NHS
Blood and Transplant

Diagnostics, Development and Research Directorate

The Investigation of Severe Non-haemolytic Febrile Transfusion Reactions

An Audit of Adherence to NBS Guidelines

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Contents

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Executive Summary

Background

The National Granulocyte Immunology Laboratory (NGIL) is part of the NHS Blood and Transplant (NHSBT) Histocompatibility and Immunogenetics (H&I) laboratory in Bristol. Requests for antibody testing are received in the NGIL following severe febrile non-haemolytic transfusion reactions (SFNHTR). Severe febrile non-haemolytic transfusion reactions may be alleviated by transfusing plasma-reduced cellular blood components such as washed red blood cells (WRBC) and platelets in platelet suspension medium (PSM). If SFNHTRs recur despite transfusing WRBCs or PSM platelets there are guidelines for further investigation and intervention in the National Blood Service Diagnostic and Cellular Therapies User Guide 2003[1]. Identification of platelet-specific and leucocyte-specific antibodies and the provision of antigen negative components, if available, are the final interventions available in the algorithm (appendix A). This audit set out to investigate how closely these guidelines were being adhered to and establish whether platelet-specific and leucocyte-specific antibody tests were impacting on clinical practice.

Aim and Objectives

Eliminate inappropriate requests for antibody screening following SNFHTR

- Establish how closely the guidelines on investigating reactions were being followed
- Establish whether the results of the tests were impacting on clinical practice

Method

A retrospective analysis of samples referred to the NGIL during the preceding two calendar years was undertaken. The information provided on the request form was used to assess each step in the NBS SFNHTR algorithm (appendix A) and was entered onto a proforma (appendix B).
The analysis identified referrals in which platelet or leucocyte specific antibodies were identified and established if matched blood components were subsequently issued.

Results

One hundred and four requests were available for analysis (on average, one a week). In only 7/104 (6.7%) tests did the results lead to the subsequent issue of matched components.
Eight request forms specified fever that exceeded the guidance threshold; two stated paracetamol and three stated the persistence of the reaction on stopping transfusion. Two stated consideration of bacterial contamination and two stated blood cultures specifically. In 6/104 (5.7%) there was an indication of discussion with an NHSBT consultant. No request forms had any specific statement of a trial of ‘washed’ products.

Recommendations

1. A clear definition of a severe febrile non-haemolytic transfusion reaction should be devised and distributed.
2. Emphasis must be placed on consideration of bacterial contamination (or other specific complications of transfusion) prior to testing.
3. All test requests must be discussed with an NHSBT consultant before any work is undertaken, to ensure steps are followed closely and appropriately.
4. Where testing is undertaken, it should be performed sequentially, with HLA antibody screening undertaken first. These tests have the highest yield and most influence practice. Should these tests be negative, further testing could then be undertaken. This would improve the cost-effectiveness of testing. Granulocyte-specific antibody testing should only be performed after consideration of the clinical picture, the use of washed components and exclusion of Human Leucocyte Antigen (HLA) and Human Platelet Antigen (HPA) specific antibodies or in the presence of continuing reactions despite HLA / HPA matched components.
5. The results of this audit should be distributed to transfusion practitioners, scientists and haematologists with an interest in blood transfusion, publicising the indications for antibody screening and the limitations of such testing.
6. Re-audit must be undertaken when these recommendations have been implemented.

Introduction and Background

The National Granulocyte Immunology Laboratory (NGIL) is a part of the NHS Blood and Transplant (NHSBT) Histocompatibility and Immunogenetics (H&I) laboratory in Bristol and processes requests from the whole country for granulocyte immunology. Requests for antibody testing are received in the NGIL following severe febrile non-haemolytic transfusion reactions. These requests seek to establish if platelet-specific, neutrophil-specific or HLA-specific antibodies are present to account for the clinical reaction. The National Blood Service (NBS) provides detailed information as to the necessary steps or therapeutic interventions that should be taken before these tests are requested. These are laid down in the NBS Diagnostic and Cellular Therapies User Guide 2003 (appendix A algorithm). This audit was designed to establish how closely these guidelines were being followed and, indirectly, to establish if the results of these tests were impacting on clinical practice (i.e. their usefulness).

Aim and Objectives

Eliminate inappropriate requests for antibody screening following SNFHTR

- Establish how closely the guidelines on investigating reactions were being followed
- Establish whether the results of the tests were impacting on clinical practice

Standard

NBS Diagnostic and Cellular Therapies User Guide, 2003 (page 26)[1]

Method

Information was gathered retrospectively on requests made for these tests in the period January 1st 2005 to 31st December 2006 (i.e. two calendar years). The cases were identified using a computer search of the records kept at the NGIL. The search identified requests booked in as 'non-haemolytic transfusion reaction' investigation. Data concerning the corresponding HLA antibody testing was obtained from the H&I Typing System (HITS) as these tests and platelet-specific antibody testing may have been performed in other H&I laboratories in different parts of the country.

A proforma was devised (appendix B), with which to interrogate the request forms received at NGIL. The proforma specifically covers each step in the algorithm taken from the Diagnostic and Cellular Therapy Services User Guide 2003, (appendix A), using a tick-box structure, to assess the presence or absence of this information on the request forms. Basic information (referring Hospital and Department, underlying condition and implicated product) was also documented if available.

A strict definition of a *severe* febrile non-haemolytic transfusion reaction (a pre-requisite to follow the algorithm) was not available in the guidelines nor could it be found on searching Medline, Google Scientific or current textbooks in Transfusion Medicine. Temperature guidelines are clear (above 38.5°C, persisting despite stopping transfusion and administering paracetamol), but other clinical parameters were not. Measures of blood pressure and oxygenation were taken as measurable surrogates of a life-threatening reaction and these were included, although there is no clear specification for the inclusion of these. We believed gathering information concerning these measurements may give an indication of the severity of the reaction, and were likely to be stated if sufficiently low to raise concern.

The corresponding results of the tests were then reviewed. Positive or negative screening tests and identified specificities were documented. Computer and paper records were searched for evidence of the issue of typed components in cases where platelet or leucocyte antibodies were detected.

Results

One hundred and twenty six computer entries relating to 118 distinct events were identified. One hundred and four were available for analysis, approximately one for each week of the study period. The others were either incorrectly coded entries (e.g. for investigation of a possible TRALI event), those discussed with NBS consultants and subsequently withdrawn, or those with insufficient sample volume to process (despite requests, further samples were not sent). The full list of exclusions can be found in appendix C.

Part A - Analysis of Request Forms

The majority of the samples were received directly from haematology departments or transfusion laboratories. The proportion received from the North region was greater than both the South East and South West regions together (see figures 1 and 2).

Figure 1 **Referring Departments**

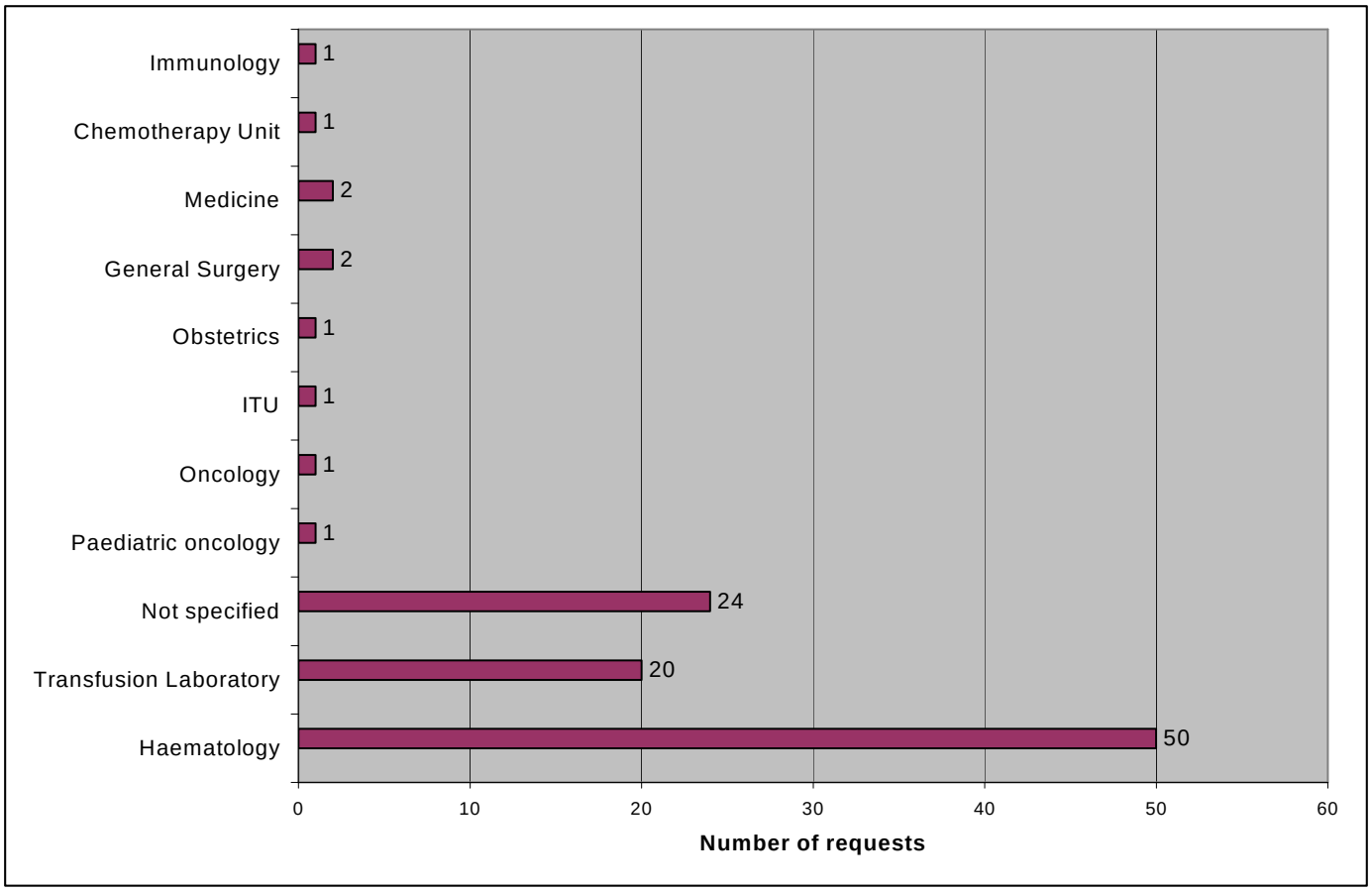
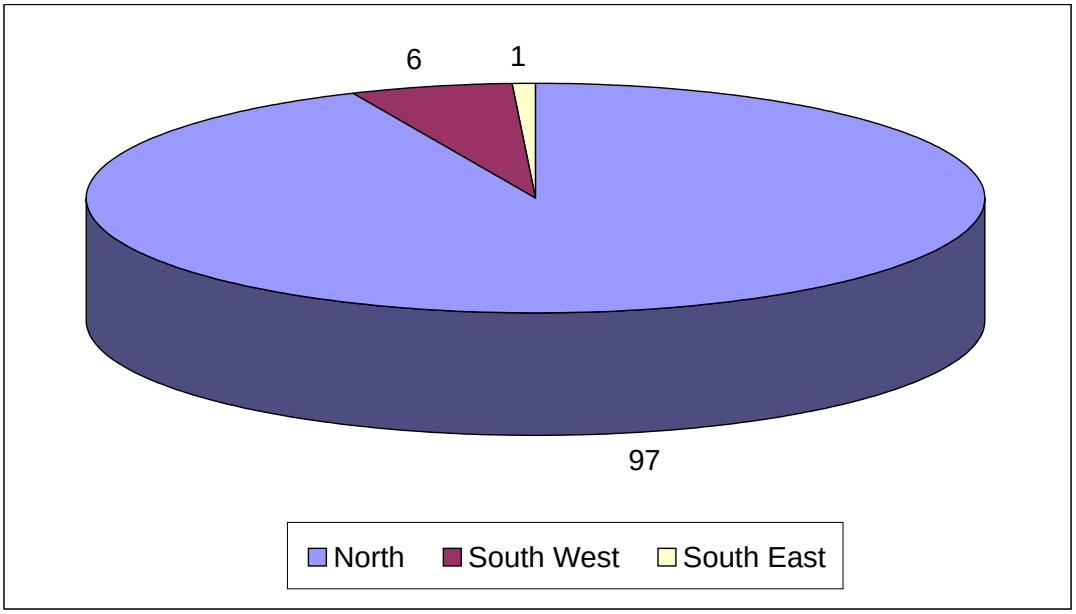


Figure 2 **Requests by Region**



The six referrals in the South West were all made by different hospitals, geographically spread over the entire region.

In the North the number of referrals showed no geographical clustering and appeared to be randomly distributed.

- Twenty hospitals referred one sample each
- Six hospitals referred two samples each
- Six hospitals referred three samples each

Figure 3 **Number of referrals made by individual hospitals in the North**

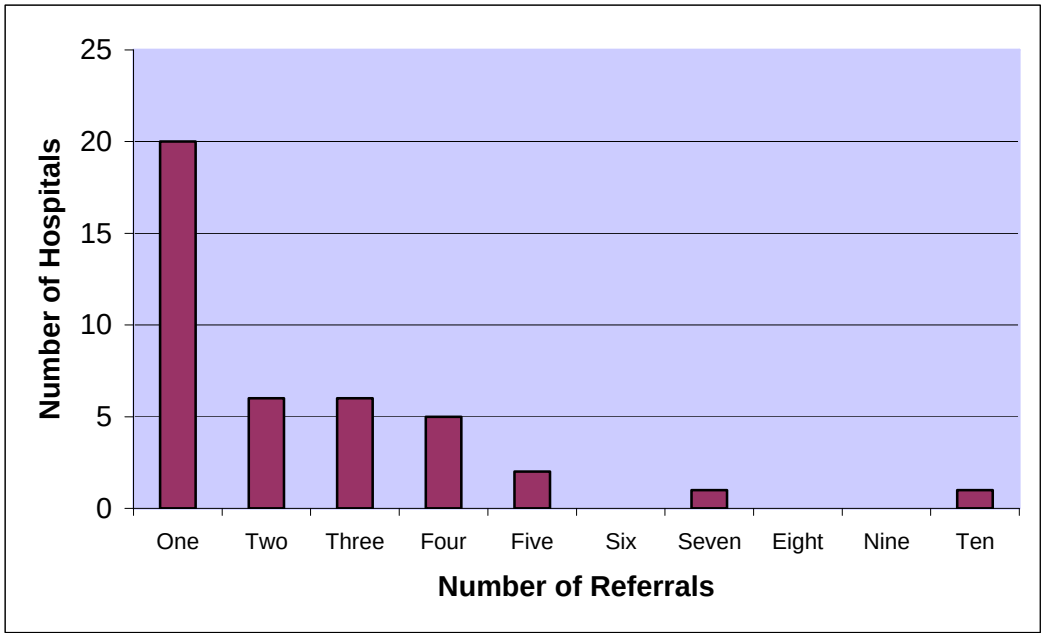
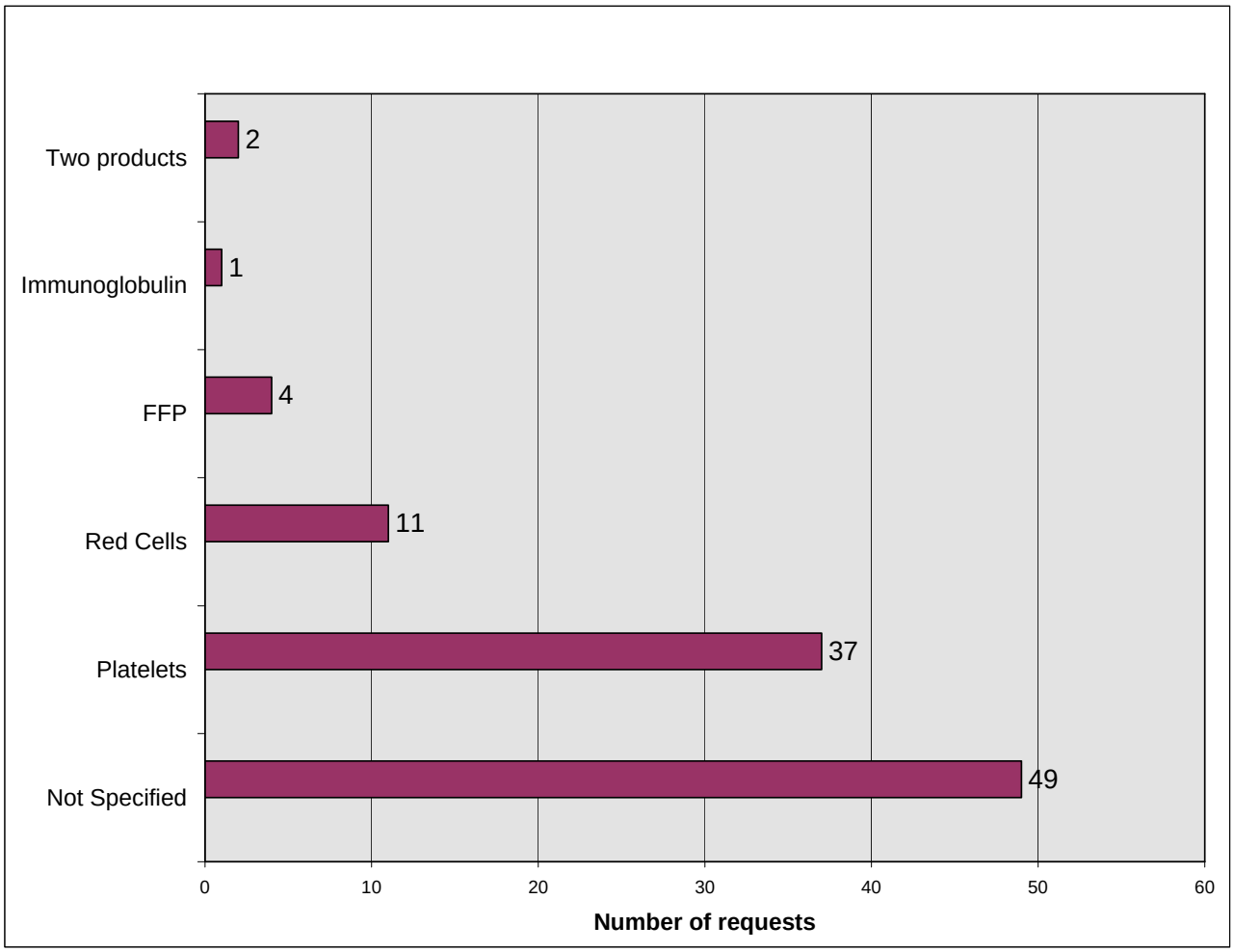


Figure 4 **Implicated Product**



In approximately half of the episodes a blood component or components were implicated on the request form, in two cases both red cells and platelets had been administered in fairly quick succession. When specified, platelet components were most often implicated.

Very few request forms contained information addressing the specific questions derived from the steps in the algorithm. There were 8/104 (7.7%) request forms that specifically referred to temperatures which exceeded the threshold, two forms made mention of paracetamol administration and three to the persistence of the reaction on stopping the transfusion. Consideration of bacterial contamination was documented on two forms and blood cultures were specifically documented on two forms. Six forms had the discussion with an NBS consultant documented. No forms contained information on ongoing reactions despite 'washed' products.

There were 8/104 (7.7%) forms which alluded to hypotensive reactions and 2/104 (1.9%) alluded to worsening hypoxia, though as stated previously these were not clearly stated pre-requisites to testing.

Part B - Antibody Screening and Results

There were 4/104 (3.8%) request forms that did not have HLA-antibody screening, 14/104 (13.5%) did not have HNA-antibody screening and 2/104 (1.9%) did not have HPA-antibody screening. Of the platelet antibody screens, 64 consisted of platelet immunofluorescence test (PIFT) screening, and 38 had both PIFT and monoclonal antibody immobilisation of platelet antigen (MAIPA) evaluation. The reasons for non-testing were not documented.

The results of these screens are summarised below in Table 1.

Table 1: Summary of Antibody Testing

	Number of Requests
Positive screens for HLA-antibodies	49
Specificities established for antibodies	30
HLA-matched products issued	7
Positive screens for granulocyte antibodies	5
Specificities established for antibodies	0
HNA-matched products issued	0
Positive screens for HPA-antibodies	7
Specificities established for antibodies	0
HPA-matched products issued	0

Discussion

Transfusion of blood components is associated with infrequent but significant morbidity[2]. All appropriate measures are therefore taken to minimise such risks. With this in mind, antibody screening following a transfusion reaction is undertaken. However, this audit has highlighted several limitations with the current system which can be addressed.

From the information provided on request forms it appears that the algorithm published by the NBS (reproduced in appendix A)[1] is not being followed prior to requests for antibody testing, although this may be followed in practice but the information not recorded. Particular mention should be made of the paucity of information received by the NGIL regarding consideration of bacterial contamination or the use of 'washed' products. In a large proportion of the requests the indications for the tests seem weak: 'rash and itching during transfusion'. This appears to be borne out by the outcome of the tests: only 7 of the 104 requests resulted in the issue of matched products. A key obstacle to appropriate testing lies in the lack of a clear definition of a severe febrile non-haemolytic transfusion reaction.

The audit itself was not without limitations, but three pertinent ones deserve specific mention. The first, mentioned above, is that evaluating the information received by the laboratory is not the same as evaluating the investigations taken prior to request by the hospital teams. This would have been technically very difficult to undertake, involving direct contact with each referring team, and would therefore have required a prospective

study and a longer study period. Whilst this would be ideal, analysis of the information sent to the specialist centre is a useful surrogate as information explaining the need for testing *should* be conveyed. Secondly, in a small number of cases only the front part of a faxed copy of the request form was received (where samples were subsequently sent on from other centres). In some, these were annotated with clinical information anyway, but there remains a possibility that some information was lost by the absence of the reverse side of the form. These represented a small number of the requests and, if they included similar text to the many other request forms, it would not have significantly altered the findings. Thirdly, advances in antibody identification techniques will have reduced the proportion of samples in which antibodies were detected but the specificities were not defined. As HLA-matched blood components are issued based upon the recipient HLA type rather than antibody specificity, it is unlikely that further resolution of the specificity in this setting would have influenced the number of matched components. It is, however, possible that, if perfect matches were not available, the defined specificities may have influenced the choice of component. There is also the possibility that in some of these patients the HLA antibodies may be an incidental finding rather than the cause of the reactions. When multiply-transfused patients have been screened, HLA antibodies can be found in approximately 50% without necessarily being associated with reactions or platelet transfusion refractoriness[3,4,5,6]. The incidence of antibody formation would be expected to be less following the introduction of universal leucodepletion in the UK in 1999[7] but HLA antibodies can be detected in 20-30% of multiparous females even if untransfused[8,9]. There is no clear way to establish causality, although they were found in a high percentage in this group who had experienced transfusion reactions.

Despite these limitations the data obtained from the audit is still very informative: it does not appear that the algorithm is being followed in the vast majority of cases, and results of testing are modifying clinical practice in only a few.

Recommendations and Action Plan

1. Clear guidance should be issued regarding a definition of a severe febrile non-haemolytic transfusion reaction. This would help to identify situations in which testing is most likely to result in a change to practice, with improvement in safety. We would suggest the term is revised to Severe Non-Haemolytic Transfusion Reaction (as fever is not always a feature of a severe reaction) and a suggestion of how it should be defined is as follows:

   '*A reaction associated with significant morbidity to the recipient, demonstrated by laryngeal or angioedema, hypotension or hypoxia, once alternative explanations have been excluded (Specifically: Anaphylaxis, C1 esterase deficiency, ABO incompatibility, Bacterial Contamination, Transfusion Associated Circulatory Overload (TACO) and Transfusion-related Acute Lung Injury (TRALI).*
   'Hypotension in this setting being defined as a fall in systolic blood pressure to below 100mmHg or by more than 20mmHg compared with the pre-transfusion value. Hypoxia being defined as a fall in oxygen saturation below 90% on air or a fall of 5% compared with pre-transfusion values'

Action: The British Committee for Standards in Haematology (BCSH) is currently developing guidelines on the diagnosis and management of acute transfusion reactions, which will address this issue.

2. The possibility of bacterial contamination or other specific complications should be stressed so that it is more widely considered (especially by non-haematology teams) and expert advice is sought prior to testing.

Action: As described in number 1

3. Those cases thought to fulfil the criteria specified by the definition should be discussed with a consultant within the NBS before any testing is undertaken, so other interventions (such as a trial of 'washed' products) could be undertaken first.

Action: To be implemented nationally following presentation to H&I clinical scientists and medical staff by March 2008. E Massey to follow up

4. Where testing is undertaken, it should be performed sequentially, with HLA antibody screening undertaken first. These tests have the highest yield and most influence practice, based on this cohort of data. Should these tests prove negative, further testing could then be undertaken. This would improve the cost-effectiveness of testing. If the tests prove positive but reactions persist or platelet transfusion refractoriness is identified despite HLA matched components, further testing for HPA antibodies would be indicated. Granulocyte-specific antibody testing should only be performed after consideration of the clinical picture, the use of washed components and exclusion of Human Leucocyte Antigen (HLA) and Human Platelet Antigen (HPA) specific antibodies or in the presence of continuing reactions despite HLA / HPA matched components.

Action: To be implemented nationally following presentation to H&I clinical scientists and medical staff by March 2008. E Massey to follow up

5. The results of this audit should be publicised to illustrate the relative merits of testing: that in some patients they are extremely useful but that a relatively low proportion of requests result in antibody findings which subsequently alter the issue of blood components.

Action: Present the findings to alert clinical teams at a national blood safety meeting (completed November 2007). Circulate the report to all hospitals. Action to be completed by March 2008

6. Following completion of the action plan a further audit should be undertaken to ascertain adherence to the new recommendations.

Glossary

Algorithm	A step-by-step procedure for the solution of a problem using specific mathematical or logical operations
Anaphylaxis	A severe and rapid multi-system allergic reaction

Angioedema	Rapid swelling of the skin, mucosa and sub-mucosal tissues
Antibody	A protein produced in the blood in response to an antigen. By becoming attached to antigens on infectious organisms, antibodies can render them harmless
Antigen	A substance, usually a protein, that can provoke an immune response
Esterase	Any enzyme that splits esters
Febrile	Relating to a raised body temperature
Granulocytes	Any of a group of white blood cells having granules in the cytoplasm
Histocompatibility	The state or condition in which the absence of immunological interference permits the grafting of tissue or the transfusion of blood without rejection
HITS	Histocompatibility and Immunogenetics Typing System
HLA	Human Leukocyte Antigen. Molecular level cell system which has an important role in determining the success or otherwise of transplantation procedures and can cause serious complications in a small number of blood transfusion cases. A system used to assess tissue compatibility
HNA	Human Neutrophil Antigen. Molecular level cell system which is present on neutrophils
HPA	Human Platelet Antigen. Molecular level cell system which is present on platelets
Hypotension	Low blood pressure
Hypoxia	Deficiency in the amount of oxygen reaching body tissues
Immunogenetics	The application of immunological knowledge and techniques to prevent and treat disease
Laryngeal	Relating to the larynx or voice-box
Leucocytes	White blood cells that engulf and digest bacteria and fungi
MAIPA	Monoclonal antibody immobilisation of platelet antigen
Morbidity	The relative incidence of a particular disease
Neutropenia	An abnormal decrease in the number of neutrophils in the blood.
Neutrophil	A neutrophil cell, especially an abundant type of granular white blood cell that is highly destructive
Non-haemolytic	Not resulting in the breakdown of red blood cells
PIFT	Platelet immunofluorescence test
Platelets	The smallest type of cells in the blood, disc-shaped, essential for clotting of blood
Systolic	Relating to or resulting from a heart contraction
TRALI	Transfusion-related acute lung injury (adverse affect of a blood transfusion)

References

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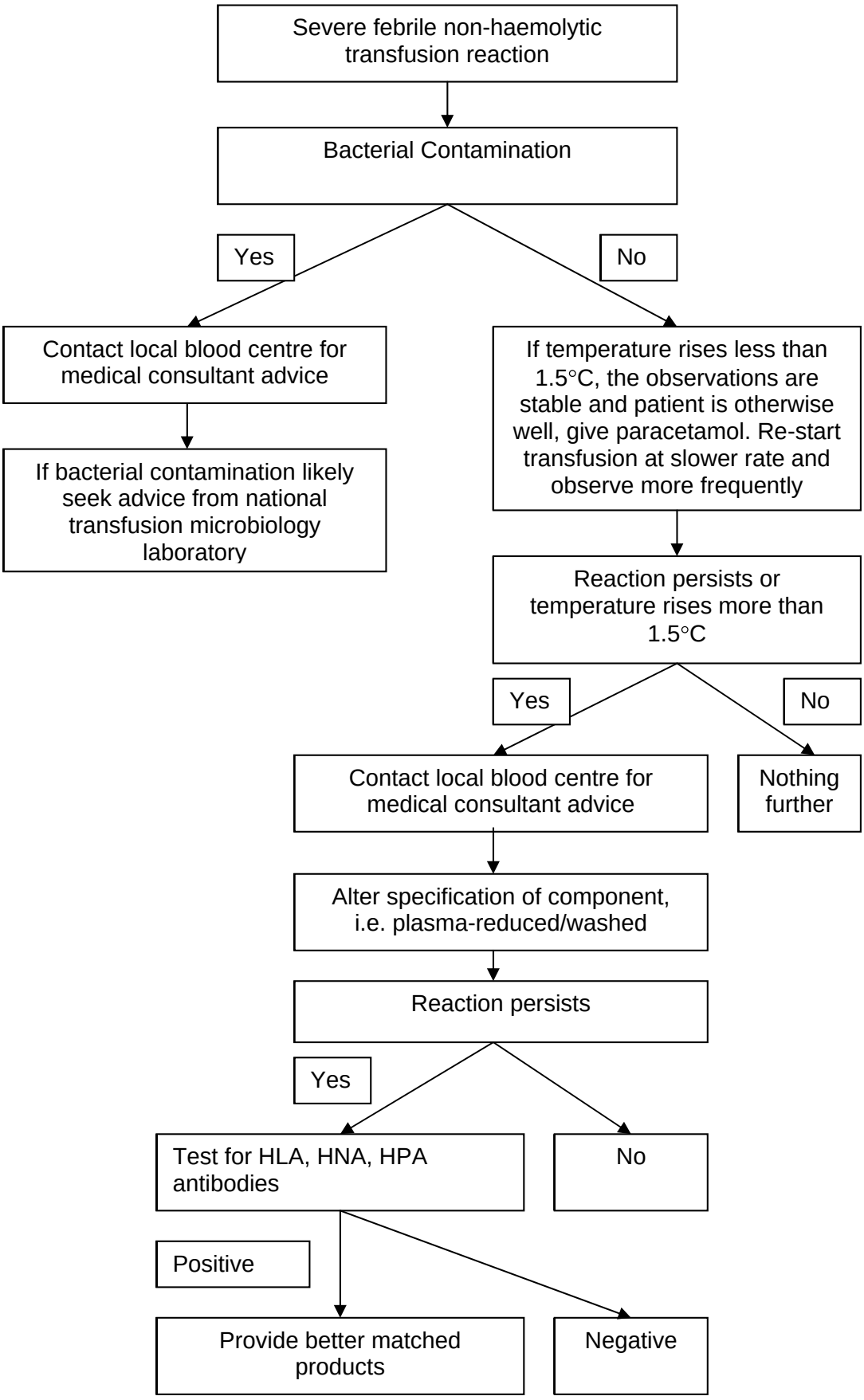
Appendix A

Algorithm for investigations of severe non-haemolytic transfusion reactions



Appendix B **Proforma**

Hospital Number	
Referring Hospital	
Zone	

	Yes	No
Meets criteria for Severe FNHTR?		
Evidence bacterial contamination considered?		
Blood cultures taken / mentioned?		
Reviewed likelihood contamination with NBS consultant?		
Mention of Paracetamol administration?		
Fever rise >1.5 degrees C?		
Reaction persists despite paracetamol/stopping transfusion?		
Advice sought at this point from NBS consultant?		
Evidence of 'washed' products given?		

Were HLA antibodies screened for?		
Were HNA antibodies screened for?		
Were HPA antibodies screened for?		

Were HLA antibodies found? (State specificity under yes)		
Were HNA antibodies found? (State specificity under yes)		
Were HPA antibodies found? (State specificity under yes)		

Appendix C Events excluded from Analysis

Reason for Exclusion	Number of Events
Investigation for TRALI incorrectly coded	3
No form accompanying sample to analyse	1
Investigation of possible auto-immune neutropenia	1
Investigation of poor increment post granulocyte infusion	1
Requests withdrawn (including those withdrawn by NBS consultants) and therefore not processed	5
Insufficient sample to process	2
Total	**13**