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# A Case of *Yersinia Enterocolitica* Sepsis in a Beta Thalassemia Patient on Deferasirox

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## Abstract

We report a case of *Yersinia enterocolitica* sepsis in a 23 year old woman with transfusion-dependent beta-thalassemia major and iron overload treated with deferasirox. Although yersiniosis is a recognized complication of iron overload syndromes treated with desferrioxamine, Y. *enterocolitica* sepsis has not previously been reported in association with deferasirox. This case underscores the importance of considering iron-avid organisms as potential pathogens and initiating appropriate broad empiric antimicrobial coverage as well as discontinuing chelating agents in iron-overloaded patients. Given the current paucity of evidence and lack of consensus regarding appropriate antibiotic regimens for Yersinia sepsis, which we review briefly, we highlight the importance of consulting an Infectious Diseases specialist early in the course of illness.

**Keywords:** Yersinia; Thalassemia; Deferasirox; Desferrioxamine; Iron overload

**Abbreviations:** *Y. enterocolitica*: *Yersinia Enterolitica*; *V. vulnificus*: *Vibrio Vulnificus*; *K. pneumonia*: *Klebsiella Pneumoniae*

## Introduction

Thalassemias are a geographically widespread group of genetic hemoglobinopathies characterized by defective globin production and hemolytic anemia [1]. Thalassemic patients are frequently transfusion-dependent and this, in addition to heightened gastrointestinal avidity for iron, creates a propensity for iron overload [1]. Infection is a major cause of morbidity in thalassemic patients and is second only to hemosiderin cardiomyopathy as a cause of mortality [1]. Transfusion predisposes patients to infection, both directly as a consequence of horizontal transmission of bloodborne infection from donor to recipient, and as a result of iron overload itself which is an independent risk factor for infection [1,2]. Specifically, iron overload confers susceptibility to *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Klebsiella* spp., *Escherichia coli*, *Streptococcus pneumoniae*, *Vibrio vulnificus*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, and *Legionella pneumophila* [1,3]. Desferrioxamine has long been administered parenterally as an iron chelating agent to patients with iron overload, however, it adds to the risk of infection by *Y. enterocolitica* [1]. This is because although Y. *enterocolitica* lacks high-affinity iron chelating siderophores to allow it to take up iron from the environment in typical hosts, it is able to bind desferrioxamine and utilize it to achieve more efficient iron uptake [1,4]. Consequently, there are multiple case reports in the literature of serious Y. *enterocolitica* infections in thalassemic patients treated with desferrioxamine [4-8]. Deferasirox is a newer iron chelating agent which is administered orally. This mode of administration has led to increasing use of deferasirox in place of desferrioxamine to mitigate iron overload. In vitro comparative studies with *Klebsiella pneumoniae* and V.*vulnificus*, both organisms whose growth is augmented by high-iron environments, demonstrated enhanced pathogen growth with desferrioxamine, but not with deferasirox [3,9]. Although no such studies were performed with Y. *enterocolitica*, it would have been thought that similar findings could have been found with this similar iron-avid organism. Furthermore, to our knowledge, there are as yet no documented cases of *Yersinia* sepsis in a thalassemic patient treated with deferasirox.

## Case Presentation

A 23-year-old woman with a history of transfusion-dependent beta-thalassemia major and chronic iron overload treated with daily oral deferasirox presented to an outpatient clinic. She complained of a two-day history of worsening lower abdominal pain, nausea, vomiting, and mild non-bloody watery diarrhea without mucus. She also reported subjective undocumented fever, diffuse myalgias, and malaise. She had experienced no symptomatic relief from standard dosing of over-the-counter ibuprofen q6h prn for three days. She was prescribed a three-day course of clarithromycin 500 mg po BID. The next day, as she was deteriorating clinically with worsening symptoms including increasing abdominal pain and increasing stool frequency, she presented to our emergency room. There was no recent or remote travel history, no animal contacts, no significant occupational exposures, no hazardous food exposure such as undercooked pork or pork products, and no recent antibiotics prior to the clarithromycin. Her most recent blood transfusion was eleven days prior to the onset of symptoms. Her only sick contact was her brother, who had a resolving upper respiratory tract infection. She was sexually active but in a monogamous relationship. Past medical history, other than her beta-thalassemia treated with washed packed red blood cells every three weeks through an implanted vascular access device, was significant only for chronic thrombocytopenia and leukocytopenia secondary to hypersplenism, and asthma treated with inhaled budesonide and salbutamol.

On presentation, she was found to have a temperature as high as 38.7°C, a blood pressure that dropped to 91/62 mm Hg and to be quite tachycardic with a heart rate of 154 beats per minute. Physical examination was significant only for diffuse abdominal tenderness and splenomegaly. Creatinine at presentation was 237 umol/L, a marked increase from a known baseline creatinine of 53 umol/L twelve days previously. In addition, initial laboratory investigations were significant for an elevated bilirubin (38 umol/L) and lactate dehydrogenase (260

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U/L), a normocytic anemia (hemoglobin 99 g/L), a leukopenia (2.9 × $10^9$/L), a thrombocytopenia (86 × $10^9$/L), and a peripheral blood smear that revealed no schistocytes. Urine beta-HCG was negative, but urinalysis revealed hematuria and 2.5 grams of proteinuria. Peripheral blood cultures were drawn, and urine was sent for culture. Posterior-anterior and lateral plain films of the chest and abdominal ultrasound were within normal limits. The patient was admitted to the Nephrology service because of acute kidney injury and started on piperacillin-tazobactam for presumed sepsis.

Because of persistent hypotension and tachycardia as well as worsening anemia, the patient received aggressive fluid resuscitation as well as multiple units of washed packed red blood cells. In consultation with hematology, iron chelation therapy was held given the increased risk of severe infection in the context of iron overload as well as the well-known association with renal dysfunction [10]. On the second day of hospital admission, blood cultures drawn at initial presentation grew Y. *enterocolitica*. All subsequent blood cultures were negative, as were stool studies.

On day three, in consultation with Infectious Diseases, oral ciprofloxacin was added for recurrent fever, persistent diarrhea and persistent abdominal pain despite piperacillin-tazobactam (in case the organism was resistant to piperacillin-tazobactam). On the fourth day of hospital admission, piperacillin-tazobactam and ciprofloxacin were discontinued and ceftriaxone was initiated as sensitivities of the positive blood cultures came back as resistant to ampicillin, but susceptible to piperacillin-tazobactam, ciprofloxacin, gentamicin, ceftriaxone, and trimethoprim-sulfamethoxazole. Infectious disease preferred to narrow down the spectrum of antibiotic therapy but also wanted to keep the patient on intravenous therapy as she was still febrile.

Once the patient became afebrile and hemodynamically stable for 48 hours, ceftriaxone was discontinued and oral ciprofloxacin was restarted and continued to complete a twenty-one day course of antibiotic therapy. At the time of discharge, seven days after admission, the patient`s diarrhea and abdominal pain had resolved and her creatinine had normalized. For her ongoing hematuria and proteinuria, she was referred to an outpatient nephrology clinic for follow up.

## Discussion

This case highlights a number of key points in the management of febrile thalassemic patients. Considering the possibility of systemic yersiniosis in these patients is critical, as is stopping iron chelation therapy as soon as the diagnosis is suspected. The occurrence of *Y. enterocolitica* bacteremia in a patient treated with deferasirox (as opposed to desferrioxamine) has not been previously documented to our knowledge and suggests that oral chelation therapy, like parenteral therapy, may predispose thalassemic patients to serious *Yersinia* infection. This is especially interesting given two in vitro studies we found which did not demonstrate growth enhancement with oral iron chelators (in contrast to intravenous or subcutaneous forms) in two other iron-avid organisms, *K. pneumoniae* and *V. vulnificus* [3,9]. While a causative relationship between deferasirox and *Y. enterocolitica* sepsis cannot be definitively inferred given the known association between chronic iron overload and *Yersinia* infection, this case raises the possibility that deferasirox, like desferrioxamine, may be associated with an increased risk of *Yersinia* sepsis.

*Y. enterocolitica* can survive at 4°C in stored blood and be transmitted horizontally via blood transfusion [2]. In thalassemic patients who become febrile or hypotensive during or shortly after blood transfusion, transmission of bloodborne infection including *Y. enterocolitica* should be considered in the differential diagnosis for transfusion reaction, and patients should be monitored closely for this. In this particular case, the patient had received her last blood transfusion eleven days prior to presentation and therefore oral inoculation via food or water is the most likely route of infection.

Another interesting point illustrated by this case is the variety of antimicrobial regimens that can be used in serious *Y. enterocolitica* infections and the lack of consensus on treatment given the paucity of primary literature on this topic. The best evidence on treatment we could find was a 1993 retrospective review of antibiotic therapy which only analyzed 43 cases of *Y. enterocolitica* sepsis and revealed 75% success of ceftriaxone in isolation, and 100% success of regimens which included fluoroquinolones [10,11]. We found no evidence addressing the efficacy of piperacillin-tazobactam in *Yersinia* sepsis, however the pathogen in this case was piperacillin-tazobactam sensitive. Covering *Yersinia* infection in thalassemic patients who present with fever or other signs of systemic inflammation in the absence of an identifiable source is prudent given the heightened risk of serious morbidity and mortality in this patient population.

## Conclusion

In conclusion, we must reiterate the importance of considering iron-avid organisms as possible pathogens in transfusion dependent patients on iron chelators presenting with a septic picture. We suggest that, as with all cases of sepsis, these patients be resuscitated aggressively and started empirically on broad-spectrum antibiotics. Consulting an Infectious Diseases specialist should be considered early in the course of illness given the lack of consensus on the appropriate antimicrobial regimen and the various possible pathogens in this patient population.

Furthermore, we believe our case raises the possibility that oral deferasirox, like the parenteral iron chelator desferrioxamine, might confer an increased risk for infections with iron-avid organisms such as *Y. enterolitica*. Ongoing research and additional case reports will be necessary to further elucidate this possibility.

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