thalassemia often are treated with iron-chelating agents to help control the level of their iron stores.

The most commonly used iron-chelating agent in practice has been deferoxamine, a trihydroxamate siderophore that is not produced by *Y. enterocolitica* but can be used by this organism as a source of iron. This may help to explain the strong association between β-thalassemia and yersiniosis, although some other bacteria also are capable of using deferoxamine as an iron source.

As is often the case, however, diminished host resistance also may play a role. Transfusion led to partial blockade of the reticuloendothelial system by lysed red cells, diminishing effective phagocytic clearance and increasing relative virulence of many organisms in experimental models of infection. Absence of a spleen, as in many of the β-thalassemic patients, would further increase the risk of invasive systemic infection, as it did for the majority of subjects in the report of Adamkiewicz et al.

Why does increased availability of iron increase bacterial virulence? The general answer is that nearly all bacteria require iron for a variety of metabolic purposes, and gaining access to soluble utilizable iron can be problematic. Ferric iron is highly insoluble. Higher eukaryotes solve this dilemma by solubilizing iron-carrier proteins such as transferrin, which delivers iron to cells that express an iron-regulated transferrin receptor. Bacteria compete for iron in vivo through a variety of mechanisms, including expression of iron-regulated systems for secreted iron chelators (siderophores) and outer-membrane siderophore receptors, or by producing receptors for directly binding host iron proteins such as lactoferrin, transferrin, hemoglobin, or heme-albumin/heme-hemopoxin complexes. Many bacteria also can utilize free heme.

Most bacteria seem to have multiple, apparently redundant systems for scavenging iron. Presumably, the multiplicity of systems enables pathogens to obtain iron in various body compartments or niches, which may vary in availability of different types of iron. Mutation of one or more of the bacterial iron-scavenging systems may reduce virulence, which can in turn be restored by increasing iron availability in the host animal.

*Yersinia* species are no exception. *Y. enterocolitica* produces at least one siderophore/receptor system (*yersiniabactin*) and can use other siderophores such as deferoxamine. *Yersinia* species also can utilize heme, and *Yersinia pestis* utilizes a particular heme-uptake system designated *hms* to store heme on the bacterial cell surface, which is essential to transmission of the bacterium from infected fleas to host animals [2].

There is no convincing single explanation for why increased iron stores in β-thalassemic patients lead to increased rates of
source infections by *Y. enterocolitica*. Many factors may be involved. For clinicians, the association is worth noting, in addition to other, perhaps better-known associations such as liver disease, iron overloading, and *Vibrio vulnificus* or *Vibrio parahaemolyticus* susceptibility [3].

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References