MANAGEMENT PROCESS DESCRIPTION MPD596/4.1

The Investigation of Suspected (Non-Bacterial) Transfusion Transmitted Infection

This Management Process Description replaces MPD596/4

Copy Number (obsolete)

Effective **17/07/18**

Summary of Significant Changes

Changed author and owner of document. Amended responsible consultant to read: "Consultant Medical Virologist"

Policy

It is the policy of the NHSBT to investigate possible cases of transfusion transmitted infection.

Purpose

To document and investigate suspected cases of (non-bacterial) transfusion transmitted infection.

Responsibilities

NHSBT Consultant Medical Virologist - Microbiology Services

- **has over all responsibility** for this process.

NHSBT's other clinical staff in Microbiology Services

- are responsible for reporting the case to, and liaising with, the **NHSBT Consultant Medical Virologist - Microbiology Services.**

The NHSBT Consultant Medical Virologist - Microbiology Services, Consultant in Epidemiology / Health Protection or NHSBT Consultant Microbiologist

- are available to provide advice at all stages of the investigation.

Definitions

MS	Microbiology Services
MS	**Clinical** Microbiology Services Clinical
MSO	Microbiology Services Office
MDT	Multi Disciplinary Team
PHE	Public Health England
NTMRL	National Transfusion Microbiology Reference Laboratory
MHRA	Medicines and Healthcare products Regulatory Agency
SABRE	Serious Adverse Blood Reactions & Events
SHOT	Serious Hazards of Transfusion reporting system
BSCARE	Blood Supply Clinical Audit Risk and Effectiveness
NCJDRSU	National CJD Research and Surveillance Unit

Applicable Documents

LET68	Draft notification letter
FRM1534	Form for clinicians
FRM1535	PTI progress sheet
FRM1533	Post transfusion inquiry record
FRM1208	NTMRL request form
FRM1	Adverse Event/Quality Incident Report
MPD577	Management of donors with confirmed positive microbiological markers
SOP3406	Reporting and Managing Adverse Events
MPD579	Responding to Information Supplied by the National CJD Research and Surveillance Unit (NCJDRSU)

Introduction

The guidance contained in this document covers action to be taken at the blood centre.

Any suspected case of transfusion transmitted (non-bacterial) infection should be documented and fully assessed to determine whether investigation of donors is required or warranted.

Because transfusion transmitted infection may be asymptomatic, cases may not be recognised or detected until months or years after the transfusion, and only come to light through incidental screening or specific testing on development of late clinical features of the infection in question. Notification may arise from a number of sources including various clinical departments, the General Practitioner, the local Health Protection teams, Solicitors and NCJDRSU.

The reasons for carrying out a post-transfusion infection investigation are several. Any or all may apply in an individual case:

- To identify an infectious donor, who can then be removed from the donor panel and referred for clinical care.
- To satisfy the clinicians that blood transfusion has been investigated as a possible source of infection.
- To satisfy the need of the recipient, or recipient's family for information about the source of the infection. This, in turn, may lead to a claim for compensation.

Post-transfusion infection investigations are usually restricted to cases involving donations which have been screened for the organism in question. Rarely, the investigation concerns an organism for which the blood has not been screened.

The EU Directive 2005/62/EC uses the term "trace-back" to refer to the process of investigating a report of a suspected transfusion-transmitted adverse reaction in a recipient in order to identify a potentially implicated donor. The NHSBT procedure is more thorough than merely tracing notified donations, and the term "trace-back" is not used for this procedure, especially in view of the potential for confusion with the term "look back".

Reporting a case

The initial report may be by telephone, email or letter. A note of any telephone conversation must be kept. The notification must be relayed to the MS clinical team who will make a preliminary assessment of the case. A notification form (e.g. FRM1534) should be completed by the clinician reporting the case, in order to obtain further details so that the case can be assessed. Further communication will usually be with the hospital haematologist with other interested parties copied in. When the notification is received, the case must be reported to the MS clinical team, via the MSO, and details should be discussed at the MDT meeting so that an assessment can be made as soon as possible about the need for an investigation. A log number must be obtained for the case from the MSO, once a decision has been made to make an investigation. The MSO must ensure that the case is logged on Qpulse, but patient details should not be given. If transmission of infection by transfusion is demonstrated, a quality incident will result. The logging and reporting of cases includes those where investigation is limited to searching donors' records for details of routine tests results. The hospital is responsible for reporting the case to the MHRA via SABRE.

Where notification is received from NCJDRSU, all necessary information is supplied directly to the MSO by fax/letter.

Assessing the case

The basis of investigation of a post-transfusion infection in a recipient is to show:

- that the recipient was not infected prior to transfusion, but had markers of infection thereafter,
- whether any of the donors whose blood components the recipient received could have been infected with the agent in question at the time of donation.

It is often not possible to show conclusively that the recipient was free of infection prior to transfusion. The identification of an infectious agent in the recipient may be made years after the event, perhaps only when the recipient shows symptoms of disease (e.g. HIV and HCV). In most cases the patient will not have been tested for evidence of the infection prior to transfusion. A pre-transfusion blood sample is almost always unavailable. It is important, therefore, to make an assessment of the facts of the case before embarking on an investigation. The assessment should take into account the clinical details, the likely timing of the infection, any other possible sources of infection, and the test results. As a very minimum, a copy of the patient's test results should be obtained, together with relevant clinical details. The likelihood of transfusion being the cause of the infection will depend in part on the residual risk of infection. Nevertheless, many investigations are carried out, even when the likelihood of transfusion transmission is remote, to satisfy patients and clinicians and sometimes to provide information where there is a claim for compensation.

The investigation

Before commencing the investigation, a complete list of the blood components received by the patient and their dates of issue or transfusion is required. Wherever possible, a printed list, preferably generated electronically from laboratory computer records, should be produced.

The following information should be sought from the hospital:

Patient details	Full Name Date of Birth Sex Ethnic Origin
Clinical details	Consultant, with speciality reason for transfusion underlying diagnosis current condition clinical evidence of post-transfusion infection
Laboratory results	Copies of laboratory reports for infectious markers any test results on samples prior to transfusion liver function test results (hepatitis cases)
Transfusion details	Computer print out of transfusion history

Once a decision has been made to start an investigation, and the list of components transfused to the patient has been received, the donors of the blood components must be identified. Where records are held on Pulse, this should be a relatively easy task, but searches involving heritage computer systems and/or paper records are often very time-consuming. When tracing records, care should be taken to ensure that all the available information, such as blood group, date of donation and issue, expiry date, and fate (i.e. hospital receiving the component) is consistent.

The donor records should then be reviewed, together with the results of routine testing of any donations given subsequent to the one which the infected recipient received (the "index donation"). An assessment of what (if any) further investigation is required can then be performed. The NHSBT Consultant Microbiologist is able to give advice on testing and interpretation of results.

Safeguarding the blood supply

Once the donors involved in the investigation have been identified and it has been decided that further investigation is required, the following actions must be carried out:

- each donor's record is flagged to prevent the issue of components from any donations taken before the donor is cleared from the investigation.
- each donor's record is annotated to record the log number of the inquiry.
- any in-date components are traced and recalled/discarded. If a component has been transfused it is not necessary to notify hospital clinicians at this stage as the recall is a precautionary measure, pending full investigation.
- donors who are notified of their involvement because samples are requested are suspended from being called to donate until cleared from the investigation.

- any action with regard to vCJD implicated donations is outlined in MPD579.

The Tests

Routine serological testing of blood donations for HCV and HIV depends upon the presence of antibody as a marker of past exposure. Lack of antibody in the transfused blood component will usually reflect absence of infection. A false negative antibody test could occur in two situations: where the donor is in the early acute phase of infection ("window period") before detectable antibodies have developed, or where there is an error in testing. Both these possibilities can be excluded if the donor has given a further donation, which is also negative in routine antibody screening tests. The existence of infection in the absence of detectable antibody on two different samples is theoretically possible, but extremely unlikely. In addition, pooled samples associated with the donations will have been subjected to genomic testing for HCV (routinely since 2002, earlier in many cases) and HIV (routinely since October 2007, earlier in some cases), making the existence of infection in donations tested by two methodologies remote in the extreme. HBV routine screening uses antigen detection and genomic testing (routine since 2009), and early infection may be detected in the genomic screening test, with a negative antigen test. Such a situation can only be clarified with a further blood sample. HEV RNA screening has been routine since 2017, and no serology screening is used. As most blood recipients have other possible sources of blood-borne infection (e.g. hospital admission, invasive medical procedures, infected sexual partner, or vertical transmission) and have not been proven free of infection before the transfusion, an exhaustive search for a rare "antibody negative but infectious" blood donor is virtually never justified.

Hepatitis B virus

The routine screening test for HBV is hepatitis B surface antigen (HBsAg). Antibody to hepatitis B core (anti-HBc) appears early during the course of HBV infection and is detectable for probably the rest of the lives of individuals who have had HBV infection. However, it does not appear before HBsAg and therefore its presence in the blood, in the absence of HBsAg, is indicative of past rather than current infection. Anti-HBc is not a routine screening test, but will be carried out in certain situations.

Routine blood donation screening in NHSBT includes pooled HBV NAT testing (since 2009), but in some cases the viral load is too low to be detected in pooled NAT testing.

Transmission of HBV to a recipient can theoretically occur because of failure of routine screening, either through laboratory errors, or because levels of HBsAg/HBV DNA in the donated blood are below the sensitivity of the assays in use. These very low levels can occur at the start of an acute infection, in which case no other markers of HBV infection will be detectable, or during lifelong carriage of HBV when viral levels have dropped. In this case, anti-HBc will be detectable.

It is entirely possible for a blood donor to have an inapparent acute HBV infection with full recovery, including elimination of HBsAg and possibly development of anti-HBs, in the time interval between two blood donations. A negative HBsAg result on the index and a subsequent donation is therefore not sufficient to eliminate the donor from the inquiry.

To do so, it is necessary to demonstrate:

- that the donor was not infected with HBV at the time of giving the index donation, and ideally
- that the donor has never had HBV infection.

Testing additional to routine HBsAg and pooled HBV NAT assays will be required to give absolute assurance that a donor has not transmitted HBV to a recipient. It is logical to test any archive samples from the index donation individually for the presence of HBV DNA and to look for anti-HBc in a subsequent donation or sample from the donor. The absence of anti-HBc in a follow-up sample will eliminate a donor from the inquiry. In the absence of a follow-up sample, a negative HBV DNA result in the index donation is required.

Actions and documentation

The main actions involved in the inquiry are listed below.

Actions	- collect recipient information - identify donations - examine relevant donor records - assess test results of index and subsequent donations from each donor - determine need for additional testing (and additional samples) - review results - report conclusion to clinician, hospital laboratory, HPA surveillance etc

Once a decision has been made that an investigation is to be undertaken then a log number must be allocated (see 'reporting a case' above) and a file must be made.

All details relating to the donors in the case and information about the recipient must be kept in the file. The PTI progress sheet (FRM1535) may be used, attached to the inside cover of the file, to provide an easily available summary of the progress of the investigation.

Details of the index donation numbers, the numbers of any subsequent archive samples which are required for testing, together with the donors' names and ID numbers, must be typed onto the Post Transfusion Inquiry Record (FRM1533) and forwarded electronically to NTMRL. Without this form it cannot be guaranteed that NTMRL will perform the correct tests on any samples received in connection with the inquiry. A copy of the Post Transfusion Inquiry Record must be included in the case file.

All requests for tests, whether from fresh or archive samples, must be accompanied by the NTMRL request form (FRM1208). The log number of the case must be included and tests must be specified in order of priority.

Samples from donors

Where archive samples or subsequent donations from a donor are not available, the donor(s) should be approached and asked to provide blood samples for further testing. A request for fresh blood samples can be made using a standard letter sent to all donors for whom a subsequent sample is not available. The letter should contain an explanation of why a sample is required. Although this information may be alarming, donors must not be asked for samples without being told the reason. The likelihood that the donor is the source of infection is remote, and therefore the letter can be reassuring; placing emphasis on the need to eliminate the donors as a source of infection, rather than the expectation of identifying one as such. It is important to give detailed information about how the blood sample can be obtained, how long the results are likely to take, how the donor will be given these results and a contact telephone number for donors who are anxious or who have questions. Once a donor has been eliminated from the inquiry he/she must be informed in writing.

In general, donors may be returned to active donation on the basis of their individual results; without waiting for results on all other donors in the inquiry. In rare situations, donor reinstatement may need to be delayed until the investigation is complete. If an external source of infection is found before all the donors have been investigated, the need to test the remaining donors will be reviewed.

Identification of an infected donor

If a donor is identified as the probable source of infection it will be usual for the donor to be permanently withdrawn from donation, the exception being HEV infection where the donor can be reinstated following viral clearance with seroconversion. The donor should be advised and referred for specialist advice in accordance with the policy for The Management of Donors with Confirmed Positive Microbiological Test Results (MPD577). A lookback will need to be carried out on any transfused components from the index donation and consideration given to lookback on other donations from the same donor. In cases of undetected acute hepatitis B infection, transfused components from the index donation will need tracing, but an earlier donation

may not have been given in the 'window period' and lookback may not be necessary. Donors who contract acute hepatitis B infection may also make a full recovery and develop sufficient immunity to hepatitis B virus to be eligible to donate again. In cases of previously undetected occult hepatitis B infection (OBI), the need to investigate other screen test negative blood components will be considered on a case-by-case basis. Where a 'culprit' donor is identified (a very rare event) the case must always be discussed with the NHSBT Consultant Medical Virologist - Microbiology Services. The recipient must be offered the opportunity for a meeting with relevant clinical staff in order to hear an explanation of the incident: this may require input from NHSBT clinical staff.

Closing the investigation

The case file must be reviewed and checked:

- to ensure that test results are complete
- that 'cleared' donors have been reinstated and informed appropriately
- that all relevant clinicians, and other interested parties, have been informed of the outcome of the investigation (this includes the clinician/GP who is responsible for telling the patient)
- that the Infection Surveillance report form has been completed and then the case reported to SHOT
- that, in the case of transmission:
  - the patient is given the opportunity to be seen by an NHSBT Consultant and advised about the legal position
  - an Adverse Event Quality Incident Report FRM1 is completed in accordance with the SOP for adverse events (SOP3406)
  - the case is reported to BS CARE.

Predicted cases

On occasion a report will be received of infection in a donor from whom a donation has been taken at a time when an infection was possibly present, thus making the components from this donation potentially infectious to the recipients. These cases have in the past usually related to hepatitis A or hepatitis E infection; infections for which routine screening was not previously carried out and for which the viraemic phase is a few days or weeks only.

These cases should be investigated by communicating with hospital clinicians/General Practitioners and making arrangements for follow up and testing of the recipients. Testing of archive sample from the index donation may be helpful in confirming viraemia, and useful for the investigation, but prompt notification of the clinicians caring for recipients is essential if the opportunity is not to be lost for the administration of immune globulin which may avert or attenuate the disease. Urgent notification to clinicians will almost always follow the route used for post-donation information, but NHSBT medical staff working in MS should be notified so a formal investigation of the outcome can be undertaken. Cases should be logged as 'predicted' cases and the Infection Surveillance forms completed in the usual way. In cases where transmission of infection is demonstrated the case should be concluded as above.