21 Transfusion-Transmitted Infections (TTI)

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Definition:

A report was classified as a transfusion-transmitted infection if, following investigation:

- **The recipient had evidence of infection following transfusion with blood components and there was no evidence of infection prior to transfusion and no evidence of an alternative source of infection;**

and, either:

- **At least one component received by the infected recipient was donated by a donor who had evidence of the same transmissible infection**

or:

- **At least one component received by the infected recipient was shown to contain the agent of infection.**

DATA SUMMARY
Total number of cases: 3

Implicated components		Mortality/morbidity	
Red cells	2	Deaths due to transfusion	0
FFP	1	Deaths probably/likely due to transfusion	0
Platelets	0	Deaths possibly due to transfusion	0
Cryoprecipitate	0	Major morbidity	3
Granulocytes	0	Potential for major morbidity (Anti-D or K only)	0
Anti-D Ig	0		
Multiple components	0		
Unknown	0		

Gender		Age		Emergency vs. routine and core hours vs. out of core hours		Where transfusion took place	
Male	1	≥18 years	2	Emergency	1	Emergency department	0
Female	2	16 years to <18 years	0	Urgent	0	Theatre	1
Not known		1 year to <16 years	1	Routine	0	ITU/NNU/HDU/Recovery	0
		>28 days to <1 year	0	Not known	2	Wards	1
		Birth to ≤28 days	0			Delivery Ward	0
		Not known	0	In core hours	0	Postnatal	0
				Out of core hours	0	Medical Assessment Unit	0
				Not known/Not applicable	3	Community	0
						Outpatient/day unit	0
						Hospice	0
						Antenatal Clinic	0
						Not known/Not applicable	1

** The data summary table shows cases reported to SHOT in 2012 (Cases 1 and 2). Incidents are described in the chapter for the year in which they were reported to the NHSBT/Public Health England Epidemiology Unit.*

Reporting

Most reports of suspected viral and bacterial transfusion-transmitted infections (TTI) are received and investigated by the UK Blood Services and reported to the NHS Blood and Transplant (NHSBT)/Public Health England (PHE) Epidemiology Unit. From here, data are included in the SHOT report even if the investigation is not yet complete, as the investigation into suspected viral TTI can take several months. These are reconciled with TTI reports made to the SHOT online reporting system which in most cases will also have been reported to the Medicines and Healthcare products Regulatory Agency (MHRA)'s online reporting system for Serious Adverse Blood Reactions and Events (SABRE). Incidents are described in this chapter for all reports made to the NHSBT/PHE Epidemiology unit in 2012. The data summary table shows cases reported to SHOT in 2012. These may differ from the cases reported to the NHSBT/PHE Epidemiology unit described in this chapter depending on the timing of reporting.

Guidance on initiating an investigation and the required reporting forms for suspected transfusion-transmitted infections (TTIs) for hospitals served by NHSBT can be found on the Requests for Investigation of Adverse Events & Reactions page at http://www.blood.co.uk/hospitals/library/request_forms/aer/.

For other Blood Services please contact the local Blood Centre.

Summary of reports made to the NHSBT/PHE Epidemiology Unit in 2012

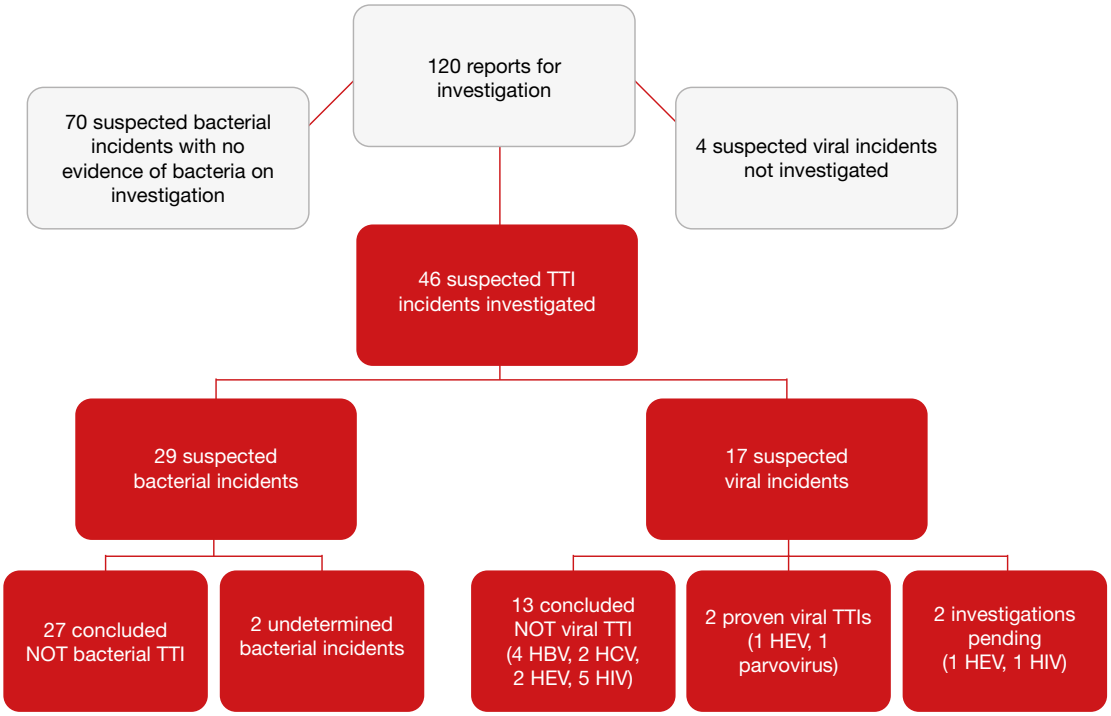

Figure 21.1: Outcome of reports of suspected TTIs made to the NHSBT/PHE Epidemiology Unit in 2012

During 2012, 46 suspected TTI incidents were reported by Blood Services and hospitals throughout the UK.

A further 70 investigations into reports of suspected bacterial incidents found no evidence of bacteria in either the recipient or the pack and were reclassified as possible transfusion reactions (see the chapter on acute transfusion reactions, Chapter 16, for reactions transferred from TTI).

A further four viral incidents were not investigated because either infection was not confirmed (1 hepatitis C); results were shown to be due to passive transfer (1 hepatitis B); infection was present prior to transfusion (1 hepatitis E); or historic hospital records were not available (1 human immunodeficiency virus (HIV)).

Learning point

- Immunoglobulin therapy can lead to passive transfer of antibodies which may be confused with infection. Careful review of the markers and timing can rule out infection before a report is made to the Blood Service. See Chapter 23 on 'unclassifiable complications of transfusion' for more information on passive transfer

Proven transfusion-transmitted infections reported in 2012

Two incidents were confirmed as TTI according to the above definition. Both were viral, one parvovirus incident (reported to SHOT in 2012, see data summary table) and one hepatitis E virus (HEV) incident (not yet reported to SHOT at the time of writing). Neither infection is currently screened for by the UK Blood Services.

Thirteen investigations of viral infections were concluded as not TTI including 2 HEV incidents.

Learning point

- Clinicians investigating suspected viral transfusion-transmitted infections (TTI) should explore all possible risk exposures in parallel with the Blood Service investigations, in order to determine the patient's most likely source of infection

Undetermined cases reported in 2012

Two bacterial cases were undetermined, as satisfactory investigation was impossible due to missing or leaking packs.

Learning point

- A lack of packs for microbiological culture can hinder the investigation of suspected bacterial transfusion-transmitted infections (TTI). Hospitals need to retain packs, even if near empty, for return to the Blood Service as the residue can be washed out and cultured. If sampling packs locally for bacterial testing, use ports rather than breaching the pack to minimise environmental contamination of the pack

Near miss

There was one near miss in a red cell pack as described in the MHRA chapter, Chapter 6.

Variant Creutzfeld-Jakob Disease (vCJD)

There were no vCJD investigations in 2012.

Investigations pending in 2011

One hepatitis B virus (HBV) TTI incident reported as pending in the SHOT 2011 report has been confirmed as proven and was reported to SHOT in 2012 (see data summary table).

Case reports of TTI from investigations started or concluded in 2012

Case 1: Jaundice and high liver enzymes 17 weeks after transfusion, hepatitis B (HBV) transmission to two recipients

A recipient of multiple transfusions during emergency cardiac surgery in August 2011 was diagnosed with acute HBV after jaundice and a high alanine aminotransferase (ALT) test result prompted HBV testing in December 2011. The recipient was not immunosuppressed and was shown to be anti-HBc (hepatitis B core antibody) negative on an archived sample from December 2008. Another identified risk was dental treatment in September 2011. The recipient gradually cleared the HBV infection over the following months.

The recipient had received red cells, fresh frozen plasma (FFP) and apheresis platelets; 15 of 16 donors of these units were cleared. One donor whose FFP had been transfused to the recipient was shown to have evidence of exposure and immunity to HBV (anti-HBc positive/anti-HB surface antibodies >100 mIU/ml) on a donation 4 months after the implicated index donation. The index donation had been HBsAg screen negative (individual sample testing) and HBV NAT negative in testing of pooled samples. Retrospective individual sample testing of the archived sample of the index donation detected HBV DNA in one of two PCR tests used in the reference laboratory. Retrospective testing of three archived donation samples given before July 2011 showed no evidence of exposure to HBV.

Lookback into the fate of the associated red cell component from the July index donation revealed chronic asymptomatic HBV infection (HBsAg and HBeAg positive) in the elderly female recipient. The recipient of red cells from the subsequent donation, at which time the donor had immunity to HBV, was HBV negative.

The white-British male donor was asymptomatic and unaware of his HBV infection. The only possible reported risk was participation in contact sports. Two transmissions occurred as a result of a donor with no reported deferrable risks donating with an early HBV infection undetectable by the screening tests in place at the time. Although HBV DNA is not a mandatory blood donation screening test it is included in the Triplex NAT screening test currently used on all donations. It was concluded that the level of HBV DNA was too low to be detected in the pooled NAT screening test.

Learning points

- Jaundice post transfusion can be due to a ‘flare up’ of existing HBV infection. This is less likely when the recipient is not immunosuppressed and can be ruled out prior to reporting to the Blood Service for investigation if the recipient can be shown to be negative prior to transfusion

Case 2: Pyrexia and lymphopenia 48 hours post transfusion, parvovirus transmission

A child given a red cell transfusion for sickle cell anaemia in September 2012 had a temperature of 41°C and lymphopenia 48 hours later. Parvovirus B19 DNA and IgG and IgM antibodies were detected approximately two weeks post transfusion.

The implicated donation was found to be parvovirus B19 DNA positive, IgM negative and IgG equivocal. A subsequent sample from the donor was positive for DNA, IgM and IgG. Both recipient and donor shared the same B19 genotype, although it was a very common form. Although classed for SHOT purposes as major morbidity, the patient recovered from the infection and was reported well by the next scheduled transfusion two weeks later although the haemoglobin was lower than expected. The 25 year old repeat donor was asymptomatic and did not report any illness before or after donation.

Case 3: Abnormal liver enzymes after multiple transfusions, hepatitis E (HEV) transmission

An adult female recipient who underwent a stem cell transplant with associated transfusion support over the autumn of 2011 developed abnormal liver function tests (LFTs) in May 2012. Testing of stored samples established that the recipient had been HEV negative in December 2011 but HEV RNA positive in February 2012. Unfortunately the recipient died in autumn 2012 from causes unrelated to the HEV infection. The stem cell donor was HEV negative.

Thirty-four donations were investigated and two donors were confirmed to be HEV RNA positive at the time of donation: Donor A had sequence data that matched that in the recipient, whereas Donor B had a virus with a divergent sequence. The recipient had received FFP from Donor A, and red cells from Donor B. Lookback on the red cell component from Donor A's donation identified an adult female transfused for a haematological condition. This second recipient was HEV RNA negative, but positive for HEV antibodies (IgG and IgM) a year after transfusion, consistent with a previous HEV infection. It was therefore likely that transmission had occurred from Donor A although the lack of HEV RNA positivity in the second recipient precluded typing to confirm Donor A as the source of the HEV infection. Donor A, a 22 year old repeat male, had not reported any illness prior to the index donation and had cleared the infection and seroconverted when tested six months later.

Learning point

- Samples pre and post-transfusion from a recipient where viral transmission is suspected are often invaluable to an investigation into a possible TTI to help exclude a pre-existing infection and date the acquisition of infection. It may be useful to search for samples in other pathology departments

Cumulative data

Table 21.1: Number of confirmed TTI incidents, by year of report with total infected recipients and outcomes (death, major morbidity, minor morbidity) in the UK between October 1996 and December 2012 (Scotland included from October 1998)

Year of report	Bacteria	HAV	HBV	HCV	HEV	HIV	HTLV	Parvo-virus B19	Malaria	vCJD/ prion
1996-97	3	1	1	1	0	1	0	0	1	0
1997-98	1	0	2	0	0	0	0	0	0	0
1998-99	6	0	2	1	0	0	0	0	0	0
1999-00	5	0	1	0	0	0	0	0	0	0
2000-01	4	0	1	0	0	0	1	0	0	0
2001-02	5	0	0	0	0	0	1	0	0	0
2003	3	1	2	0	0	1	0	0	1	1
2004	0	0	0	0	1	0	0	0	0	0
2005	2	1	1	0	0	0	0	0	0	1
2006	2	0	0	0	0	0	0	0	0	1
2007	3	0	0	0	0	0	0	0	0	0
2008	4	0	0	0	0	0	0	0	0	0
2009	2	0	0	0	0	0	0	0	0	0
2010	0	0	0	0	0	0	0	0	0	0
2011	0	0	1	0	0	0	0	0	0	0
2012	0	0	0	0	1	0	0	1	0	0
Number of incidents	**40**	**3**	**11**	**2**	**2**	**2**	**2**	**1**	**2**	**3**
Number of infected recipients	**43**	**3**	**13**	**2**	**3**	**4**	**2**	**1**	**2**	**4**
Death due to, or contributed to, by TTI	11	0	0	0	0	0	0	0	1	3
Major morbidity	28	2	13	2	1	4	2	1	1	1
Minor morbidity	4	1	0	0	2	0	0	0	0	0

Bacterial infection

The last reported confirmed bacterial TTI was in 2009. This predates universal bacterial screening throughout the UK Blood Services and is not necessarily a consequence of screening as packs are released as 'negative-to-date' which may be before bacteria have multiplied sufficiently to trigger an initial screening reaction. A total of 33 bacterial incidents have been due to the transfusion of platelets.

Learning points

- It is important to remain vigilant for potential bacterial transmission because bacterial screening of platelets will not prevent release of all contaminated packs. See the chapter on acute transfusion reactions, Chapter 16, for advice on when to request bacterial investigations following an acute transfusion reaction
- Be aware that bacterial transmissions also have the potential to occur via red cells

Viral infection

The year of transfusion may have been many years prior to the year in which the case is investigated and reported to SHOT because of the chronic nature of some viral infections. Since 1996, 23 confirmed incidents of transfusion-transmitted viral infections have been reported, involving a total of 28 recipients. HBV is the most commonly reported proven viral TTI in the UK.

No screening was in place for human T cell lymphotropic virus (HTLV) at the time of the documented transmissions. There is currently no screening for hepatitis A (HAV), HEV or parvovirus B19.

The two HIV incidents were associated with window period donations (anti-HIV negative/HIV RNA positive) before HIV NAT screening was in place. A third window period donation in 2002 was transfused to an elderly patient, who died soon after surgery. The recipient's HIV status was therefore not determined and not included in Table 21.1.

Parasitic infection

In both malaria transmissions, malaria antibody testing was not applicable at the time according to information supplied at donation.

vCJD

The vCJD incidents took place in 1996/97 prior to the introduction of leucodepletion and other measures taken by the UK Blood Services to reduce the risk of vCJD transmission by blood, plasma and tissue products[82].

The outcome for one infected recipient was assigned to major morbidity (Table 21.1) because although there was post-mortem evidence of abnormal prion proteins in the spleen the patient had died of a condition unrelated to vCJD and had shown no symptoms of vCJD prior to death.

Despite international research efforts there is currently no suitable test available for screening blood donations for vCJD.

COMMENTARY

Although documented HBV transfusion transmission had not, until recently, been reported in the UK since 2005, HBV remains the most commonly reported viral TTI. Although very low, the risks for an infectious HBV donation entering the blood supply in the UK[83] remain higher than for HIV and HCV because the window period (the period when virus is present and the donation is infectious but not detected by screening tests) for HBV is longer than for the other two viruses. The latest incident involved a donor with no reported deferrable risk who donated in the very early stages of infection, before levels of DNA and HBsAg had reached levels detectable by the screening tests. The 10 incidents previously recorded in SHOT were also due to acute infection with undetectable HBsAg on screening. HBV DNA testing on pools of 24 has been performed by the UK Blood Services since 2009 as part of the triplex HBV/HCV/HIV NAT test employed, but is not mandatory for blood donations in the UK. Between April 2009 and December 2012 HBV NAT screening in the UK has identified five cases of acute HBV in blood donors that were not detected by HBsAg screening.

The parvovirus incident was the first case of proven parvovirus B19 (B19V) transmission in the UK since SHOT started in 1996. Three other possible parvovirus cases reported to the NHSBT/PHE unit in 2007, 2008 and 2010 were not concluded to be TTI. Red cells were implicated in this case but there are case reports in the literature of B19V transmissions from all blood components[84,85]. Infection is usually asymptomatic and the consequences were limited in this incident but depend on the host[86]. Those at greatest risk of a serious outcome are seronegative patients with increased erythropoiesis, pregnant women and immunocompromised patients. However, B19V is common, with infection generally conferring lifelong immunity, and a high proportion of blood recipients will be immune. In the UK outbreaks often occur in late winter and early spring on a 3-4 year epidemic cycle[87] with 2012 being an epidemic year. Donors are often asymptomatic at the time of highest viraemia, and cannot be reliably excluded based on symptoms. The UK Blood Services do not perform parvovirus screening on blood donations although plasma products are screened for high titres of B19V RNA by the manufacturers.

The HEV transmission was the second proven HEV TTI incident in the UK since SHOT began. The first incident, reported in 2004, was investigated after a repeat donor reported onset of jaundice 23 days post donation. Lookback identified two recipients: one who had received red cells and developed mild jaundice and abnormal liver function tests with rapid recovery, and one who had received platelets and had no evidence of infection. It is possible that this second recipient had received passive transfer of antibody in the plasma included in the platelet pool, or from other transfused components. HEV is usually self limiting but sometimes has a more chronic outcome in immunocompromised cases [88,89]. Previously HEV has been associated with consuming contaminated food and water in endemic countries where sanitation may be poor. However there are increasing reports of HEV infection acquired in industrialised countries. This includes the UK, where numbers of cases have increased substantially since 2010, with non-travel cases accounting for the majority of cases in 2011/12[90]. There was an increase in reports of suspected HEV transmissions, five in all, made to the Blood Service in 2012 probably due to increased awareness of the potential for HEV to be transmitted via blood[91]. The UK Blood Services do not perform HEV screening on blood donations. A study is currently underway to investigate HEV incidence and transmissibility in blood donations in England.

Although no proven bacterial TTIs have been reported in SHOT since 2009 it is important to remain vigilant[92] as bacterial screening will not prevent all bacterial contamination. Possible transmissions should be reported as soon as possible to ensure that the associated packs can be recalled (see the MHRA chapter, Chapter 6 on recall fails and the recommendation in the chapter on acute transfusion reactions, Chapter 16). Ideally packs should be returned to the Blood Service for testing to avoid contamination when sampling the pack.

Recommendations

- Retain suspected bacterially contaminated packs, even if near empty, for return to the Blood Service as the residue can be washed out and cultured. Report a suspected bacterial transfusion-transmitted infection (TTI) promptly to the Blood Service to allow recall of any associated packs for testing. If sampling packs locally for bacterial testing, use ports rather than breaching the pack to minimise environmental contamination of the pack

Action: Clinicians, Transfusion and Microbiology Laboratory Managers (see also the chapter on acute transfusion reactions, Chapter 16, previous recommendation on recall)

- Hospitals and Blood Centres investigating a possible viral TTI are reminded of the importance of locating any archived recipient samples (transfusion-related or not) for testing. It is important that laboratories facilitate access to those samples (with due consent of appropriate parties including the patient)

Action: Clinicians, Transfusion Laboratory Managers, Hospital Transfusion Team (HTT)

Previous recommendations still active

- Even if TTI is excluded in a case of ATR, the case should still be reported to SHOT as an ATR If necessary

Action: HTTs, Clinicians

- Clinicians investigating suspected viral TTIs should explore all possible risk exposures in parallel with the Blood Service investigations, in order to determine the patient's most likely source of infection. This includes checking records and testing samples taken prior to the implicated transfusion(s) to check that the recipient was not infected prior to transfusion

Action: Clinicians, UK Blood Services