LEADING ARTICLE

# FEBRILE TRANSFUSION REACTION: WHAT TO DO NEXT?

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SINGAPORE MED J 1993; Vol 34: 105-106

A prospective study on multi-transfused thalassaemic children published in this Journal alerts us to the fact that the commonest manifestation of blood transfusion reactions is a febrile reaction.

In Singapore the incidence of reported febrile transfusion reactions is less than 1% of all blood transfusions. If patients' temperatures were routinely taken at hourly intervals and carefully noted during transfusion and a few hours thereafter, probably more febrile reactions would be recorded. Doctors who have to administer blood or blood products to patients requiring frequent blood transfusions will at one time or another face the problem of febrile transfusion reaction. If this happens, what to do next? An understanding of the cause and effect of febrile transfusion reaction would help us to approach this problem logically.

## DEFINITION

Febrile transfusion reaction is defined as a rise in temperature of at least 1°C during and within one or two hours after the transfusion of blood or blood components. It must be distinguished from febrile episodes unrelated to transfusion.

## AETIOLOGY

Febrile transfusion reaction can be classified under haemolytic or non-haemolytic types. Acute haemolytic reaction due to red cell antigen-antibody incompatibilty is now a rarity due to the practice of effective cross-matching techniques. Hence most of the febrile reactions are non-haemolytic in nature. Many febrile reactions are caused by recipient antibodies directed against donor leucocytes or platelet antigens as a result of immunization by previous transfusion or pregnancy.

Anti-leucocyte antibodies causing febrile reactions comprise two categories: (1) leucoagglutinins directed against granulocyte-specific antigens, and (2) lymphocytotoxins directed against HLA-antigens of lymphocytes[1,2]. The relative importance of these various antibodies in causing febrile transfusion reactions is not yet established. Some have concluded that granulocyte-specific agglutinins are more important than HLA antibodies in causing febrile reactions[3] but others have reached the reverse conclusion[4]. These two antibodies tend to occur together, so that establishing the aetiology of a febrile reaction is often based only on detection of anti-HLA antibodies, although the less commonly available assay for leucoagglutinins is more specific. Platelet-specific antibodies causing febrile reactions are relatively rare.

Febrile reactions caused by anti-leucocyte antibodies can also rarely result from passive administration of donor plasma containing high-titered leucoagglutinins incompatible with the recipient's leucocytes[1,2,5,6].

Perkins et al[7] found that the number of leucocytes necessary to raise the temperature of a sensitized recipient by 1° C is very variable. Minimum quantities range from $2.5 \times 10^8$ to $25 \times 10^8$ white cells per transfusion.

Febrile reactions due to contaminated pyrogenic bacterial products in blood are now rare as a result of universal use of disposable blood containers and tubing. Bear in mind that bacteraemia during transfusion may be unrelated to the transfusion.

## CLINICAL FEATURES

When patients develop febrile reactions following transfusion they do not start to feel cold and shivering for at least half an hour after the transfusion has started. This is followed by tachycardia and a sudden rise in body temperature. At the peak of the reaction the subject might develop nausea, headache or back pain. Defervescence of fever usually occurs in 2 to 24 hours after termination of the transfusion. If the patient's plasma contains potent leucocyte antibodies, flushing may develop within 5 minutes of the start of the transfusion, presumably due to complement activation. Most reactions are usually mild but occasionally associated with pulmonary infiltrates and, rarely, shock or death.

Infants appear to be incapable of shivering in the early phase of febrile transfusion reaction but they do show pallor and their skin feels cold. Sometimes the rise in temperature is accompanied by a temporary refusal to feed and by diarrhoea.

## TREATMENT

Immediate management of febrile transfusion reaction includes the following steps:

1. Stop the transfusion of blood or blood products immediately since fever may also occur in a haemolytic reaction.
2. Keep the intravenous line open by normal saline drip. Keep the patient warm. Collect blood samples and return the blood units to the blood bank to exclude haemolytic transfusion reaction.
3. Give paracetamol to stop the fever. Intravenous hydrocortisone can also be given in patients with severe symptoms. Antihistamines do not affect fever, but may be used to suppress a concomitant urticaria or anaphylactoid reaction.
4. Monitor the patient closely at 15 or 30 minute intervals. Check the temperature, pulse rate, blood pressure and fluid balance.
5. If the patient requires further transfusion(s), send blood samples for antibody screen and compatibility testing. If repeated febrile reactions occur, investigate for HLA antibodies.

## PREVENTION

Patients with febrile transfusion reactions are often transfused previously and require further transfusion. What to do next when patient needs more blood or blood products? Prevention of subsequent febrile non-haemolytic transfusion reactions is a

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more important consideration than their immediate management. If a patient experiences one febrile non-haemolytic reaction, the odds are one in eight that he will have a similar reaction to the next blood transfusion. This may be overcome by transfusing leucocyte-depleted blood or suppressing the reactions by drugs[1].

**a) Removal of leucocytes from red cell concentrates**

There are several ways of removing leucocytes from red cell concentrates:

*i) By differential sedimentation*

By simple centrifugation and removal of the buffy coat, the residual leucocytes in the unit of blood can be reduced to less than $0.5 \times 10^9$, ie less than 20% of the original number[7]. This could prevent or attenuate majority of non-haemolytic febrile transfusion reactions in multi-transfused patient

*ii) By washing red cells*

The use of cell-washer machine removes about 80-90% of leucocytes but also removes 3-30% of the red cells. If one attempts to remove 90% of the leucocytes, the loss of red cells is even greater[8].

*iii) By using filters to remove leucocytes*

There are several types of leucocyte filters[9-11]. Filters made of cellulose acetate (Erypur-G, Organon Technika), polyester (Sepacell R-500, Asaki) or cotton wool (Imugard, Terumo) may be used. Using blood stored for less than 5 days, filters of all three types remove 95-100% of leucocytes and 90% of platelets with a red cell loss of 10%[12-14]. Filtration of one unit of blood is completed in 30-40 minutes and some filters can be used to filter more than one unit of blood. Filters inserted in administration sets at the bedside, rather than in the laboratory, are also available, eg Pall leucocyte filters[10].

The study on multi-transfused thalassaemic children published in this Journal on the use of leucocyte-poor red cell concentrates prepared by centrifugation and by using filter (Sepacell R-500A) showed a significant reduction in the frequency of total transfusion reactions with the latter method. Other study[15] showed that frequencies of reactions to filtered blood varied significantly according to the type of filter and were as follows: Erypur, 0.7%; Imugard, 2.7%; Leucostop, 0.7%; Miropore, 2.1%; Sepacell, 0.6%.

*iv) By freezing the thawing red cells*

Suspensions of red cells which have been frozen in glycerol, thawed and washed thoroughly appear to be free from the risk of causing febrile transfusion reactions[16]. Ninety-eight percent or more of the leucocytes and 100% of the platelets and plasma are removed from each unit of blood; the red cell loss is about 10%.

**b) Use of drugs to suppress febrile reactions**

Suppression of febrile reactions by drugs is used when leucocyte depleted blood is not available, and for patients receiving platelet concentrates, who have a past history of febrile reactions. Studies have shown that pyrogenic reactions could be modified by the previous administration of antipyretic drugs[17]. There is no good evidence that antihistamines prevent febrile reactions[18], although it may be beneficial in urticarial reaction. Intravenous hydrocortisone could be used if the symptoms were severe.

There are other factors which could moderate the severity of febrile reactions. Many clinical impressions have been reported that febrile reactions are more severe when transfusions are given rapidly[19]. Therefore it might be better to use a moderate rate of transfusion, eg 500ml in one hour in non-urgent cases. Keeping the patient thoroughly warm throughout the transfusion could play a part in reducing the severity of febrile reaction.

## RECOMMENDATIONS

Following the immediate management of a febrile transfusion reaction and investigations to exclude acute haemolysis, a decision has to be made as to when to give leucocyte-poor blood transfusion. It is generally recommended that leucocyte-poor red cell units should not be given until patients have demonstrated at least two febrile non-haemolytic reactions to standard red cell units and a failure to respond to antipyretic premedication. Only about 15% or one out of eight patients experiencing a febrile non-haemolytic transfusion reaction for the first time will demonstrate a second reaction upon subsequent exposure, and premature use of leucocyte-depleted units is expensive and inappropriate.

When there are clinical indications for leucocyte-depleted blood, it seems advisable to start by providing blood depleted of leucocytes by centrifugation since a large proportion of patients may benefit from it. If the patient still experiences febrile reactions, blood passed through a leucocyte-filter or washed red cells and frozen-thawed cells should be used. If patients with repeated febrile reactions have high levels of anti-leucocyte or HLA antibodies, the most effective method of preparing leucocyte-poor red blood cells is to use frozen-thawed red blood cells.

It is more difficult to remove leucocytes from platelet concentrates. Washing of platelet preparation effectively removes plasma but does not significantly reduce the number of leucocytes. Bedside filters especially designed for leucocyte removal have shown promise.

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