Infections and Illnesses in Children with Hb E Beta-Thalassemia: A Prospective Controlled Study

Arunee Jetsrisuparb MD*, Charoon Jetsrisuparb MD*

* Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

The authors performed a prospective, controlled, 3-year, follow-up study on infections and illnesses in Hb E beta-thalassemic pediatric patients. Fifty severe and 24 non-severe patients and 24 controls were included. Siblings with an age difference of no more than 4 years served as controls. All patients and controls were asked to write postcards every two weeks to report on their illnesses and treatments. The respective median follow-up was 32.5, 35.5 and 34 months in 1,501, 707 and 785 patient-months at 11.50 ± 4.74, 10.50 ± 4.18 and 10.75 ± 4.56 years of age (± SD) for the severe, non-severe Hb E beta-thalassemic patients, and controls. The rate per 1,000 patient-months of infections was not significantly different between groups despite having 26 (52%) splenectomised patients in the severe group. The infection rate among severe, non-severe, Hb E beta-thalassemic patients and controls was not significantly different. Regular blood transfusions and iron chelation might decrease infections among Hb E beta-thalassemic pediatric patients.

Keywords: Hemoglobin E, Hb E, Beta-Thalassemia, Infection, Illnesses, Prospective controlled study


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Thalassemias, a class of genetic disease characterized by abnormal globin chain synthesis, are a continuing health problem in several regions of the world. The clinical manifestations result from decreased, or absent, production of normal globin chains(1). Thalassemias are, therefore, classified according to the deficiency in the globin chain, the main subtypes being alpha- and beta-thalassemia(1).

Hemoglobin (Hb) E beta-thalassemia is an important cause of childhood chronic disease worldwide, and patients are generally classified as thalassemia intermedia because they have inherited a beta-thalassemia allele and Hb E, which together produce mild beta+-thalassemia. However, there is significant variability in the clinical expression, ranging from a mild form of thalassemia intermedia to transfusion-dependent conditions(2).

Several retrospective studies on Hb E beta-thalassemia from Thailand have reported infection was a serious and sometimes fatal problem among thalassemic patients(3-5). However, few prospective studies with a control group have been conducted and the one conducted was prior to 1988 among 50 adult Hb E beta-thalassemic patients with a control group (who were not more than 3 years different in age). Another study was conducted with 47 patients without controls(6,7). The studies were one-year in duration and included non-severe and severe infections among hospitalized and non-hospitalized patients. In their study, mild infections such as upper respiratory tract infections, pharyngitis, skin infection, gingivitis, and diarrhea, were more common among thalassemic patients than the controls and neither sex nor splenectomy made any significant difference in the incidence of infections. However, the incidence of pericarditis occurred more frequently among splenectomised than non-splenectomised patients(4).

In the severe infection study, they found 30% (15 of 50) of patients developed severe infection, necessitating hospitalization and three patients died of severe sepsis(7).

Schilio et al compared the incidence of febrile upper respiratory tract infections and the duration of fever in a group of 56 patients suffering
from Cooley disease (between 2 and 14 years of age, of whom ten were splenectomised), treated with a high transfusion regimen and iron-chelating therapy, compared with a control group comprising normal or beta-thalassemia carrier siblings of a similar age. No significant difference was found between the two groups, albeit the details of methodology were not stated.

The studies of immunity in pediatric thalassemic patients revealed that the phagocytic activity of white blood cells, the cell-mediated immune response (CMIR), the humoral antibody, and complement system were not different from normal controls nor between splenectomised and non-splenectomised patients. T-cell activation in Hb E beta-thalassemic patients was normal. Several reports of immune abnormalities underlying susceptibility to infections in thalassemia have been reported.

In beta-thalassemia major, the humoral immunity, T-lymphocytes and activated T-cells were not different from the control group and did not correlate with risk of infection. Beta-thalassemia had an abnormal alternative pathway of the complement system, in which the immune complex was increased and there was suppression of myeloid series and granulopoiesis.

Despite being a worldwide problem, no controlled prospective study concerning illnesses and infections between severe and non-severe Hb E beta-thalassemic pediatric patients has been done. Moreover, after the studies by Aswapokee et al, several changes in the thalassemia treatment protocol have been adopted such as regular blood transfusion, iron chelation, broader immunization requirements and improvements to the Thai healthcare system. Therefore, the present study should provide significant baseline data for planning thalassemia treatments and counseling thalassemic patients and their families.

Material and Method

This was a prospective, 3-year, follow-up study (between March 2003 and 2006) of illnesses among Hb E beta-thalassemic pediatric patients at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. The present study was approved by the Ethics Committee of Khon Kaen University as per the Helsinki Declaration. All of the patients and control subjects and their parents/guardians freely entered the study after the project was explained and they had given written informed consent. The patient’s siblings-normal or carriers not more than 4 years different in age and never having received a blood transfusion—were asked to enter the present study as control subjects.

Several guidelines for grading the severity of the clinical manifestations of thalassemias have been published as well as new treatment recommendations given for regular blood transfusions and iron chelation (i.e., to keep Hb between 9.5-10.5 g/dL, to promote normal growth, to allow normal physical activities and to adequately suppress bone marrow activity and the size of the liver and spleen). It is, therefore, difficult to classify the severity of thalassemia according to the factors being treated. Moreover, the clinical manifestation in non-severe thalassemia might occur early in life, after a high fever or certain other illnesses, so ‘age of onset’ might not be an appropriate criterion for grading severity. The Hb level is used as one of the scoring criteria such that > 7.5, 6-7.5 and < 6 g/dL, respectively, are scored 0, 1 and 2. When combined with other criteria, the respective severity category for 0-3.5, 4-7 and 7.5-10 was mild, moderate, and severe thalassemia, which was not practical because before being referred to the authors’ hospital most of the patients with an Hb < 7 g/dL had been already blood transfused. The authors, therefore, adapted the Hb level set out by Ho et al and Sripichai et al and classified the presented patients to severe and non-severe forms.

The diagnosis of Hb E beta-thalassemia was therefore done by Hb-typing and DNA analysis. The authors’ respective criteria for the non-severe and severe forms were: (1) an average steady state Hb of > 7.5 g/dL without splenectomy; and, (2) an average steady state Hb of < 7.5 g/dL (or splenectomised because of a very large spleen or severe anemia despite frequent blood transfusions). The authors then ensured that the Hb of pre-transfused blood was between 9.5 and 10.5 g/dL to allow thalassemic patients to have normal growth and suppress over-erythropoiesis. Most of the presented patients had been treated with a regimen that might change the Hb levels, thus the authors checked their average Hb levels at steady-state before starting the regular blood transfusion regime. To confirm a non-severe form, their Hb needed to be >7.5 g/dL.

The presented patients had received regular, leukocyte-poor, packed red cell transfusion (10 mL/kg) whenever their pre-transfused Hb fell below 9 g/dL at 3-4 week intervals. Desferrioxamine (Desferal®) was given by the parents at home (a 20-40 mg/kg/d,
subcutaneously infusion in 8-10 hr, depending on the level of serum ferritin, 2-7 times/wk).

In splenectomised patients, penicillin or amoxicillin plus paracetamol was only to be taken for a significant fever and with advice to see a doctor as soon as possible.

Only one patient received pneumococcal vaccine before splenectomy because the vaccine was not generally available and the cost was beyond the means of patients.

In Thailand, there has been a national policy to give Hepatitis B vaccine since 1990 and the authors assumed patients born after 1990 were vaccinated. All of these patients have annual check-ups for: (1) anti-HIV antigen, (2) hepatitis B surface antigen and anti-hepatitis B antigen, (3) anti HCV, (4) direct anti-globulin test, (5) ultrasonography for gallstones, (6) liver function test, (7) lung function test, and (8) echocardiography (details to be reported elsewhere).

Twenty-four postcards per year, for each patient and control, were given to the patients (or their parents/guardians) to report all illnesses under supervision of their parents/guardians and to be returned to the researchers every two weeks. The details recorded included: the kinds of symptoms or illnesses the patients and the controls had and the treatment(s) received. The patients and their parents had hospital appointments every 3-4 weeks when the researchers confirmed the postcard information via a physical examination and conversation with the parents and patients.

The incidence density per 1,000 person-months of all illnesses was analyzed with a 95% confidence interval (CI).

**Results**

There were 50 severe, 24 non-severe cases of Hb E beta-thalassemic patients and 24 control siblings entering the present study and all of them regularly returned 100% of the postcards over 32.5, 33.5 and 34 median months, respectively. The person-months in the severe group numbered 1,501, vs. 707 for the non-severe and 785 for the controls. The characteristics of the patients and their siblings are presented in Table 1. The incidence density of all illnesses and the rate per 1,000 person-months in each group, the rate differences between the severe vs. non-severe, severe vs. control, and non-severe vs. control persons and their respective 95% confidence intervals are presented in Table 2.

The most common illnesses were common cold, bronchitis and pharyngitis at 90.61, 83.45 and 89.17 per 1,000 person-months in the severe, non-severe patients and control group, respectively, (no statistically significant difference was found between groups) (Table 2). The authors combined these symptoms in the same group because the clinical presentations of the three diseases were difficult to separate definitively.

Other infections—viz., diarrhea, chickenpox, dengue hemorrhagic fever, gingivitis, skin rash—were rarely found and the difference in their incidence between groups was not statistically significant (Table 2). Additionally, sinusitis was found in only one patient in the severe-group; however, it was diagnosed as allergic sinusitis since she had only mild thalassemic facies, not bony changes or a nasal obstruction.

Chest discomfort was found in 6.7 and 5.7 per 1,000 patient-months in the severe and non-severe

<table>
<thead>
<tr>
<th>Number</th>
<th>Severe</th>
<th>Non-severe</th>
<th>Control</th>
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<tbody>
<tr>
<td>50</td>
<td>24</td>
<td>24</td>
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</tr>
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</table>

Sex ratio, M:F 23:27 10:14 14:10

Age, beginning of study 11.50 ± 4.74 10.50 ± 4.18 10.75 ± 4.56

Mean, average steady-state Hb ± SD (g/dL) 6.90 ± 0.92 8.45 ± 0.64 ND

Number of patients who had regular or occasional blood transfusions 48 16 0

Volume of blood given (mL/kg/yr) 101.59 ± 35.21 87.65 ± 67.03 0

Number of splenectomised patients 26 (52%) 0 0

Serum ferritin at beginning of study 1,842.98 ± 1,289.06 1,382.65 ± 1,035.01 ND

Number of patients received Desferal® 50 22 0

Person-months 1,501 707 785

ND = not done

Table 1. Characteristics of severe, non-severe Hb E beta-thalassemic pediatric patients and controls
Table 2. Comparison of illnesses between severe, non-severe Hb E beta-thalassemic pediatric patients and controls

<table>
<thead>
<tr>
<th>Illness</th>
<th>Severe Rate</th>
<th>Severe Rate</th>
<th>Severe Rate</th>
<th>Non-Severe Rate</th>
<th>Non-Severe Rate</th>
<th>Control Rate</th>
<th>Control Rate</th>
<th>Severe &amp; Non-severe Difference</th>
<th>95% CI</th>
<th>Severe &amp; Control Difference</th>
<th>95% CI</th>
<th>Non-severe &amp; Control Difference</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Common cold, bronchitis, pharyngitis</td>
<td>136/1,501</td>
<td>90.61/1,000</td>
<td>59/707</td>
<td>83.45/1,000</td>
<td>70/785</td>
<td>89.17/1,000</td>
<td>7.16/1,000</td>
<td>-19.41, 33.72</td>
<td>1.43</td>
<td>-24.48, 27.35</td>
<td>-5.72 -35.60, 24.16</td>
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<td></td>
</tr>
<tr>
<td>Fever</td>
<td>24/15.99</td>
<td>15/4.00</td>
<td>21.22/4.00</td>
<td>7/1.33</td>
<td>1/0.67</td>
<td>8.92/1.27</td>
<td>-5.23/0.67</td>
<td>-17.11, 6.66</td>
<td>7.07</td>
<td>-2.98, 17.13</td>
<td>12.30 -0.04, 24.64</td>
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<tr>
<td>Acute diarrhea</td>
<td>6/4.00</td>
<td>4/4.00</td>
<td>5.66/4.00</td>
<td>1/1.33</td>
<td>1/0.67</td>
<td>1.27/1.27</td>
<td>-1.66/0.67</td>
<td>-7.68, 4.36</td>
<td>2.72</td>
<td>-2.05, 7.50</td>
<td>4.38 -1.50, 10.27</td>
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<td></td>
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<tr>
<td>Gingivitis</td>
<td>2/1.33</td>
<td>4/4.00</td>
<td>1.33/4.00</td>
<td>1/0.67</td>
<td>1/0.67</td>
<td>1.33/1.27</td>
<td>1.33/1.27</td>
<td>1.33, 3.89</td>
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<td>1.33, 3.89</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Measles</td>
<td>1/0.67</td>
<td>1/1.33</td>
<td>1.33/4.00</td>
<td>1/0.67</td>
<td>1/0.67</td>
<td>0.67/1.27</td>
<td>0.67/1.27</td>
<td>1.14, 2.47</td>
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<td>1.14, 2.47</td>
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<tr>
<td>Chickenpox</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1.41/1.27</td>
<td>1.41/1.27</td>
<td>1.41, 2.40</td>
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<td>1.41, 2.40</td>
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<td>Viral rash</td>
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<td>1.41, 2.40</td>
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<tr>
<td>Dengue hemorrhagic fever</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1.41/1.27</td>
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<td>1.41, 2.40</td>
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<td>1.41, 2.40</td>
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<tr>
<td>Abdominal pain</td>
<td>13/8.66</td>
<td>6/4.00</td>
<td>8.49/4.00</td>
<td>3/3.82</td>
<td>3/3.82</td>
<td>3.82/3.82</td>
<td>3.82/3.82</td>
<td>3.82/3.82</td>
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<td>3.82/3.82</td>
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<tr>
<td>Allergic rash</td>
<td>6/4.00</td>
<td>2/2.83</td>
<td>2.83/2.83</td>
<td>4.00/2.83</td>
<td>4.00/2.83</td>
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<td>4.00/2.83</td>
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<tr>
<td>Arthralgia</td>
<td>3/2.00</td>
<td>2.00/2.83</td>
<td>2.00/2.83</td>
<td>2.00/2.83</td>
<td>2.00/2.83</td>
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<td>2.00/2.83</td>
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<tr>
<td>Chest discomfort</td>
<td>10/6.66</td>
<td>4/5.66</td>
<td>6.66/5.66</td>
<td>6.66/5.66</td>
<td>6.66/5.66</td>
<td>6.66/5.66</td>
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<td>6.66/5.66</td>
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<tr>
<td>Epistaxis</td>
<td>36/23.98</td>
<td>1/1.41</td>
<td>1.41/1.41</td>
<td>1.41/1.41</td>
<td>1.41/1.41</td>
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<td>1.41/1.41</td>
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<tr>
<td>Eye edema</td>
<td>4/5.10</td>
<td>5.10/1.41</td>
<td>5.10/1.41</td>
<td>5.10/1.41</td>
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<td>5.10/1.41</td>
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<tr>
<td>Fatigue</td>
<td>7/4.66</td>
<td>4.66/1.33</td>
<td>4.66/1.33</td>
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<td>4.66/1.33</td>
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<td>4.66/1.33</td>
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<tr>
<td>Headache</td>
<td>11/7.33</td>
<td>7/9.90</td>
<td>9.90/1.41</td>
<td>7/8.92</td>
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<td>8.92/1.41</td>
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<tr>
<td>Muscle cramp</td>
<td>4/2.66</td>
<td>2.66/1.41</td>
<td>2.66/1.41</td>
<td>2.66/1.41</td>
<td>2.66/1.41</td>
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<td>2.66/1.41</td>
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<tr>
<td>Skin rash</td>
<td>1/1.41</td>
<td>1/1.41</td>
<td>1.41/1.41</td>
<td>1.41/1.41</td>
<td>1.41/1.41</td>
<td>1.41/1.41</td>
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<tr>
<td>Throat bleeding</td>
<td>2/1.33</td>
<td>1.33/1.33</td>
<td>1.33/1.33</td>
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<td>1.33/1.33</td>
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Only one patient in the severe group was treated for sinusitis every month.
groups but not in the control group. There was no statistically significant difference between the severe and non-severe groups but there was between the severe and control groups. There was no statistically significant difference between the non-severe and control groups (Table 2).

Interestingly, epistaxis was found in 24.0, 1.4 and 1.3 per 1,000 patient-months in each group, respectively (Table 2), and there was a statistically significant difference between the severe and non-severe groups, and the severe and control groups, but not between the non-severe and control groups.

The reported patients did not report any leg ulcers nor were any found when the physical examination was performed.

All of the illnesses reported were not severe and most of the patients had symptomatic treatments at home or at nearby clinics or hospitals as outpatients. Only one boy in the severe group (with diarrhea) was hospitalized for one day for intravenous fluid therapy.

In the severe group, the authors had 26 splenectomised patients (52%) 15 males and 11 females, the median age of splenectomy was 6 years (range, 3-14), the median duration of post-splenectomy 4.8 years (range, 0.2-10.8).

The authors also did not find any severe infection in the splenectomised patients during the prospective study period. The authors had no case of acute cholangitis even though there were eight (16%) and four (15.4%) patients who had gallstones in the severe and non-severe group and most of them had no symptoms of abdominal pain. All patients were anti-HIV negative.

Discussion

Twenty years ago, infections both mild and severe, were reportedly common among Hb E beta-thalassemic patients leading to death especially among splenectomised patients. Wasi et al studied viral infections in Hb E beta-thalassemia patients and found that patients were more susceptible to Coxsackievirus B but not to rubella, herpes simplex, cytomegalovirus, adenovirus or *M. pneumoniae*. In contrast to bacterial infections, splenectomised patients did not show evidence of increased viral infections.

The authors controlled, prospective study shows that there was no statistically significant difference in the infection rate between severe, non-severe patients and control groups, similar to Schiliro et al. Thus, the immunity in pediatric thalassemic patients, the phagocytic activity of the white blood cells, CMIR, humoral antibody and complement system, were not different from the normal controls nor between splenectomised and non-splenectomised patients, just as there were 26 (52%) splenectomised patients in the severe group. T-cell activation in Hb E beta-thalassemic patients was normal. In beta-thalassemia major, the humoral immunity, T lymphocytes, and activated T-cell were not different from the control group and did not correlate with the risk of infection.

Modell et al found that blood transfusions helped to decrease infections in thalassemic patients. However, infections were still the most common cause of death as they found 48 episodes of severe infection in 129 thalassemia intermedia with one in 54 patient-years being pneumonia, while other severe infections were one in 63 patient-years. These were severe infections resulting in death in 10 of 55 thalassemic patients.

Pittis et al found monocytes in thalassemic patients had problems with phagolysosomal fusion, which was partly solved by iron chelation. Matzner et al found that iron overloaded patients had abnormal neutrophil chemotaxis and migration, natural killer cell activity and decreased b-interferon release. The presented patients also had regular blood transfusions and iron-chelation therapy as indicated among patients studied by Schiliro et al. The present study might support Pittis and Matzner’s conclusion.

Rahav et al studied the occurrence of infections necessitating hospitalization in 92 homozygous beta-thalassemia patients who had been followed for decades (median 22 years; range 9-30 years; total 2,043 patient-years) and found that *Staphylococcus aureus* was the major pathogen possibly related to infections associated with intensive chelation with deferoxamine. Indeed, there was a significant increase in the rate of infection over time, notably after 15 years. A direct correlation between iron overload and infection was evident only before the initiation of iron-chelating treatment. Paradoxically, following initiation of deferoxamine, the infection rate increased. The findings of Rahav et al supported the prospective study in adult cases of Hb E beta-thalassemia in Thailand 20 years ago when iron chelation was not used and iron overload correlated with an increased rate of infection. Increasing infection, especially by *Staphylococcus aureus*, a skin pathogen after initiation of deferoxamine, might be caused by non-sterile technique during parenteral...
administration of medications. Oral iron chelation might have solved this problem.

Heier(29) reported that patients splenectomised for thalassemia had an 800-fold increase in sepsis. Serious infections were usually evident within 2 years after splenectomy and were common if patients had been splenectomised under two years of age(29). The presented patients had splenectomy performed at the median age of six years and the duration post-splenectomy was 4.8 years. Issaragrisil et al found that splenectomised patients had more frequent infections than non-splenectomised ones in their retrospective study(3). However, in a prospective study, Aswapokee et al found that age, sex, and splenectomy status did not have any significant effect on the incidence of infections(7).

The British Committee for Standards in Hematology recommended that all splenectomised patients and those with functional hyposplenism should receive pneumococcal immunization. Patients not previously immunized should also receive Hemophilus type b vaccine, Meningococcal group C conjugate vaccine and influenza vaccine. Notwithstanding vaccinations, life-long prophylactic antibiotics are recommended (e.g., oral phenoxymethyl penicillin or erythromycin)(30).

Most of the presented splenectomised patients did not receive the foregoing vaccines because they are costly and therefore not readily available. The authors gave Penicillin, Amoxicillin, or Erythromycin (in case of Penicillin hypersensitivity) at home, to be taken only when the patients had significant fever with advice to seek a doctor at once, should this occur. This is practical for the presented patients and the outcome of the present study supports this. If the authors were to give splenectomised patients every day antibiotics, the drugs would be in short supply and if they had some infections, it would delay treatment leading to more severe infections, and possibly death. Thus, home use of antibiotics is to be reserved for a significant fever only. Awareness of infection helps decrease severe infections among splenectomised patients.

The authors did not find pericarditis, confirmed by electrocardiography and echocardiography, while Aswapokee et al found it in 7 of 97 adult cases of Hb E beta-thalassemic patients(6).

Thalassemic leg ulcers were not found in the presented patients while Aswapokee et al documented 14 episodes in 97 adult cases of Hb E beta-thalassemic patients(6). Premawardhena et al studied Hb E beta-thalassemia in Sri Lanka and did not find leg ulcers in patients unable to function without transfusion (11 patients). But they found a respective eight of 25, 20 of 37, three of 14, and three of 22 patients in Group 1 with minimal blood transfusion (> 20 years old, 0-20 units, < 20 years old, 0-10 units), Group 2 (> 20 years old, 21 units, < 20 years old, > 11 units), Group 3 post-splenectomy patients in whom the following changes occurred over two years (improved quality of life > 3 points, increased growth > 25%, improved growth > 3 cm per year), and Group 4 (growth < 3rd percentile for height, QOF > 5, and delayed sexual maturation(31).

The cause of chronic leg ulcers in thalassemic patients is not clear, but might be caused by chronic anemia, iron overload, decreased plasma zinc, platelet aggregation, or high Hb F(1). Regular blood transfusions and iron chelation might play a role in the correction of these abnormalities; a hypothesis supported by the presented results as most of the presented patients treated by this regime had no leg ulcers, and by Premawardhena et al who found that chronic leg ulcers were not found in the group unable to function without transfusion(31).

Epistaxis was found significantly more often in the severe group than the non-severe and control groups as was also the case in Eldor’s studies, who reported that a mild hemorrhagic tendency was observed in a group of beta-thalassemia major patients. This included easy bruising and frequent epistaxis. Disturbances in the coagulation system were also described in this condition, which probably resulted from liver damage associated with this disease. There was, however, no quantitative or qualitative correlation between the hemorrhagic manifestation and the abnormalities in the clotting mechanism. In most of the thalassemia major patients, and in some with thalassemia minor, diminished platelet aggregation to ADP, collagen, ristocetin, and epinephrine were found. These anomalies could not be corrected by the re-suspension of thalassemic platelets in normal plasma(31,32).

Chest discomfort was significantly different between the severe and controlled groups, perhaps caused by hepatosplenomegaly.

Even though the present study was conducted by postcard responses sent in every 2 weeks, the authors stressed to the participants that they write immediately about any illness and that they should write every two weeks whether or not they had any illness. The authors thought this frequency and
style of reporting would help to ensure compliance and good information. Moreover, when each subject came to hospital every month, the authors endeavored to confirm the postcard information. In fact, the postcard responses were well done: since all of the patients and all parents had good responses, there was no selection bias.

In summary, this prospective study revealed that the infection rates in severe (including splenectomised), non-severe Hb E beta-thalassemic pediatric patients, and control subjects were not significantly different. The treatment with regular blood transfusions and iron chelation were beneficial in Hb E beta-thalassemic pediatric patients and no leg ulcers were found.

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