Appendix A. Adverse Reaction Case Definition Criteria

Allergic reaction: The result of an interaction of an allergen with preformed antibodies. In some instances, infusion of antibodies from an atopic donor may also be involved. It may present with only mucocutaneous signs and symptoms.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: 2 or more of the following occurring during or within 4 hours of cessation of transfusion: • Maculopapular rash • Urticaria (hives) • Pruritus (itching) • Generalized flushing • Localized angioedema • Edema of lips, tongue and uvula • Erythema and edema of the periorbital area • Conjunctival edema • Respiratory distress; bronchospasm • Hypotension **Probable:** **ANY 1** of the following occurring during or within 4 hours of cessation of transfusion : • Maculopapular rash • Urticaria (hives) • Pruritus (itching) • Localized angioedema • Edema of lips, tongue and uvula • Erythema and edema of the periorbital area • Conjunctival edema **Possible:** N/A	**Definitive:** N/A **Probable:** N/A **Possible:** N/A	**Grade 1:** No immediate risk to the life of the patient **AND** Responds quickly to symptomatic treatment. **Grade 2 – 4:** Involves respiratory and/or cardiovascular systems and presents like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous symptoms, there are airway symptoms, hypotension, or associated symptoms like hypotonia and syncope. The respiratory signs and symptoms may be laryngeal (tightness in the throat, dysphagia, dysphonia, hoarseness, stridor) or pulmonary (dyspnea, cough, wheezing, bronchospasm, hypoxemia). Such a reaction usually occurs during or shortly after cessation of transfusion. For the purpose of classification, this type of allergic reaction would be graded as: **2: severe** **3: life-threatening** **4: death**.	**Definite:** Occurs during or within 2 hours of cessation of transfusion **AND** No other evidence of environmental, drug or dietary risks. **Probable:** Occurs during or within 2 hours of cessation of transfusion **AND** Other potential causes are present in an individual with known susceptibility (atopic; previous allergic reactions to transfusions). **Possible**: Occurs 2 - 4 hours after cessation of transfusion **OR** Other causes such as medication or exposures likely, but transfusion cannot be ruled out.

Acute hemolytic transfusion reaction (AHTR): Rapid destruction of red blood cells during, immediately after, or within 24 hours of cessation of transfusion. Clinical and laboratory signs of hemolysis are present. No single criterion exists to definitively diagnose this rare disorder. See Appendix D for common antibodies associated with AHTR.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: Occurs during, immediately after, or within 24 hours of cessation of transfusion with **ANY** of the following: • Chills/rigors • Fever • Back/flank pain • Hypotension • Hemoglobinuria occurring during or shortly after cessation of transfusion • Epistaxis • Oliguria/anuria • Renal failure • Disseminated intravascular coagulation (DIC) • Pain and/or oozing at IV site **AND EITHER** ABO incompatibility or other allotypic RBC antigen incompatibility **OR** Clerical check indicates that the patient's name and blood group on the blood unit are different than the recipient's name and blood group.	**Definitive:** Positive direct antiglobulin test (DAT) for anti-IgG or anti-C3 **AND** Positive elution test with alloantibody present on the transfused red blood cells **AND** 2 or more of the following: • Elevated LDH • Elevated bilirubin • Low haptoglobin • Hemoglobinuria • Low fibrinogen • Elevated plasma hemoglobin	**Use severity grades as defined in Appendix C.**	**Definite:** ABO or other allotypic RBC antigen incompatibility is known **OR** Serologic work-up is consistent with AHTR and no other cause of acute hemolysis is present. **Probable:** No serologic evidence of AHTR **OR** Blood bank testing may show abnormal results but AHTR may also be due to erythrocyte auto-antibodies in the recipient. **Possible:** Evidence of non-immune contributing factors such as hemolysis-inducing mechanical factors (e.g. malfunction of a pump, use of a blood warmer, use of hypotonic solutions, etc.) is present.
Probable: Same as definitive case criteria.	**Probable:** Incomplete laboratory confirmation to meet definitive case definition criterion.		
Possible: N/A	**Possible:** N/A		

Delayed hemolytic transfusion reaction (DHTR): The recipient develops antibodies to RBC antigen(s) between 24 hours and 28 days after cessation of transfusion. Clinical signs of hemolysis are usually present. If performed, post-transfusion LDH and bilirubin levels increase and subsequently fall back to baseline in the following days. See Appendix D for common antibodies associated with DHTR.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: Patient may be asymptomatic or have symptoms that are similar to but milder than AHTR. Examples of symptoms include: • Chills/rigors • Fever • Jaundice • Back/flank pain • Hypotension • Hemoglobinuria/ hematuria • Oliguria/anuria. **NOTE:** These symptoms are **NOT** required to meet definitive case criteria. **Probable:** Same as definitive case criteria. **Possible:** N/A	**Definitive:** Positive direct antiglobulin test (DAT) for antibodies developed between 24 hours and 28 days after cessation of transfusion **AND EITHER** Positive elution test with alloantibody present on the transfused red blood cells **OR** Newly-identified red blood cell alloantibody in recipient serum **AND EITHER** Inadequate rise of post-transfusion hemoglobin level or rapid fall in hemoglobin back to pre-transfusion levels **OR** Otherwise unexplained appearance of spherocytes. **Probable:** Newly-identified red blood cell alloantibody demonstrated between 24 hours and 28 days after cessation of transfusion **BUT** Not enough laboratory evidence to meet definitive criteria. **Possible:** N/A	**Use severity grades as defined in Appendix C.**	**Definite:** Meets **definitive** case definition criteria **AND** No other explanation for drop in hemoglobin. **Probable:** Meets **probable** case definition criteria **AND** No other explanation for drop in hemoglobin. **Possible:** Meets **definitive** or **probable** case definition **BUT** Other explanation(s) for drop in hemoglobin are present.

Delayed serologic transfusion reaction (DSTR): Demonstration of new, clinically significant alloantibodies against red blood cells between 24 hours and 28 days after cessation of a transfusion despite an adequate, maintained hemoglobin response. See Appendix D for common antibodies associated with DSTR.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: Absence of clinical signs of hemolysis. **Probable**: N/A **Possible**: N/A	**Definitive:** Demonstration of new, clinically-significant antibodies against red blood cells between 24 hours and 28 days after cessation of a transfusion that were not present in the pre-transfusion specimen **BY EITHER** Positive direct antiglobulin test (DAT) **OR** Positive antibody screen with newly identified RBC alloantibody. **Probable**: N/A **Possible**: N/A	**Use severity grades as defined in Appendix C.**	**Definite**: Meets **definitive** case definition criteria. **Probable**: N/A **Possible**: N/A

Hypotensive transfusion reaction: A drop in blood pressure occurring during or within one hour of cessation of transfusion. Other symptoms, such as facial flushing, dyspnea, or abdominal cramps may occur but usually hypotension is the sole manifestation.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: **ALL OF THE FOLLOWING:** • Hypotension - Adults (18 years and older): Drop in **systolic** BP of greater than or equal to 30 mmHg **AND** **Systolic** BP less than or equal to 80 mmHg. - Infants, children and adolescents (1 year to less than 18 years old): Greater than 25% drop in systolic BP (e.g., drop in baseline systolic BP of 120mmHg to below 90mmHg). - Neonates and small infants (less than 1 year old OR any age and less than 12 kg body weight): Greater than 25% drop in baseline value using whichever measurement is being recorded (e.g., mean BP). • Occurs less than 15 minutes after the start of the transfusion • Responds rapidly (within 10 minutes) to cessation of transfusion and supportive treatment. • All other adverse reactions presenting with hypotension must be excluded. **Note**: If the patient meets the criteria for another adverse transfusion reaction presenting with hypotension, the more specific adverse reaction should be reported. **Probable**: Same as definitive criteria **EXCEPT:** Onset is between 15 minutes after start and 1 hour after cessation of transfusion **OR** The patient does not respond rapidly to cessation of transfusion and supportive treatment. **Possible:** N/A	**Definitive:** N/A **Probable:** N/A **Possible:** N/A	**Grade 1:** The recipient required no more than discontinuation of transfusion and symptom management **AND** No long-term morbidity resulted from the reaction. **Grade 2:** The recipient required in-patient hospitalization or prolongation of hospitalization due to hypotension or hypotension led directly to long-term morbidity (e.g., brain damage) **AND** Vasopressors were not required. **Grade 3:** The recipient required vasopressors. **Grade 4:** The recipient died as a result of the hypotensive transfusion reaction or as a result of treatment directly related to resolving symptoms of the reaction.	**Definite:** Meets the **definitive** protocol criteria **AND** The patient has no other conditions that could explain hypotension. **Probable:** Meets the **probable** case definition criteria **OR** Other conditions that could explain hypotension are unlikely but not fully excluded. **Possible:** Meets **definitive** or **probable** case definition criteria **BUT** Other conditions that could readily explain hypotension are present.

Febrile non-hemolytic transfusion reaction (FNHTR): Fever and/or chills **without** hemolysis occurring in the patient during or within 4 hours of cessation of transfusion. If transfusion-related, the most common cause is a reaction to passively transfused cytokines or a reaction of recipient antibodies and leukocytes in the blood product. If blood culture of patient or residual component is performed, the results should be negative. Laboratory findings should show no evidence of acute hemolysis.

Case Definition Criteria		**Severity**	**Imputability**
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: Occurs during or within 4 hours of cessation of transfusion **AND EITHER** Fever (greater than or equal to 38°C oral or equivalent and a change of at least 1°C from pre-transfusion value) **OR** Chills/rigors are present. **NOTE:** FNHTR can be present in absence of fever if chills or rigors occur. **Probable:** N/A **Possible:** N/A	**Definitive:** N/A **Probable:** N/A **Possible:** N/A	**Use severity grades as defined in Appendix C.**	**Definite:** Patient has no other conditions that could explain symptoms. **Probable:** Other conditions present that could explain symptoms are unlikely but cannot be ruled out. **Possible:** Other conditions are present or were present before the transfusion that most likely explain symptoms.

Post transfusion purpura (PTP): Thrombocytopenia usually arising 5-12 days following transfusion of cellular blood components with findings of antibodies in the patient directed against the Human Platelet Antigen (HPA) system.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: Thrombocytopenia (decrease to less than 20% of pre-transfusion count) **Probable:** Drop in platelets to levels between 20% and 80% of pre-transfusion count. **Possible:** N/A	**Definitive:** Alloantibodies in the patient directed against HPA-1a or other platelet specific antigen detected at or after development of reaction. **Probable:** Same as definitive laboratory criteria. **Possible:** HPA antibodies not tested or negative.	**Use severity grades as defined in Appendix C.**	**Definite:** Meets **definitive** or **probable** case definition criteria **AND** Occurs 5-12 days post-transfusion **AND** Patient has no other conditions to explain thrombocytopenia. **Probable:** Meets **definitive** or **probable** case definition criteria **AND EITHER** Occurs less than 5 or more than 12 days post-transfusion **OR** Other condition(s) present that could explain thrombocytopenia are unlikely but cannot be ruled out. **Possible:** Meets **definitive or probable** case definition criteria **AND** Alternate explanations for thrombocytopenia are more likely **OR** Meets **possible** case definition criteria.

Transfusion-associated circulatory overload (TACO): Infusion volume that cannot be effectively processed by the recipient either due to high rate and/or volume of infusion or an underlying cardiac or pulmonary pathology.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: New onset or exacerbation of 3 or more of the following within 6 hours of cessation of transfusion: • Acute respiratory distress (dyspnea, orthopnea, cough) • Evidence of positive fluid balance • Elevated brain natriuretic peptide (BNP) • Radiographic evidence of pulmonary edema • Evidence of left heart failure • Elevated central venous pressure (CVP)	**Definitive:** N/A	**Use severity grades as defined in Appendix C.**	**Definite:** No other explanations for volume overload are possible. **Probable:** Transfusion is a likely contributor to volume overload **AND EITHER** The patient received other fluids as well **OR** The patient has a history of cardiac insufficiency that could explain the volume overload. **Possible:** The patient has a history of pre-existing cardiac insufficiency that most likely explains volume overload.
Probable: N/A	**Probable:** N/A		
Possible: N/A	**Possible:** N/A		

Transfusion-associated dyspnea (TAD): Respiratory distress within 24 hours of cessation of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction. Respiratory distress should not otherwise be explained by a patient's underlying or pre-existing medical condition.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: Acute respiratory distress that occurring within 24 hours of cessation of transfusion **AND** TRALI, TACO, and allergic reaction are ruled out. **Probable:** N/A **Possible:** N/A	**Definitive:** N/A **Probable:** N/A **Possible:** N/A	**Use severity grades as defined in Appendix C.**	**Definite:** Patient has no other conditions that could explain symptoms. **Probable:** Other present conditions are unlikely but not fully excluded. **Possible:** Other present conditions are more likely to explain symptoms.

Transfusion-associated graft vs. host disease (TAGVHD): The introduction of immunocompetent lymphocytes into susceptible hosts. The allogeneic lymphocytes engraft, proliferate and destroy host cells. If performed, marrow study shows hypoplasia, aplastic anemia, or marked hypocellularity with a lymphohistiocytic infiltrate.

Case Definition Criteria		Severity	Imputability
Signs/Symptoms	**Laboratory/Radiology**		
Definitive: A clinical syndrome occurring from 2 days to 6 weeks after cessation of transfusion characterized by: • Fever • Characteristic rash: erythematous, maculopapular eruption centrally that spreads to extremities and may, in severe cases, progress to generalized erythroderma and hemorrhagic bullous formation. • Hepatomegaly • Diarrhea **Probable:** Same as definitive case criteria. **Possible:** Same as definitive case criteria.	**Definitive:** Liver dysfunction, i.e., elevated ALT, AST, Alkaline phosphatase, and elevated bilirubin **AND** Pancytopenia **AND** WBC chimerism in the absence of alternative diagnoses **AND** Characteristic histological appearance of skin biopsy or liver biopsy. **Probable:** Meets definitive criteria **EXCEPT** Biopsy negative or not done. **Possible:** Meets definitive criteria **EXCEPT** Chimerism not present or not done.	**Grade 1:** N/A **Grade 2:** Patient had marked symptoms and responded to treatment. **Grade 3:** Patient had severe symptoms and required life-saving treatment (e.g., immunosuppression). **Grade 4:** Patient died from TAGVHD.	**Definite:** Meets **definitive** or **probable** case definition criteria **AND** There are matching chimeric alleles in the donor and recipient. **Probable:** Meets **definitive** or **probable** case definition criteria **BUT** Alleles could not be tested in the donor to match to the recipient. **Possible:** Meets **possible** case definition criteria **OR** Alternative explanations are more likely (e.g. solid organ transplantation).

Transfusion-related acute lung injury (TRALI): Acute hypoxemia with PaO_2/fraction of inspired oxygen [FIO_2] ratio of 300 mmHg or less combined with chest x-ray showing bilateral infiltrates in the absence of left atrial hypertension (i.e., circulatory overload). Onset of TRALI is abrupt in association with transfusion.

Case Definition Criteria		**Severity**	**Imputability**
Signs/Symptoms	**Laboratory/Radiology**		

Definitive:
NO evidence of acute lung injury (ALI) prior to transfusion
AND
ALI onset during or within 6 hours of cessation of transfusion
AND
Hypoxemia defined by any of these methods:
• PaO_2 / FiO_2 less than or equal to 300 mm Hg
• Oxygen saturation less than 90% on room air
• Other objective evidence
AND
No evidence of left atrial hypertension (i.e. circulatory overload).
 	
Probable:
N/A
 	
Possible:
N/A
	Definitive:
	Bilateral infiltrates on chest radiograph
	
	Probable:
	N/A
	
	Possible:
	N/A
		Use severity grades as defined in Appendix C.	**Definite:**
			No alternative risk factors for ALI during or within 6 hours of cessation of transfusion.
			
			Probable:
			N/A
			
			Possible:
			Evidence of other risk factors for acute lung injury during or within 6 hours of cessation of transfusion are present, such as:
			• Direct Lung Injury
			  • Aspiration
			  • Pneumonia
			  • Toxic inhalation
			  • Lung contusion
			  • Near drowning
			• Indirect Lung Injury
			  • Severe sepsis
			  • Shock
			  • Multiple trauma
			  • Burn injury
			  • Acute pancreatitis
			  • Cardiopulmonary bypass
			  • Drug overdose

Transfusion-transmitted infection: A bacteria, parasite, virus, or other potential pathogen transmitted in donated blood to transfusion recipient.

Pathogens of well-documented importance in blood safety.

These pathogens have public health significance for hemovigilance, are well-documented blood stream pathogens and/or, are routinely screened for in blood donors. All infectious organisms are available from the full drop-down pathogen list in NHSN.

Bacterial	Viral	Parasitic	Other
Escherichia coli *Klebsiella oxytoca* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Staphylococcus epidermidis* *Staphylococcus lugdunensis* Syphilis (*Treponema pallidum*) *Yersinia enterocolitica*	Cytomegalovirus (CMV) Enterovirus Epstein Barr (EBV) Hepatitis A Hepatitis B Hepatitis C Human Immunodeficiency Virus 1 (HIV-1) Human Immunodeficiency Virus 2 (HIV-2) Human Parvovirus B-19 Human T-Cell Lymphotropic (or, leukemia) Virus-1 (HTLV-1) Human T-Cell Lymphotropic (or, leukemia) Virus-2 (HTLV-2) West Nile Virus *(Flaviviridae*)	Babesiosis (*Babesia* spp.) Chagas disease (*Trypanosoma cruzi*) Malaria (*Plasmodium* spp.*)*	Creutzfeldt-Jakob Disease, Variant (vCJD)

Investigation triggers for infections potentially transfusion-transmitted:

1. Identification by testing (e.g., gram stain, other smear/staining, culture, or other method) of an unexpected bacterial, mycobacterial, or fungal organism in a recipient within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected pathogen.
2. Identification of an unexpected virus in the recipient by testing (e.g., culture, direct fluorescent antibody or polymerase chain reaction) within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected virus.
3. Identification of an unexpected parasite in the recipient by blood smear, histopathology or stool testing for ova/parasites within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected parasite.
4. Any of the above laboratory findings in the recipient unit upon residual testing.
5. Unexplained clinical events occurring after transfusion that are consistent with transfusion-transmitted infection, such as:
   a. Encephalitis, meningitis, or other unexplained central nervous system abnormalities.
   b. Sepsis with or without multi-organ system dysfunction.
   c. Hemolytic anemia and/or fever (e.g., in cases of transfusion-associated babesiosis or malaria).
   d. Recipient death.
6. For pathogens routinely screened in the blood donor, any infection in the recipient occurring within 6 months after transfusion if:
   a. The index donation testing was negative but
   b. The donor was subsequently found to be infected, and
   c. The recipient had no pre-transfusion history of the same infection.

For a decision on imputability, consider various types of evidence such as the following:

1. Evidence of contamination of the recipient unit upon residual testing.
2. Pre- and post- transfusion infection status (e.g., seroconversion) in the recipient.
3. Evidence of other recipients with infection from the same organism who received blood from the same donor.
4. Evidence of the donor infection with the same organism.

Transfusion-transmitted infection (continued): A bacteria, parasite, virus, or other potential pathogen transmitted in donated blood to transfusion recipient.

<table>
<tr><th colspan="2">Case Definition Criteria</th><th>Severity</th><th>Imputability</th></tr>
<tr><th>Signs/Symptoms</th><th>Laboratory/Radiology</th><th rowspan="2"></th><th rowspan="2"></th></tr>
<tr><td>Definitive:
N/A

Probable:
N/A

Possible:
N/A</td><td>Definitive:
Laboratory evidence of a pathogen in the transfusion recipient.

Probable:
N/A

Possible:
N/A</td></tr>
<tr><td colspan="2">NOTE: An investigation can be initiated based on clinical events occurring after transfusion that are consistent with transfusion-transmitted infection. However; there must be laboratory evidence of the suspected pathogen in the transfusion recipient to call an adverse reaction a transfusion-transmitted infection.</td><td>Use severity grades as defined in Appendix C.</td><td>Definite:
Evidence that the recipient was not infected with this organism prior to transfusion
AND
Laboratory evidence of infection with the same organism in the donor by testing of the donor, the recipient unit (or retained segment), or co-component from the original donation
OR
Laboratory evidence of infection with the same organism in another recipient that received blood from the same donor.

Probable:
Any <u>two</u> of the following:
Evidence that the recipient was not infected with this organism prior to transfusion
OR
Laboratory evidence of infection with the same organism in the donor by testing of the donor, the recipient unit (or retained segment), or co-component from the original donation
OR
Laboratory evidence of infection with the same organism in another recipient that received blood from the same donor.

Possible:
Recipient infection fails to meet imputability criteria for definite, probable or ruled out because essential information is missing, not available, or cannot be obtained.

Doubtful:
Laboratory evidence that the recipient had was infected with this organism prior to transfusion.

Ruled Out:
Laboratory evidence that the donor was negative for infection at the time of donation.</td></tr>
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