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Original Article

# The incidence of nontransfusion-transmitted infectious diseases in β thalassemia major patients at Cipto Mangunkusumo Hospital

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**ABSTRACT**

***Background*** The statement that thalassemic children are more prone to infection than normal children has been accepted as a part of thalassemia literatures for years. Recently this concept has been questioned, and certainly it has impressed the clinicians that the incidence of infection in thalassemia in early childhood is reduced by adequate blood transfusion although this has not been documented. However, iron overload favors bacteria to acquire iron necessary for their growth. Excess iron deposit may damage immune response in thalassemic patients.

***Objective*** The aim of this study was to find out whether there was any increasing episode of nontransfusion-transmitted infectious diseases in thalassemic patients.

***Design*** Observational, cross sectional study.

***Setting*** Thalassemia outpatient clinic at the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

***Patient*** Two hundreds subjects by consecutive sampling, grouped by their total volume of transfusion into ≥5 liters or <5 liters groups.

***Results*** The numbers of patients receiving transfusion ≥5 liters who had 1,2,3,4 and 5 times episodes of influenza in 6-month period were 69, 20, 3, 2, and 2 out of 173 patients respectively and in patients receiving transfusion less than 5 liters,14/27 had influenza for 1-2 times in 6-month period. The incidence of diarrhea in patients receiving transfusion ≥5 liters was 11.5%, once to twice in 6 months and in patients receiving transfusion less than 5 liters, 7/27, 1-2 times in 6 months. There was no difference in the incidence of influenza and diarrhea between the two groups.

***Conclusion*** It seemed that there was no any increasing incidence of nontransfusion-transmitted infectious diseases in thalassemic patients in accordance with total volume of blood transfusions **[Paediatr Indones 2003;43:216-219].**

***Keywords:*** *thalassemia, immune response, incidence of infection.*

The thalassemia syndrome was first described by Cooley and Lee in 1925. Between 1925 and 1940 was the period of the explanation of genetic inheritance of the disease. Thalassemia is a hereditary disease affecting hemoglobin synthesis. This is an autosomal recessive disease; heterozygous individuals or carriers are clinically asymptomatic with, at most, minor hematological abnormalities. Homozygous or compound heterozygous patients are usually manifested as thalassemia major who require regular blood transfusions and intensive iron chelating therapy to sustain a reasonable quality of life.[1,2]

There are two rationales regarding studies on immune response in thalassemia. The first one is to underlie the patient's susceptibility to infections, the second is related to the destruction of thalassemic red cells especially immune hemolysis. There are at least three aspects to consider before designing studies on immune function responsible for infections in thalassemia i.e., etiologic agents involved, nonimmune predisposing

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factors, and immunological dysfunction related to clinical consequences of the disease such as splenectomy and iron overload.[3] Apart from transfusion-related viral infection and unique fungal infection, bacterial infection is the leading infection with significant morbidity and mortality. The major components of immunity against bacterial infection are phagocyte system and opsonization processes which are related to immunoglobulins and complements. These factors are found to be defective in thalassemic patients especially those who underwent splenectomy or with iron overload. Splenectomy removes a major organ with filtering and phagocyte functions and also reduces antibody production particularly in response to carbohydrate antigen. Asplenic individuals are at risk of developing fulminant sepsis caused mostly by encapsulated bacteria.[4-8] Iron overload favors bacteria to acquire iron necessary for their growth. Excess iron may damage immune effector cells and hamper their functions including neutrophil and monocyte activities against bacteria. Data from studies of lymphocyte function in thalassemia are controversial. Patterns of infections in thalassemic patients do not suggest significant lymphocyte dysfunction as a predisposing factor. Abnormalities of lymphocyte in thalassemic patients were reported related to iron overload and blood transfusion.[9-10] Among them were disproportion of T4/T8 lymphocytes and diminished NK activity.[3] To our knowledge, in Indonesia, there had been no data about immune response in thalassemic patients. The aim of this studies was to know whether there was any increasing incidence of nontransfusion-transmitted infectious diseases in thalassemic patients.

## Methods

This was an observational cross sectional study. Beginning on December 2001, 200 thalassemic patients who visited thalassemia outpatient clinic at the Department of Child Health, Cipto Mangunkusumo Hospital, were recruited. The inclusion criteria were confirmed diagnosis of thalassemia, visit to our clinic with parents, and the parents agreed and signed the informed consent.

We asked several questions to the parents and wrote it down on a questionnaire. The answers depended completely on the memory of the parents (by recalling). The questions asked were as follows: (1) Was there any incidence of influenza in the last 6 months? If yes, how many times in the last six months? If yes, how long the children suffer from the disease until recovered? (2)Was there any incidence of diarrhea in the last 6 months? If yes, how many times in the last six months? If yes, how many times it occurred in one day? If yes, how long the children suffered from the disease until recovered? (3)How many times did the patients visit other health center besides our clinic in the last 6 months?

After filling 200 questionnaires, we divided them into two groups: those who received transfusion less than 5 liters and those who received transfusion ≥5 liters. Since the parents of our patients were mostly low educated, we were uncertain whether they could remember the incidence of any diseases in 6 months. So, we made two tables of the incidence of diseases, in 6 months and 3 months.

## Results

Of 200 β-thalassemia patients, 173 patients received transfusion ≥5 liters and 27 patients received less than 5 liters. The distribution of the subjects according to age is shown in **Table 1**.

**TABLE 1.** DISTRIBUTION OF SUBJECTS ACCORDING TO AGE

| Age | Total volume of transfusions | | Total |
|---|---|---|---|
| | <5 liter | ≥5 liter | |
| 1-5 | 21 | 36 | 57 |
| 6-10 | 6 | 76 | 82 |
| >10 | 0 | 61 | 61 |
| **Total** | **27** | **173** | **200** |

There were only 39% of parents answering the questionaires completely. The rest of the parents (61%) could remember only until the last three months. Assuming that the respondents could not remember any incidence of diseases, we calculated the incidence of diseases in six months. **Table 2**

**TABLE 2.** INFLUENCE OF TOTAL VOLUME OF TRANSFUSIONS TO THE INCIDENCE OF INFLUENZA IN 6 AND 3 MONTHS

| | | Total volume of transfusions (n) <5 liter | ≥5 liter | Total |
|---|---|---|---|---|
| **Incidence of influenza in 6 months** | 0 | 13 | 77 | 90 |
| | 1 | 11 | 69 | 80 |
| | 2 | 3 | 20 | 23 |
| | 3 | 0 | 3 | 3 |
| | 4 | 0 | 2 | 2 |
| | 5 | 0 | 2 | 2 |
| | Total | 27 | 173 | 200 |
| **Incidence of influenza in 3 months** | 0 | 13 | 81 | 93 |
| | 1 | 13 | 79 | 92 |
| | 2 | 1 | 10 | 11 |
| | 3 | 0 | 3 | 4 |
| | Total | 27 | 173 | 200 |

**TABLE 3.** LENGTH OF ILLNESS FROM INFLUENZA ACCORDING TO TOTAL VOLUME OF TRANSFUSIONS

| Days | Total volume of transfusions (n) <5 liter | ≥5 liter | Total |
|---|---|---|---|
| 1 – 4 days | 8 | 61 | 70 |
| >4 days | 6 | 35 | 40 |
| Total | 16 | 94 | 110 |
| <7 days | 6 | 17 | 19 |
| ≥7 days | 2 | 4 | 6 |
| **Total** | **8** | **21** | **25** |

**TABLE 4.** INCIDENCE OF DIARRHEA IN 6 AND 3 MONTHS ACCORDING TO TOTAL VOLUME OF TRANSFUSIONS

| | | Total volume of transfusions (n) <5 liter | ≥5 liter | Total |
|---|---|---|---|---|
| **Incidence of diarrhea in 6 months** | 0 | 19 | 152 | 171 |
| | 1-2 | 7 | 20 | 27 |
| | 3 | 1 | 0 | 1 |
| | 5 | 0 | 1 | 1 |
| | Total | 27 | 173 | 200 |
| **Incidence of diarrhea in 3 months** | 0 | 19 | 154 | 173 |
| | 1-2 | 8 | 19 | 27 |
| | >2 | 0 | 0 | 0 |
| | Total | 27 | 173 | 200 |

shows the incidence of influenza in six and three months in subjects who received transfusion ≥5 liters and subjects who received transfusion less than five liters.

All subjects could answer completely the incidence of diseases in the last three months.

**Table 3** shows that the lenght of illness day of influenza in both groups was the same and there were no differences in the length of illness in both groups.

**Table 4** shows the incidence of diarrhea in six and three months.

## Discussion

This study was a cross sectional study using questionnaire. The technique has limitations in level of confidence from the respondents. The term influenza seemed not understand properly. Therefore,

we realized that the term influenza and diarrhea in this study could not represent infection completely. The subjects were not divided proportionally into two groups because at first we did not know the amounts of transfusion to avoid bias.

From the results, it was concluded that the incidence of influenza in thalassemic patients was similar to that of normal children. There were 6 out of 16 patients in group receiving transfusion <5 liters and 35 out of 94 patients in group with ≥5 liters transfusion who had lenght of illness of more than 4 days. Whether there was a relationship with multiple transfusions must be questioned further because it can also happen in non thallasemic children especially in those with malnutrition.

The incidence of diarrhea in thalassemic patients was similar to that of normal children. There was one child who had diarrhea 3 times and one child who had 5 times in 6 months. But we were not sure this had relationship with the thalassemia only, since risk factors like sanitation and hygiene could not be excluded in this study. That was the reason why the length of illness in some patients was more than 7 days.

Our findings are similar to that of the study of Lombardi *et al*[11] which reported that β thalassemia major patients who had multiple transfusions had partial immune deficiency which was proven by the decreased activity of lymphocyte CD4+helper/inducer and increased activity of CD+8suppressor/cytotoxic, but there was no relationship between the clinical manifestation and the increased incidence of infection.

In conclusions, the incidence of influenza in thalassemic children is similar with that of normal children while the incidence of diarrhea in thalassemic children was 1-4 times in 6 months, which was also similar with that of normal children. There was no difference in the incidence of diseases as well as in length of illnesses between the two groups of transfusion.

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