CLINICAL ARTICLES

Infection Due to *Yersinia enterocolitica* in a Series of Patients with β-Thalassemia: Incidence and Predisposing Factors

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Over 15 years, 14 patients with yersiniosis in two North American comprehensive thalassemia clinics (0.6 cases per 100 patient-years) presented with fever (100%), diarrhea (86%), right-lower-quadrant abdominal pain (71%), bacteremia (57%), a palpable abdominal mass (36%), and pharyngitis (28%). Clinically apparent infection occurred within 10 days of blood transfusion in 57% of patients. Nine patients (64%) had only a modest elevation in serum level of ferritin (<2,000 μg/L). Patients with focal abdominal findings had a higher body iron burden, as estimated by the serum ferritin level, and significant intraabdominal suppurative complications. Two patients were not receiving iron-chelating therapy with deferoxamine; one patient was receiving the experimental chelator deferiprone (L1). Iron-loaded patients with β-thalassemia are at greatly increased risk for severe yersiniosis, even when their body iron burden (as indicated by the serum ferritin level) is only moderately elevated and they are not receiving iron-chelating therapy with deferoxamine.

Both increased amounts of body iron and the availability of a siderophore from another microbe—such as the iron-chelating agent deferoxamine, a siderophore elaborated by *Streptomyces pilosus*—can be exploited for the growth of *Yersinia* [1]. Since the first description of invasive *Yersinia enterocolitica* infection in two children with β-thalassemia in 1970 [2, 3], reports of this complication in more than 80 thalassemic patients have been published [4–51]. Nonetheless, limited information is available on the incidence and spectrum of presentation of *Y. enterocolitica* infections in patients with β-thalassemia. We examined the incidence and clinical presentation of *Y. enterocolitica* infection in a large cohort of patients over a 15-year period and reviewed the literature reporting this complication of iron overload in other patients with β-thalassemia.

Patients and Methods

The case records of 177 patients with β-thalassemia diagnosed between 1979 and 1994 in two programs of comprehensive care for thalassemia in Canada (at The Hospital for Sick Children [Toronto, Ontario] and The Montreal Children's Hospital [Montreal, Quebec]) were retrospectively reviewed for infection with *Y. enterocolitica.* Patient-years of observation were calculated as the sum of the years of medical history available during this time period. In parallel, the number of *Y. enterocolitica* isolations from the population of Ontario (Canada's most populous province; population, 10 million) during a period of active surveillance (1981–1991) by the National (Canadian) Center for Yersinia, the reference laboratory for Ontario, was noted, thereby providing an estimate of infection rates in the general population.

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The clinical presentation, investigation, and treatment of all thalassemic patients developing this complication were reviewed. The severity of iron loading was estimated by determination of the concentration of serum ferritin; values provided are those obtained closest to the onset of infection, during a period when the patient was clinically well.

For the purpose of this analysis, invasive disease with *Y. enterocolitica* was defined by a positive culture of a specimen from a nonenteric site, such as blood or a surgical sample.

Results

Incidence of infection and characteristics of patients. Of 177 patients with severe β-thalassemia during a 15-year period (total patient-years, 2,183), 14 patients (8%, a frequency of 0.6

Received 29 September 1997; revised 7 April 1998.

Presented in part at the 36th Annual Meeting of the American Society of Hematology, held in Nashville, Tennessee, in 1994.

Financial support: The Medical Research Council of Canada, The Ontario Thalassemia Foundation, The Cooley's Anemia Foundation of America (fellowship award to Dr. Berkovitch), and the Dr. John Crookston Award of the Canadian Haematology Society to Dr. Adamkiewicz. Dr. Olivieri is a scientist of The Medical Research Council of Canada.

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Clinical Infectious Diseases 1998; 27:1362–6

1058–4838/98/2706–0003$03.00

infections per 100 patient-years) had infection with *Y. enterocolitica.* Of these 14 patients, nine had invasive disease (frequency, 0.4 per 100 patient-years). Twelve patients were homozygous or compound-heterozygous for β-thalassemia; one patient had double-heterozygosity for β-thalassemia and hemoglobin Lepore, and another for β-thalassemia and hemoglobin E. All patients were receiving transfusions at the time of yersinia infection. Seven patients were splenectomized. As indicated by the serum ferritin concentration at diagnosis of yersinia infection (mean ± SD, 2,207 ± 1,362 μg/L), most patients were moderately iron-loaded.

All but two patients were taking nightly subcutaneous deferoxamine at the time of diagnosis of infection. One patient (number 4) had begun therapy with the iron-chelating agent deferiprone (L1) 3 months prior to diagnosis of infection; this patient was also receiving prednisone for associated autoimmune hemolytic anemia. One patient (number 14) was intermittently transfused. One patient (number 8) was receiving transfusions but was not treated with iron-chelating therapy; this patient underwent splenectomy 6 months following infection with *Yersinia* and subsequently has been transfusion-free for >14 years. All patients were negative for antibody to HIV.

Clinical presentation. The mean (±SD) age at diagnosis of yersinia infection in thalassemic patients was 13 (±5) years. Diagnosis followed a prodromal illness of variable duration (5 ± 4 days; range, 1–10 days). Eight of the 14 patients were admitted 1–10 days following a RBC transfusion. All patients presented with fever. Nine patients presented with focal abdominal findings, including both pain and tenderness to abdominal palpation in the right-lower, right-upper, and left-lower quadrants (table 1); an abdominal mass was palpable in five patients. Two patients did not have diarrhea. Four patients presented with pharyngitis.

The mean value of the serum ferritin concentrations determined around the time of the yersinia infection was significantly greater for patients with focal abdominal findings (2,656 ± 1,352 μg/L) than for patients who did not present with focal abdominal findings (1,086 ± 459 μg/L; $P < .05$).

Investigation and treatment. The source of positive culture specimens and surgical and antibiotic treatment are presented in table 1. *Yersinia* typing was available for isolates from 11 patients: all were of biotype 4 and serotype 0:3. Eight patients had significant infection-related findings at surgery or imaging, including suppuration or abscess formation (in 5 patients), perforations (4), marked adenitis (4), cecal ileitis (4), appendicitis (3), and necrosis (3). One patient developed a liver abscess. Seven patients relapsed after initial diminishment of symptoms and signs or following surgery. Two patients required hemicolectomy.

Over the period 1981–1991, 65 nonenteric isolations of *Y. enterocolitica* were reported in the province of Ontario. Hence, invasive yersinia infection was diagnosed in patients with β-thalassemia at a frequency 5,000-fold greater than that in the general population.

Discussion

When compared with that observed in the general population, the incidence of invasive yersiniosis in iron-loaded patients with β-thalassemia in two Canadian centers was strikingly elevated. Even higher rates of infection have been recently reported in Italy, where ~10% of thalassemic patients in one center had *Y. enterocolitica* infection diagnosed over a 1-year period [50]. Differences in rates between centers may reflect true differences in incidences due to geographic variations in *Y. enterocolitica* [52], variation in individual patient risk, or different methods of reporting. Clearly, mild cases of yersinia infection that may not present with clinical symptoms or signs will be unreported [28].

As well as the incidence of yersinia infection, the age of patients with β-thalassemia, including those in the present series, was usually higher at the time of infection than that of infected patients in the general population [53, 54]. Fever was the only invariable finding associated with *Y. enterocolitica* in this series of patients. In more than half the patients, a severe, suppurative pseudoappendicitis was noted. A palpable abdominal mass was a common finding, and blood cultures were frequently positive. Almost one-third of patients presented with pharyngitis, a recognized feature of yersinia infection [52]. These and other clinical findings observed in this series and in previous reports are summarized in tables 1 and 2.

Factors possibly predisposing to *Y. enterocolitica* infection were examined in this cohort. Although iron loading is considered the major risk factor for infection with *Y. enterocolitica,* previous investigators of thalassemic patients either have not examined the magnitude of the body iron burden or have reported similar degrees of iron loading (as estimated on the basis of the serum ferritin concentration) in patients who did and did not develop *Y. enterocolitica* infection [50]. By contrast, we observed a higher mean concentration of serum ferritin in patients who developed infection associated with focal intraabdominal findings than in patients who did not have these symptoms and signs.

This observation may be consistent with a hypothesis that increased intestinal growth of *Yersinia* in iron-loading states may induce mucosal changes and lead to local invasion [28]. The significance of reports of *Y. enterocolitica* infections in patients with β-thalassemia minor [17, 55] is not clear; these may reflect the small but finite risk of yersinia infection in populations where the carrier state for β-thalassemia is common.

While it has been suggested that the risk of yersinia infection is greater for patients receiving iron-chelating therapy with deferoxamine than for iron-loaded but untreated individuals [20, 56, 57], two of our patients were not receiving deferoxamine at the time of infection, consistent with previous observations [34] that iron overload is an independent risk factor. It is unknown whether deferiprone, an experimental synthetic chelator that is less effective than deferoxamine [58], used by a patient in this series, can serve as a siderophore for *Y. enterocolitica.*

Table 1. Clinical and surgical symptoms and signs of infection due to *Yersinia enterocolitica* in 14 patients with β-thalassemia. All patients had fever and all survived.

Patient no.	Patient's age (y)/ sex	Serum ferritin level (μg/L)	Clinical/surgical findings	Culture specimen(s)	Antibiotics
1 [32]	19/F	5,400	RUQ, RLQ pain, mass, rash/cecal ileitis, perforation, hemicolectomy	Blood, sputum, skin lesion	Cfaz, Net, TMP-SMZ, Mtz, Pip, Tm, Cm
2	19/M	4,260	RLQ pain, pharyngitis	Blood, stool	Amp, Chl
3	8/M	3,783	RLQ pain, vomiting, pharyngitis/appendicitis, perforation; relapse: RLQ abscess (CT performed)	Stool	Amp, Cm, Gm, TMP-SMZ, Mtz
4	13/M	2,380	Abdominal pain, vomiting, myalgia, pharyngitis; relapse: RLQ pain	Stool	Clox, Ctax, TMP-SMZ
5 [43]	17/M	2,278	RLQ pain, mass, pharyngitis/ileitis, suppurative and necrotic adenitis, liver abscess, perforation	Surgical	Ctax, TMP-SMZ, Cpfx
6	9/M	1,949	RUQ, RLQ pain, vomiting, cellulitis at Dfo site, RLQ abscess (CT performed)	Stool	Cfur
7	6/M	1,778	LLQ pain, RLQ mass, vomiting/appendicitis, cecal inflammation, necrotic adenitis	Lymph nodes, stool	Gm, TMP-SMZ, Amp, Mtz
8	14/M	1,760	RLQ pain, mass/appendicitis, abscess, perforation	Blood, stool, surgical	Gm, Chl
9	19/M	1,760	Vomiting	Blood, stool	Ctri
10	7/F	1,640	RLQ pain, vomiting, relapse (LLQ pain and mass), polyarthralgia/marked adenitis	Blood, stool	Clox, Cm, Gm, Pen, TMP-SMZ
11	22/F	1,335	RLQ, LLQ pain and mass, relapse (abscess)/cecal inflammation, necrotic adenitis	Blood	Cfur, Ctan, Ctax, TMP-SMZ, Mtz
12	14/F	993	Abdominal pain, arthralgia, myalgia	Stool	Gm, Amp, TMP-SMZ
13	8/F	820	Rash	Blood, stool	Gm, TMP-SMZ
14	13/M	771	None reported	Blood	Amp, Ctri, Gm, TMP-SMZ

NOTE. All except patients 4 and 14 reported diarrhea. Amp = ampicillin; Cfaz = cefazolin; Cfur = cefuroxime; Chl = chloramphenicol; Clox = cloxacillin; Cm = clindamycin; Cpfx = ciprofloxacin; Ctan = cefotetan; Ctax = cefotaxime; Ctri = ceftriaxone; Dfo = deferoxamine; Gm = gentamicin; LLQ = left-lower-quadrant; Mtz = metronidazole; Net = netilmicin; Pen = penicillin; Pip = piperacillin; RLQ = right-lower-quadrant; RUQ = right-upper-quadrant; Tm = tobramycin; TMP-SMZ = trimethoprim-sulfamethoxazole.

The temporal relationship of yersinia infection and blood transfusion was an unexpected finding in these patients. More than half of the patients presented with clinically apparent infection in the 10 days following a blood transfusion. While cultures of the blood units in question were not available in retrospect to confirm these as a source of infection, *Y. enterocolitica,* which grows well in units of blood during storage in the cold [59], has previously been reported as a significant cause of transfusion-related bacterial infection [60].

Our patients did not develop fulminant bacteremia soon after transfusion, as is the case with transfusion-related bacterial infections [60]. This suggests that either low levels of bacteria contaminated the blood units, leading to a more gradual infection in these patients, or transfusion increased the risk of infection by some other mechanism. A temporal relationship between infection and transfusion has not previously been observed in patients with thalassemia [50, 61]. Other exposure risks, including ingestion of undercooked pork [52], reported as a source of infection in an iron-loaded patient [61], were not evaluated in this study. Further studies of yersiniosis in regularly transfused patients may shed light on the most common source of infection in these patients.

Recommendations arising from this and other series indicate that fever, even in the absence of diarrhea and abdominal findings, in a patient with iron overload should alert the clinician to the possibility of yersinia infection. For patients with β-thalassemia, especially if symptoms occur shortly following a blood transfusion, clinical suspicion should be heightened. Given the high frequency of and morbidity caused by invasive infection with *Y. enterocolitica,* expectant management, including administration of broad-spectrum antibiotics [62] and surgical consultation, should be initiated promptly for patients at potential risk. Patients with a higher iron burden may be at greater risk for intraabdominal suppurative complications.

Acknowledgments

The authors thank Dr. Hans Hitzler, Dr. Carlos Alvarado, and Michael Adamkiewicz for kindly translating the text and Dr. Frank Berkowitz for helpful comments. They thank Mary Saukas and Dr. Geoffrey Dougherty for assistance and Susan Scorizzi for assistance with the manuscript. Additional bacterial typing was performed by Al Borczyk, of the National Center for Yersinia.

Table 2. Clinical symptoms and signs and surgical findings associated with infection due to *Yersinia enterocolitica* in patients with thalassemia major: summary of published findings, 1970–1995.

Finding	No. (%) of patients
Clinical (n = 92)	
Fever	85 (92)
Abdominal pain	68 (74)
Diarrhea	67 (73)
Bacteremia	52 (57)
RLQ pain	48 (52)
Vomiting	42 (46)
Abdominal mass	15 (16)
Pharyngitis	11 (12)
Involvement of other sites*	9 (10)
Reactive arthritis	5 (5)
Relapse	12 (13)
Shock	11 (12)
Death	6 (7)
Intraabdominal† (n = 50)	
Adenitis	30 (60)
Abscess	23 (46)
Appendicitis	19 (38)
Cecal ileitis	19 (38)
Necrosis	12 (24)
Perforation	5 (10)
Liver abscess	3 (6)

NOTE. Data are from [2–51] and the present report. RLQ = right-lower-quadrant.

* Pneumonia [4, 5, 36, 46], soft tissue ([4, 8, 29] and present report), osteomyelitis [2, 3, 8], meningitis [22], and pericarditis [38].

† During laparotomy, CT, or ultrasonography.

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