

COMMENT



The risk of severe bacterial infection in non-transfusion-dependent thalassemia

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The nationwide population study by Lin et al.¹ showed that patients with transfusion-naïve thalassemia were at risk for hospitalization due to non-typhoidal *Salmonella* (NTS) infection. The results in the study indicate that patients with NTS infections may have to be managed carefully in the emergency department or other relevant units; this may also be the case for patients with non-transfusion-dependent thalassemia (NTDT) or a thalassemia trait. However, the severity of anemia was not evaluated in this study as an important confounder among patients with thalassemia. Additionally, the results may have been affected to a greater extent than expected by different baseline characteristics, including the code of diagnosis of thalassemia.

Although NTS induces invasive infections, such as bacteremia, most cases present with gastroenteritis symptoms, such as fever, vomiting, abdominal pain, diarrhea, and bloody stools. It is difficult to estimate the risk of serious illness based on the initial symptoms. Regarding follow-up, patients are often told to return to the hospital in case of serious illness for appropriate interventions. It is usually challenging to establish strict and uniform criteria for admission. Therefore, the decision is left to the discretion of the physician, based on the patient's condition. Patients with a significant risk of severe disease may be hospitalized at an earlier stage. When deciding whether to hospitalize the patient, their underlying disease should be taken into consideration.

Patients with thalassemia, including those with NTDT, present with microcytic anemia and resemble iron deficiency anemia.² The severity of anemia may be a crucial confounder in this study. As such, an increasing number of patients with severe anemia might be hospitalized, regardless of the severity of the NTS infection. Moreover, patients with NTDT can develop iron overload and organ dysfunction, which are not dependent on transfusion therapy.³ Serum ferritin levels might reflect the extent of iron overload, although it can be confounded by its increase with inflammation.

According to the study's limitations, patients' past thalassemia history may have contributed to their hospital admission. Yet, the effect was a minor concern, since the patients with severe thalassemia were excluded from the study. In patients with thalassemia, postsplenectomy, iron overload, and iron chelation therapy have reportedly increased the risk of severe bacterial infections.⁴ Importantly, although patients with these histories were excluded from this study, there have been reports of severe bacterial infections in individuals with NTDT.^{5,6} Predisposing

factors for infections in patients with thalassemia include several immune abnormalities.⁴ Considering the risk in NTDT, the physician's preparedness might not be negligible. Furthermore, hospitalizations or the decision to hospitalize have been reported to be strongly or moderately influenced by one or more nonmedical factors, including lack of information about baseline conditions, inadequate access to outpatient specialty care, and a recent emergency department visit.^{7,8} Hospitalization should be associated with other potential factors having no direct relationship with NTS severity, which were not adjusted between the groups.

In bacterial enterocolitis, a definitive diagnosis cannot be made in the early course of the disease. Moreover, the results of the stool culture return after several days. As the authors stated, several hospitalized patients possibly represented many severely ill patients. However, due to the retrospective nature of this study, there were no standardized admission criteria for all the settings. Since admission depended on the treating physicians' intentions, information bias was a very important factor and should have been considered. Thus, the results of this study may have overestimated the severity of NTS infection in patients with less severe thalassemia.

Since thalassemia has a severe disease burden in some regions, and NTDT has emerged due to globalization, the risk of infections in patients with NTDT needs to be investigated more thoroughly. A multinational prospective cohort study is ideal for comparing the incidence of invasive NTS infections between patients with and without thalassemia. The admission criteria for patients with NTS infections, such as fever duration, dehydration status, and severity of abdominal pain should be defined in future studies. In addition, investigating anemia severity or ferritin level would be helpful in understanding risks for hospitalization.

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