



# Biovigilance Component Adverse Reactions – Case Definition Exercises

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## **Slide 1 – Biovigilance Component Adverse Reactions – Case Definition Exercises**

Welcome to the National Healthcare Safety Network Biovigilance Component Hemovigilance Adverse Reaction training session.



# Background



- These definitions were developed by the Adverse Reaction Working Group:
  - ◆ Group convened by AABB for the purpose of developing subject matter requirements for the blood transfusion recipient reporting module (Hemovigilance) in National Healthcare Safety Network (NHSN)
  - ◆ Comprised of transfusion medicine specialists, AABB, and CDC staff
  - ◆ Definitions based on International Society of Blood Transfusion (ISBT) draft definitions
  - ◆ Reviewed and approved by Adverse Reaction Working Group members, CDC, FDA, and HHS.
- Intended to provide blood transfusion service departments with standard definitions for transfusion reactions. Through NHSN reporting, facilities can track reactions and provide data for aggregate analysis
- Facilities can use these definitions regardless of NHSN participation.

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## Slide 2 – Background

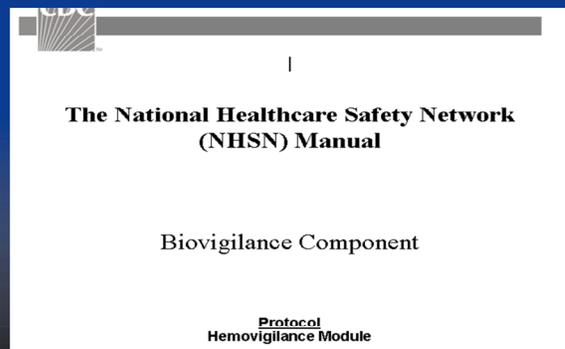
These definitions were developed by the Adverse Reaction Working Group. The group was composed of transfusion medicine specialists, AABB members, and CDC staff. The definitions are based on the draft definitions developed by the International Society of Blood Transfusion (ISBT). They were developed to provide blood transfusion services departments with standard definitions so facilities reporting to NHSN can use the same terms and same language when tracking adverse reactions. Using the same terms and applying the definitions consistently will allow us to provide better data for aggregate analysis. Facilities can use these case definitions regardless of their participation in HNSN.



# Getting Started



- Intended audience: transfusion medicine specialists, department managers, physicians, and other patient care staff intending to collect information on recipient blood transfusion reactions.
- Use NHSN Hemovigilance Module protocol for reference. Available at this link:  
[http://www.cdc.gov/ncidod/dhqp/nhsn\\_biovig.html](http://www.cdc.gov/ncidod/dhqp/nhsn_biovig.html)
  - ◆ Appendix B – case definitions
  - ◆ Appendix C – severity grade and imputability



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## Slide 3 – Getting Started

This training is intended for transfusion medicine specialists, department managers, physicians, and other patient care staff intending to collect information on recipient blood transfusion reactions. Please use the NHSN Hemovigilance Module protocol for reference. The case definitions are in Appendix B, and guidelines for severity grading and imputability assessment are in Appendix C of the NHSN Hemovigilance Module protocol, which can be accessed at:  
[http://www.cdc.gov/ncidod/dhqp/nhsn\\_biovig.html](http://www.cdc.gov/ncidod/dhqp/nhsn_biovig.html)



## Key Terms



- Case definition criteria – Provide surveillance criteria for defining a case
  - ◆ Definitive
  - ◆ Probable
  - ◆ Possible
- Grade – Severity of the reaction
- Imputability – Relationship of the transfusion to the reaction

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### Slide 4 – Key Terms

Here we will review the key terms in Hemovigilance Adverse Reaction Reporting. There are three terms used to describe an adverse reaction. First are the case definition criteria. This categorizes how well the reaction meets the case definition. The case definition criteria range from definitive to possible. Second is the severity grade of the reaction. Third is imputability, which indicates how likely the transfusion caused the reaction. It is important to understand the relationship between the case definition and imputability. A reaction can closely fit a case definition, but have a low probability (i.e., possible imputability) of being related to the transfusion. For example, you can have a definitive hypotensive transfusion reaction, if a patient's blood pressure drops by greater than 30mm Hg within 15 minutes of starting transfusion and blood pressure improves with discontinuation of transfusion; however the imputability may only be possibly related to transfusion if other conditions (e.g., excessive blood loss, septic shock) could readily explain hypotension.



# Case Definition Criteria: Overview



Case Definition Criteria		Grade (Severity)	Relationship to Transfusion (Imputability)
Signs & Symptoms	Laboratory/ Radiology		
Definitive:	Definitive:	Grade 1:	Definite:
Probable:	Probable:	Grade 2:	Probable:
Possible:	Possible:	Grade 3:	Possible:
		Grade 4:	

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## Slide 5 – Case Definition Criteria: Overview

This slide shows the general criteria used to classify each adverse reaction. The case definition can have criteria for signs and symptoms, laboratory and radiology findings, or both and are categorized as definitive, probable, or possible. All case definitions have definitive criteria, but not all have probable or possible criteria. If the case definition meets one criterion for signs and symptoms and another for laboratory and radiology findings, use the lower of the two criteria. The severity grade and imputability score are described in subsequent slides.



# Adverse Reactions



- Allergic reaction
- Hemolytic transfusion reaction
  - ◆ Acute hemolytic transfusion reaction (AHTR)
  - ◆ Delayed hemolytic transfusion reaction (DHTR)
  - ◆ Delayed serologic transfusion reaction (DSTR)
- Hypotensive transfusion reaction
- Febrile non hemolytic transfusion reaction (FNHTR)
- Post transfusion purpura (PTP)
- Transfusion associated circulatory overload (TACO)
- Transfusion associated dyspnea (TAD)
- Transfusion associated – graft vs. host disease (TA-GVHD)
- Transfusion-related acute lung injury (TRALI)
- Infection
- Other – diagnosis known but not one of the above (specify in text field)
- Unknown pathophysiology

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## Slide 6 – Adverse Reactions

This slide lists the 12 adverse reactions available to enter into the hemovigilance module. There is also an option to enter other reactions and describe the reaction in a text field if it doesn't fit into any of the 12 adverse reactions provided. Use the Other category when the diagnosis of the reaction is known but it does not fit one of the 10 listed case definitions. Use the unknown pathophysiology category when the type and cause of reaction can not be determined.



# Severity Grade



- Use general grade definitions (listed here) unless there are specific definitions provided for a particular reaction
  - ◆ **Grade 1 (Non-Severe):** Medical intervention (e.g. symptomatic treatment) required but lack of such would not result in permanent damage or impairment of a body function
  - ◆ **Grade 2 (Severe):** Inpatient hospitalization or prolongation of hospitalization directly attributable to the event and/or:  
Persistent or significant disability or incapacity **OR**  
A medical or surgical intervention that is necessary to preclude permanent damage or impairment of a body function
  - ◆ **Grade 3 (Life-threatening):** Major intervention required following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death
  - ◆ **Grade 4 (Death):** The recipient died following an adverse transfusion reaction. [Note: Grade 4 should be used only if death is possibly, probably, or definitely related to transfusion.]

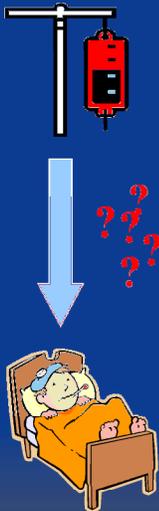
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## Slide 7 – Severity Grade

These are the general severity grades. Some adverse reactions have severity grades that are specific to that reaction, but most can be graded using this table. Grade 1 is for non-severe reactions where little to no intervention is required to prevent harm. Medical interventions from Grade 1 are for symptomatic relief (e.g., diphenhydramine for itching, acetaminophen for fever) only and if not given the reaction would not progress to hospitalization. Grade 2 reactions occur when some kind of medical intervention is required to prevent injury, hospitalization, or prolongation of hospitalization. In Grade 3 reactions medical intervention is required to prevent death. Grade 4 reactions result in death. Note that grade 4 should be used only if death is possibly, probably, or definitely related to transfusion.



# Imputability



- Once the investigation of the adverse transfusion reaction is completed, this is the assessment of the strength of the relationship between the transfusion and the adverse reaction
  - ◆ **Definite (certain):** Conclusive evidence beyond reasonable doubt that the adverse reaction can be attributed to the transfusion
  - ◆ **Probable (likely):** Evidence is clearly in favor of attributing the adverse reaction to the transfusion
  - ◆ **Possible:** Evidence is indeterminate for attributing the adverse reaction to the transfusion or to an alternate cause
  - ◆ **Doubtful:** Evidence is clearly in favor of attributing the adverse reaction to causes other than transfusion (not reported in NHSN)
  - ◆ **Ruled Out:** Conclusive evidence beyond reasonable doubt that the adverse reaction can be attributed to causes other than the transfusion (not reported in NHSN)
  - ◆ **Not determined:** The relationship between the adverse reaction and the transfusion is unknown or not stated.

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## Slide 8 – Imputability

Once the investigation of the adverse transfusion reaction is completed, the imputability assessment is based on the strength of the relationship between the transfusion and the adverse reaction, or another way of saying how likely the adverse reaction was caused by the transfusion. Definite imputability requires conclusive evidence beyond reasonable doubt that the adverse event can be attributed to the transfusion. Probable imputability is where the evidence is clearly in favor of attributing the adverse event to the transfusion, but other potential causes are present. Possible imputability is where the evidence is indeterminate for attributing the adverse event to the transfusion or an alternate cause for adverse reaction is likely. Doubtful imputability occurs when there is evidence clearly in favor of attributing the adverse event to causes other than the transfusion. A transfusion-related adverse event is ruled-out when there is conclusive evidence beyond reasonable doubt that the adverse event can be attributed to causes other than the transfusion. Adverse reactions for which imputability is *doubtful* or *ruled out* should not be routinely reported in this component of NHSN. The only time *doubtful* or *ruled out* categories should be used is when a reaction that was initially reported in the system to be transfusion-related was later determined not to be transfusion related based on new or additional information. The imputability is not determined when the relationship between the adverse reaction and the transfusion is unknown or not stated.



# Case 1



Demographics Relevant Past History	66 y/o Male (DOB 01/01/1942) Patient had not been previously transfused.
Pre-transfusion Vital Signs	BP: 166/95, P 85, RR 20, T 36.8.
01/03/2008 13:15	Infusion of fresh frozen plasma. Half-way through the transfusion, patient c/o itchiness on his arms, bilaterally. Transfusion rate slowed, but, within 5 minutes, multiple bright red macula appeared on both his forearms
01/03/2008 13:25	Transfusion stopped. Diphenhydramine administered with relief of symptoms.
Laboratory	Negative for evidence of hemolysis

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## Slide 9 – Case 1

Now we will look at the first of our 13 example adverse reaction training cases. Each case summary provides patient demographics and relevant past medical history, pre-transfusion vital signs, a brief description of the reaction, and relevant laboratory information. After reviewing the case, determine the most compatible adverse reaction and rank it as definitive, probable, or possible based on the case definitions. Also provide a severity grade and determine the imputability of the adverse reaction to the transfusion. After each case we will go over rationale for choosing the adverse reaction, severity, and imputability.

For the remainder of this presentation, a copy of the Adverse Reaction Definitions and Case Definition Criterion will help with categorizing the adverse reactions. It can be found in Appendix B of The National Healthcare Safety Network (NHSN) Manual: Biovigilance Component Protocol for Hemovigilance Module.

Please read case #1 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



# Case 1- Allergic Reaction Investigation Result



Diagnosis :	Allergic Reaction
Case Definition Criteria:	Definitive
Severity:	Grade 1 Non-severe
Imputability:	Definite

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## Slide 10 – Case 1: Allergic Reaction Investigation Result

Case 1 is the result of an interaction of an allergen with preformed antibodies.

Its presentation is consistent with a definitive allergic reaction with grade 1 severity and definite imputability.



# Case 1 - Allergic Reaction Case Definition Criteria



**Definition:** The result of an interaction of an allergen with preformed antibodies.

**Definitive** - Any combination (2 or more) of the following occurring during the transfusion:

- **Morbilliform rash with or without pruritus**
- **Urticaria (hives)**
- Generalized flushing
- Localized angioedema
- Edema of lips, tongue and uvula
- Pruritus, erythema, and edema of the periorbital area
- Conjunctival edema
- Respiratory distress, bronchospasm
- Hypotension.

**Probable** - N/A

**Possible** - N/A

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## Slide 11 – Case 1: Allergic Reaction Case Definition Criteria

The patient met the definitive criteria by having 2 clinical finding associated with an allergic reaction. In this case the patient had a morbilliform rash and urticaria occurring during the transfusion, which meets the case definition requirement of 2 or more signs or symptoms consistent with an allergic reaction. Please note that this case definition only has definitive criteria. As we mentioned earlier, not all case definitions have probable or possible criterion.



# Case 1 – Allergic Reaction Severity Grade



- **Grade 1 (Non-Severe): No immediate risk to the life of the patient AND responds quickly to symptomatic treatment**

Grades 2 -4 involve respiratory and/or cardiovascular systems and present like an anaphylactic reaction. There is anaphylaxis when, in addition to mucocutaneous symptoms, there are airway symptoms or hypotension.

- **Grade 2 (Severe):** Inpatient hospitalization or prolongation of hospitalization directly attributable to the reaction and/or:
  - ◆ Persistent or significant disability or incapacity**OR**
  - ◆ A medical or surgical intervention that is necessary to preclude permanent damage or impairment of a body function.
- **Grade 3 (Life-threatening):** Major intervention required following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death.
- **Grade 4 (Death):** The recipient died following an adverse transfusion reaction. [Note: Grade 4 should be used only if death is possibly, probably or definitely related to transfusion.]

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## Slide 12 – Case 1: Allergic Reaction Severity Grade

The severity grade for case 1 is grade 1 or non-severe as the reaction was relatively mild and responded quickly to diphenhydramine. Even if untreated this reaction would likely have been self-limiting and not resulted in any harm to the patient.



# Case 1 – Allergic Reaction Imputability



## Definite:

- **No other environmental, drug or dietary risks AND**
- **Occurs within 1-2 hours of transfusion.**

## Probable:

- Other potential causes in an individual with known susceptibility (atopic; previous allergic reactions to transfusions) AND
- Occurs within 1-2 hours of transfusion.

## Possible:

- Other likely causes such as medication or exposures but transfusion cannot be ruled out, usually a first reaction of this sort AND
- Occur 2-4 hours after transfusion.

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### Slide 13 – Case 1: Allergic Reaction Imputability

The imputability to this transfusion is definite as there were no other environmental, drugs or dietary risks for the allergic reaction and the reaction occurred within 1-2 hours of transfusion.



## Case 2



Demographics	81 y/o M (DOB: 03/15/1927) Blood type A -
Pre-transfusion Vital Signs	BP 130/85, P 85, RR 20, T 37.2
04/08/2008 RBC1 02:45 – 04:30 RBC2 04:55 – 08:00	Pt received 2 units packed red blood cells. 15 minutes after completion of the 2 <sup>nd</sup> unit, the blood bank discovered that a wrong unit may have been issued for this patient. Upon checking, one of the bags had the name and hospital number of another patient whose blood type was B+.
04/08/2008 08:45	Pt c/o shaking chills, dyspnea, chest pain, nausea, and experienced oxygen desaturation.
Laboratory	Over next 24 hours, patient developed: Acute renal failure with a urine output at 40 ml/hr (no dialysis required), A rise in creatinine from baseline of 1.2 mg/dl, LDH, potassium and bilirubin, Drop in Hgb from 10.7 to 8.3.
	He remained hemodynamically stable, his urine output was back to normal the next day, and renal function continued to improve. He was discharged with a creatinine of 2.0 mg/dL.

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### Slide 14 – Case 2

Please read case #2 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 2 – Acute Hemolytic Transfusion Reaction (AHTR) Investigation Result



Diagnosis : **Acute Hemolytic Transfusion Reaction**

Case Definition Criteria: **Definitive**

Severity: (Use standard) **Grade 2 Severe**

Imputability: **Definite**

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### **Slide 15 – Case 2: Acute Hemolytic Transfusion Reaction (AHTR) Investigation Result**

Case 2 resulted from a rapid destruction of red blood cells immediately after or within 24 hours of a transfusion. It is a definitive acute hemolytic transfusion reaction with a grade 2 severity and definite imputability.



## Case 2 – AHTR Signs & Symptoms



**Definition:** Rapid destruction of red blood cells immediately after or within 24 hours of a transfusion.

**Definitive:** Occurs during, immediately after, or **within 24 hours of transfusion** WITH any of the following:

**Chills/rigors**

Fever

Back/flank pain

Hypotension

Hemoglobinuria occurring during or shortly after transfusion

Epistaxis

**Oliguria/anuria**

Renal failure

Disseminated intravascular coagulation (DIC)

Pain and/or oozing at IV site

AND EITHER

Known 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.**

**Probable:** Any combination of clinical features as above, but incomplete laboratory confirmation.

**Possible:** N/A

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### Slide 16 – Case 2: AHTR Signs & Symptoms

This case meets the definitive criteria in two ways. The reaction occurred within 24 hours of transfusion and was associated with one or more signs and symptoms consistent with an acute hemolytic transfusion reaction (i.e., chills/rigors and oliguria). In addition, a clerical check indicated that the patient's name and blood group on the blood unit were different than the recipient's name and blood group.



## Case 2 – AHTR Laboratory/Radiology



**Definitive:** Serologic work-up c/w hemolytic transfusion reaction:

- Positive direct antiglobulin test for anti-IgG or anti-C3 AND
- Positive elution test with alloantibody present on the transfused red blood cells

**AND  $\geq$  2 of the following:**

Elevated LDH

Elevated bilirubin

Low haptoglobin

Hemoglobinuria

Low fibrinogen

Elevated plasma hemoglobin.

**Probable:** Incomplete definitive criteria laboratory confirmation.

**Possible:** N/A

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### Slide 17 – Case 2: AHTR Laboratory/Radiology

Acute hemolytic transfusion reaction has both clinical and laboratory criteria. Remember we said that some adverse reaction will have only clinical and other only laboratory criteria. In this case, the laboratory criteria are only probable since we don't have information on direct antiglobulin or elution tests. In this case we have definitive clinical evidence for an acute hemolytic transfusion reaction, but only probable laboratory criteria therefore we classify it as a probable acute hemolytic reaction.



## Case 2 – AHTR Severity Grade



- **Grade 1 (Non-Severe):** No immediate risk to the life of the patient AND responds quickly to symptomatic treatment
- **Grade 2 (Severe):** Inpatient hospitalization or prolongation of hospitalization directly attributable to the reaction and/or:
  - ◆ **Persistent or significant disability or incapacity**
  - OR
  - ◆ A medical or surgical intervention that is necessary to preclude permanent damage or impairment of a body function.
- **Grade 3 (Life-threatening):** Major intervention required following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death.
- **Grade 4 (Death):** The recipient died following an adverse transfusion reaction. [Note: Grade 4 should be used only if death is possibly, probably or definitely related to transfusion.]

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### Slide 18 – Case 2: AHTR Severity Grade

The severity grade for case 2 is grade 2. Development of acute renal failure and medical intervention was required to prevent further harm to the patient.



## Case 2 – AHTR Imputability



### **Definite:**

- Occurs during, immediately after, or within 24 hours of transfusion
- AND EITHER**
- There is known ABO or other allotypic RBC antigen incompatibility
- OR**
- Serologic work-up c/w AHTR
- AND**
- No other cause of acute hemolysis.

### **Probable:**

- No serologic evidence AND
- Blood bank testing usually shows abnormal results but AHTR may also be due to erythrocyte auto-antibodies in the recipient.

### **Possible:**

- Evidence of non-immune contributing factors e.g., mechanical factors inducing hemolysis (malfunction of a pump, a blood warmer, use of hypotonic solutions, etc.).

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### **Slide 19 – Case 2: AHTR Imputability**

The imputability to this transfusion is definite as the reaction occurred immediately after (45 minutes) and there was documentation of a known ABO incompatibility.



## Case 3



Demographics PMH	31 y/o F (DOB: 02/14/1977) Admitted on 11/12/08 with fever and pulmonary infiltrates and placed on IV Antibiotics.
Pre-transfusion Vital Signs	BP 118/78, P 110, RR 22, T37.0
11/15/2008 RBC1 21:30 to 11/16/2008 00:15 RBC2 01:00 – 02:00	Had fever prior to transfusion on 11/15/08, given acetaminophen. Just prior to transfusion the temperature was 37.0 (oral). During the second unit of RBCs the patient developed high fever 40.1 (PO) and had chills. The transfusion was stopped.
11/30/2008	Pt developed an anti-Jkb antibody within two weeks after a transfusion. The 2 Blood units given were tested and one was found to be Jkb positive. Hemoglobin pre-tx of the Jkb+ unit was 10.3. Hgb post transfusion of Jkb+ unit was 10.5. Hgb continued to decrease and 2 weeks after was 8.4.

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### Slide 20 – Case 3

Please read case #3 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



# Case 3 – Delayed Hemolytic Transfusion Reaction (DHTR) Investigation Result



Diagnosis :	Delayed Hemolytic Transfusion Reaction
Case Definition Criteria:	Probable
Severity: (Use standard)	Grade 1 Non-Severe
Imputability:	Probable

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## **Slide 21 – Case 3: Delayed Hemolytic Transfusion Reaction (DHTR) Investigation Result**

In Case #3 the recipient developed antibody to RBC antigens between 24 hours and 28 days after a transfusion and clinical or biological signs of hemolysis.

This case represents a probable delayed hemolytic transfusion reaction with a grade 1 severity and probable imputability.



# Case 3 – Delayed Hemolytic Transfusion Reaction Signs & Symptoms



**Definition:** The recipient develops antibody to RBC antigens between 24 hours and 28 days after a transfusion and clinical or biological signs of hemolysis are present.

**Definitive:**

- Patient may be asymptomatic or have similar, but milder symptoms to AHTR.

Examples of milder symptoms include: (NOTE: these are NOT required to meet the case definition criteria)

**Chills/rigors**

**Fever**

Jaundice

Back/flank pain

Hypotension

Hemoglobinuria/ hematuria

Oliguria/ anuria.

**Probable: Same as above except there is no serologic confirmation of HTR.**

**Possible: N/A**

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## Slide 22 – Case 3: DHTR Signs & Symptoms

This patient had fever and chills during the transfusion suggestive of a hemolytic transfusion reaction which could make this either a definitive or probable since the criteria are the same. For DHTR reactions, the laboratory results are needed to differentiate between definitive and probable.



## Case 3 – DHTR Laboratory/Radiology



**Definitive:** Any of the following:

- Positive direct antiglobulin (Coombs) test AND EITHER
  - ◆ Positive elution test with alloantibody present on the transfused red blood cells OR
  - ◆ Newly identified red blood cell alloantibody

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.

Note: If performed, post transfusion increase in LDH and bilirubin which subsequently falls back to baseline in the following days.

**Probable:** Newly identified red blood cell alloantibody.

**Possible:** N/A

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### Slide 23 – Case 3: DHTR Laboratory/Radiology

This case has a newly identified red blood cell alloantibody and an inadequate rise of post-transfusion hemoglobin level; however because there is not a positive direct antiglobulin (Coombs) test, this case only meets the probable delayed hemolytic transfusion reaction criteria.

The severity grade is 1 because there was no medical intervention or risk of harm to the patient.



## Case 3 – DHTR Imputability



### Definite:

- Newly identified red blood cell alloantibody AND
- Occurs between 24 hours and 28 days after a transfusion AND
- Positive direct antiglobulin test with identification of a new antibody either in the serum or eluate AND
- No other explanation for drop in hemoglobin.

### Probable:

- **Occurs between 24 hours and 28 days after a transfusion AND**
- **No other explanation for drop in hemoglobin AND**
- **No confirmation on serologic testing.**

Possible: N/A

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### Slide 24 – Case 3: DHTR Imputability

This case had newly identified red cell alloantibodies, the reaction occurred between 24 hours and 28 days after a transfusion, and there was no other explanation for drop in hemoglobin. However there was no confirmation direct antiglobulin test, so the imputability drops from definite to probable.



## Case 4



Demographics	46 y/o M (DOB: 03/12/1962)
Pre-transfusion Vital Signs	BP 168/95, P 68, RR 20, T 37.0
04/20/2008 RBC1 08:00 – 09:45 RBC2 10:00 – 12:00 04/21/2008 RBC1 08:00 – 09:45 RBC2 10:00 – 12:00	Antibody screen on pre-transfusion sample of 04/19/2008 was negative. Patient received components of phenotype E+, Jka+ on 4/20 & 4/21/08.
05/03/2008	Testing showed presence of Anti-E & Anti-Jka antibodies (development of irregular antibodies associated with blood transfusion). Patient's post transfusion hemoglobin level was stable and unchanged.

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### Slide 25 – Case 4

Please read case #4 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 4 – Delayed Serologic Transfusion Reaction Investigation Result



Diagnosis :	Delayed Serologic Transfusion Reaction
Case Definition Criteria:	Definitive
Severity: (standard)	Grade 1 Non-Severe
Imputability:	Definite

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### **Slide 26 – Case 4: Delayed Serologic Transfusion Reaction Investigation Result**

The case demonstrates new, clinically significant alloantibodies against red blood cells developing between 24 hours to 28 days after a transfusion despite an adequate hemoglobin response to transfusion that was maintained. Case #4 is a definitive delayed serologic transfusion reaction with a grade 1 severity and definite imputability.



## Case 4 – DSTR Signs & Symptoms



**Definition:** Demonstration of new, clinically significant alloantibodies against red blood cells between 24 hours to 28 days after a transfusion despite an adequate hemoglobin response to transfusion that is maintained.

**Definitive:** No clinical or laboratory signs of hemolysis.

**Probable:** N/A

**Possible:** N/A

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### Slide 27 – Case 4: DSTR Signs & Symptoms

The case definition criterion for this adverse reaction does not have any clinical signs or symptoms. It is based only on laboratory findings described on the next slide.



## Case 4 – DSTR Laboratory/Radiology



**Definitive: After a transfusion there is demonstration of new, clinically significant antibodies against red blood cells which were not present in the pre-transfusion specimen EITHER THROUGH:**

- Positive direct antiglobulin test OR
- **Positive antibody screen with newly identified RBC alloantibody.**

Probable: N/A

Possible: N/A

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### **Slide 28 – Case 4: DSTR Laboratory/Radiology**

This case demonstrates a new, clinically significant antibody against red blood cells which were not present in the pre-transfusion specimen. This case was detected by a positive antibody screen with newly identified RBC alloantibody. However it could also have been detected by a positive direct antiglobulin test. There are no probable or possible case definitions, so this adverse reaction is definitive and these reactions will always be severity grade of 1 since there are no clinical findings.



## Case 4 – DSTR Imputability



### Definite:

- Recent RBC transfusion with subsequent formation of newly identified RBC alloantibody

### OR

- Positive direct antiglobulin test.

**Probable:** N/A

**Possible:** N/A

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### Slide 29 – Case 4: DSTR Imputability

The imputability of the transfusion to the reaction is definite because the patient had a RBC transfusion with subsequent formation of newly identified RBC alloantibody within the 24 hour to 28 day timeframe for this reaction. Of note, this is the only adverse reaction that has definite as the only imputability grade.



## Case 5



Demographics PMH	18 y/o M (DOB: 08/25/1990), Blood type O + The patient is under treatment for AML M1 (ANC: 0). Pt was unstable for 24h with a clinical suspicion of sepsis. He was transferred to ICU and begun on multiple broad-spectrum antibiotics as well as pressors the morning of the transfusion.
Pre-transfusion Vital Signs	BP 100/50, P 115, RR 22, T 37.8
09/09/2008 10:00 Bedside leukoreduced AS-1 RBC's Patient O (Rh +) Unit O (Rh -)	Five minutes after the beginning of the transfusion, the patient's blood pressure dropped from 105/53 to 70/30 mmHg. The transfusion was interrupted, and the patient was given a bolus of saline. His pressure returned to the previous baseline within 10 min. The transfusion was then re-initiated, and the patient's pressure again dropped. Boluses of saline and then Albumin did not lead to a pressure increase, and pressor doses were increased, without effect. The patient died of a cardiac arrest after a prolonged (1h) period of hypotension.
Laboratory/Radiology	The transfusion reaction investigation revealed no evidence of immunohematologic incompatibility. A bacterial culture of the unit showed no growth.

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### Slide 30 – Case 5

Please read case #5 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 5 – Hypotensive Transfusion Reaction Investigation Result



Diagnosis :	Hypotensive Transfusion Reaction
Case Definition Criteria:	Possible
Severity:	Grade 4 Death
Imputability:	Probable

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### **Slide 31 – Case 5: Hypotensive Transfusion Reaction Investigation Result**

This case meets the criteria for a hypotensive transfusion reaction as the patient had a drop in systolic and/or diastolic blood pressure of > 30 mm Hg occurring during or within one hour of completing transfusion. Case #5 is a possible hypotensive transfusion reaction with a grade 4 severity and probable imputability.



## Case 5 – Hypotensive Transfusion Reaction Signs & Symptoms



**Definition:** Drop in systolic and/or diastolic blood pressure of > 30 mm Hg occurring during or within one hour of completing transfusion.

**Definitive:**

**All of the following:**

- Hypotension (>30 mm Hg drop in systolic and/or diastolic blood pressure)
- Occurs within 15 minutes after the start of the transfusion.
- Responds rapidly (within 10 minutes) to cessation of transfusion and supportive treatment.
- All other categories of adverse reactions presenting with hypotension must have been excluded.\*

\*Note: If the patient meets the criteria for another, more specific adverse transfusion reaction (with hypotension as a symptom of that reaction), the specific adverse reaction should be reported rather than the hypotension.

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### Slide 32 – Case 5: Hypotensive Transfusion Reaction Signs & Symptoms

This case meets the possible hypotensive transfusion reaction criteria. The patient had a >30 mm Hg drop in systolic blood pressure (105/53 to 70/30), the drop in blood pressure occurred 5 minutes after initiating blood transfusion, and responded to cessation of transfusion and a bolus of normal saline. However, the patient had “clinical suspicion of sepsis,” which could also explain the hypotension.

An investigation into other transfusion-related causes of hypotension did not reveal another potential cause.

Please note that if transfusion reaction investigation reveals that the patient meets the criteria for another, more specific adverse transfusion reaction with hypotension as a symptom of that reaction, the more specific adverse reaction should be reported rather than the hypotension.



## Case 5 – Hypotensive Transfusion Reaction Signs & Symptoms



- **Probable:** Same as definitive except:
  - ◆ Onset is > 15 minutes after start of transfusion OR
  - ◆ Patient does not respond within 10 minutes to cessation of transfusion and supportive treatment.
  
- **Possible:**
  - ◆ Same as definitive EXCEPT other conditions are present or were present before the transfusion that could explain the hypotension.

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### **Slide 33 – Case 5: Hypotensive Transfusion Reaction Signs & Symptoms**

This slide shows the probable and possible case definitions for hypotensive transfusion reaction. These are the same as the definitive criteria except a probable case does not respond quickly to cessation of blood transfusion or supportive treatment and a possible has other conditions present that can explain the hypotensive reaction.



## Case 5 – Hypotensive Transfusion Reaction Severity Grade



- Grade 1
  - ◆ Recipient required no more than discontinuation of transfusion and symptomatic management AND
  - ◆ No long-term morbidity.
- Grade 2
  - ◆ Recipient required inpatient hospitalization or prolongation of hospitalization due to hypotension; or hypotension led directly to long-term morbidity (e.g., brain damage) AND
  - ◆ Vasopressors are not required
- Grade 3
  - ◆ Recipient required vasopressors.
- Grade 4
  - ◆ Recipient died as a result of hypotensive transfusion reaction or as a result of treatment directed at resolving symptoms of hypotensive transfusion reaction.

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### Slide 34 – Case 5: Hypotensive Transfusion Reaction Severity Grade

The patient developed hypotension within minutes of starting the transfusion and subsequently died making this a grade 4 severity reaction.



## Case 5 – Hypotensive Transfusion Reaction Imputability



### Definite:

- Meets **definitive** protocol criterion.
- The patient has no other conditions that could explain hypotension.

**Probable:** Other conditions that could explain hypotension are unlikely but not fully excluded.

**Possible:** **Other conditions that could readily explain hypotension are present.**

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### Slide 35 – Case 5: Hypotensive Transfusion Reaction Imputability

The imputability of the transfusion to the hypotensive reaction is probable. The reaction meets the definitive case definition, but the patient was septic and on pressors which could also explain his hypotension. However, the temporal relationship to the start of the transfusion and the hypotension make it the most likely cause of the event.



## Case 6



Demographics	34 y/o Female (DOB 02/14/1974) Blood type: A+
Pre-transfusion Vital Signs	BP: 118/76, P 86, RR 20, T 37.6
0900 - 1115 Leukocyte-reduced AS-1 Red Blood Cells, Group O+	<p>Thirty min after the end of transfusion, the patient's temperature had risen to 38.8°C. She had a brief episode of shaking chills at about the same time.</p> <p>Acetaminophen was given, and the patient's temperature reduced to 37.8°C within 2h. She had no other episodes of increased temperature within 24h before or 24h after transfusion.</p>
Laboratory information	Transfusion reaction investigation revealed no clerical errors and plasma that had remained yellow. Her DAT was negative prior to transfusion and weakly positive with anti-C3 following transfusion. An acid eluate of the RBCs was negative.

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### Slide 36 – Case 6

Please read case #6 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 6 – FNHTR Investigation Result



Diagnosis :	Febrile Non-Hemolytic Transfusion Reaction
Case Definition Criteria:	Definitive
Severity: (standard)	Grade 1 Non-severe
Imputability:	Definite

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### **Slide 37 – Case 6: Febrile Non Hemolytic Transfusion Reaction Investigation Result**

This patient developed fever and/or chills within 4 hours of transfusion and without hemolysis. Case #6 is a definitive febrile non-hemolytic transfusion reaction with a grade 1 severity and definite imputability.



## Case 6 – Febrile Non Hemolytic Transfusion Reaction Sign & Symptoms



**Definition:** Fever and/or chills without hemolysis occurring in the patient during or within 4 hours of transfusion.

**Definitive:**

- **Fever ( $\geq 38^{\circ}\text{C}$  oral or equivalent and a change of  $\geq 1^{\circ}\text{C}$  from pre-transfusion value) AND**
- **Occurs during or within 4 hours of transfusion.**

**Probable:** N/A

**Possible:** N/A

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### Slide 38 – Case 6: FNHTR Sign & Symptoms

This case meets the definitive case definition for febrile non-hemolytic transfusion reaction. The patient's temperature rose to  $38.8^{\circ}\text{C}$  and she had a brief episode of shaking chills 30 minutes after completion of the transfusion.

Febrile non-hemolytic transfusion reaction case definition is based on clinical signs and symptoms and does not have laboratory criteria. The laboratory data are only used to rule out other cause of fever related to transfusion. In this case, laboratory data indicate that

this was not likely related to a hemolytic transfusion reaction.



## Case 6 – FNHTR Severity Grade



- **Grade 1 (Non-Severe):** **Medical intervention (e.g. symptomatic treatment) required but lack of such would not result in permanent damage or impairment of a body function.**
- **Grade 2 (Severe):** Inpatient hospitalization or prolongation of hospitalization directly attributable to the event and/or:
  - ◆ Persistent or significant disability or incapacity**OR**
  - ◆ A medical or surgical intervention that is necessary to preclude permanent damage or impairment of a body function.
- **Grade 3 (Life-threatening):** Major intervention required following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death.
- **Grade 4 (Death):** The recipient died following an adverse transfusion reaction. [Note: Grade 4 should be used only if death is possibly, probably or definitely related to transfusion.]

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### Slide 39 – Case 6: FNHTR Severity Grade

The reaction severity is grade 1. The patient received acetaminophen for her fever, but even without this intervention she would not have sustained any persistent or significant disability.



## Case 6 – FNHTR Imputability



**Definite:** Meets **definitive** protocol criterion and the patient has no other conditions that could explain symptoms.

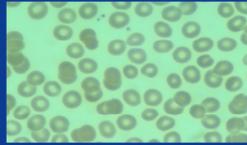
**Probable:** Other conditions that could explain fever/chills are unlikely but not fully excluded.

**Possible:** Other conditions are present or were present before the transfusion that could explain the symptoms.

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### Slide 40 – Case 6: FNHTR Imputability

The reaction meets the case definition for a febrile non-hemolytic transfusion reaction and there are no other conditions identified that could explain the hypotensive event. The likelihood the febrile episode was related to the transfusion is high which corresponds to a definite imputability.



# Case 7



Demographics	18 y/o F (DOB: 06/15/1990)
History	The patient, a nulliparous, never-transfused female, was involved in a motorcycle accident, fracturing her spleen, and experiencing intrabdominal hemorrhage.
Pre-trans. VS	BP 90/60, P 100, RR 20, T 37.0
07/05/2008 – 07/12/2008 6 AS-1 RBCs, 4 FFP, 2 apher. Platelets	The patient was managed conservatively over the next two weeks with multiple transfusions but without splenectomy. All transfusions were given within the first week. One unit of K (+) RBCs had been administered the day of admission.
08/02/2008	On Day 28, an anti-K and a positive DAT was first identified. RBC eluate was weakly positive for anti-K. (The positive DAT persisted for two weeks, disappearing coincidentally with mixed field typing for K.)
08/08/2008	The patient was found to be HPA-1A (-) and on Day 34, to have anti-HPA-1A in her plasma. Her platelet count was too low to obtain an accurate platelet-associated immunoglobulin test result.
08/11/2008	Three days later her platelet count, which had been in the 150-180,000/uL range after the first two weeks of her treatment, suddenly dropped to 10-12,000/uL. It remained in this range for 6 d, without any specific therapies.
08/16/2008	Her platelets then slowly began to rise toward the normal range, reaching 200,000/uL on Day 42.

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## Slide 41 – Case 7

Please read case #7 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 7 – Post Transfusion Purpura Investigation Result



Diagnosis :	Post Transfusion Purpura
Case Definition Criteria:	Probable
Severity: (standard)	Grade 1 Non-severe
Imputability:	Definite

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### **Slide 42 – Case 7: Post Transfusion Purpura Investigation Result**

Post transfusion purpura (PTP) occurs patients develop antibodies directed against the Human Platelet Antigen (HPA) system and is characterized by thrombocytopenia usually arising 5-12 days following transfusion of cellular blood components. Case #7 represents a probable post transfusion purpura transfusion reaction with a grade 1 severity and definite imputability.



## Case 7 – PTP Signs & Symptoms



**Definition:** Characterized by 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.

**Definitive:** Thrombocytopenia (decrease to < 20% of pre-transfusion count)  
AND occurs 5-12 days post-transfusion.

**Probable:**

- **Clinical presentation largely consistent with definition**
- BUT**
- **Timeframe not met**
- OR**
- Thrombocytopenia (decrease to < 20% of pre-transfusion count) with competing explanations
- OR**
- Drop in platelets between 20% and 80% of pre-transfusion count.

**Possible:**

- Clinical and laboratory presentation c/w definition. HPA antibodies present; but alternate explanations more likely OR
- Clinical presentation c/w definition; however, HPA antibodies not tested or neg.

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### Slide 43 – Case 7: Post Transfusion Purpura Signs & Symptoms

The patient had a significant drop in platelet count. However the drop in platelet count occurred approximately 30 days after transfusions which is outside the 5-12 day time frame for a definitive transfusion purpura transfusion reaction making this a probable transfusion purpura transfusion reaction.



## Case 7 – PTP Laboratory/Radiology



**Definitive:** Alloantibodies in the patient directed against HPA -1a or other platelet specific antigen detected at or after development of reaction.

**Probable:** Alloantibodies in the patient directed against HPA-1a or other platelet specific antigen detected at or after development of reaction.

**Possible:** HPA antibodies not tested or negative.

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### **Slide 44 – Case 7: PTP Laboratory/Radiology**

For this adverse reaction alloantibodies directed against HPA-1a or other platelet specific antigen detected associated with development of thrombocytopenia satisfy laboratory criteria for the definite and probable case definitions. Since the clinical data only meet the probable clinical case definition, this case is classified as probable. If HPA antibody testing was negative or not done, the case would be classified as only a possible case.

The reaction severity is grade 1. The patient did not require any medical intervention and did not sustain any persistent or significant disability or incapacity.



## Case 7 – PTP Imputability



**Definite: Protocol criterion = Definitive or Probable**

**Probable: N/A**

**Possible: Protocol criterion = Possible**

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### **Slide 45 – Case 7: PTP Imputability**

The imputability of the transfusion to the post transfusion purpura transfusion reaction is definite. For this adverse reaction, if the clinical and laboratory data meet either the definitive or probable case definitions, the imputability is definite. You will note that there is not a probable imputability for post transfusion purpura transfusion reaction; the only options are definite and possible.



## Case 8



Demographics PMH	45 y/o F (DOB: 02/15/1963) Chronic Coumadin therapy due to previous deep venous thromboses secondary to Factor V Leiden mutation admitted with spontaneous subarachnoid hemorrhage.
Pre-transfusion Vital Signs	140/70, P 70, RR 20, T 36.9
03/14/2008 FFP	Multiple units of plasma transfused over first 36 h: 8 in first 12h, 6 in second 12h, 6 in third 12h period. Patient begun on furosemide; recovered with minor neurologic deficits.
03/16/2008 Laboratory/Radiology	Investigation by Transfusion Service of unusual plasma usage rate (without hemorrhage) uncovered: 1) Post-Tx chest x-ray - Bilateral dependent pulmonary infiltrates and increased cardiac silhouette size by radiography. 2) Decreased oxygen saturations. 3) Investigation negative for evidence of hemolysis.

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### Slide 46 – Case 8

Please read case #8 and determine the type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 8 – Transfusion Associated Circulatory Overload Investigation Result



Diagnosis : **Transfusion associated circulatory overload**

Case Definition Criteria: **Definitive**

Severity: (standard) **Grade 2 Severe**

Imputability: **Definite**

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### **Slide 47 – Case 8: Transfusion Associated Circulatory Overload Investigation Result**

Case #8 is a definitive transfusion associated circulatory overload (TACO) transfusion reaction with a severity grade 2 and definite imputability. TACO results when volume infused cannot be effectively processed by the recipient either due to high rates and volumes of infusion or underlying cardiac or pulmonary pathology.



## Case 8 – Transfusion Associated Circulatory Overload Signs & Symptoms



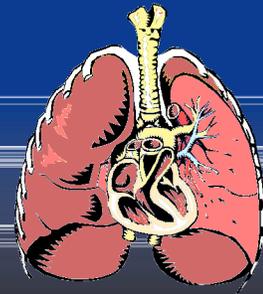
**Definition:** Volume infusion that cannot be effectively processed by the recipient either due to high rates and volumes of infusion or underlying cardiac or pulmonary pathology.

**Definitive:** Characterized by new onset or exacerbation of  $\geq 3$  of the following within 6 hours of transfusion:

- **Acute respiratory distress (dyspnea, orthopnea, cough)**
- **Evidence of positive fluid balance**
- Elevated BNP (Brain Natriuretic Peptide)
- **Radiographic evidence of pulmonary edema**
- Evidence of right heart failure
- Elevated CVP (central venous pressure).

Probable: N/A

Possible: N/A



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### Slide 48 – Case 8: TACO Signs & Symptoms

Case #8 developed new-onset acute respiratory distress (decreased oxygen saturation), had evidence of positive fluid balance, and radiographic evidence of pulmonary edema within six hours of transfusion. Thus the patient had at least 3 of the 6 clinical meets the definitive case definition for transfusion associated circulatory overload transfusion reaction which meets the definitive case definition for TACO transfusion reaction.



## Case 8 – TACO Severity Grade



**Grade 1 (Non-Severe):** Medical intervention (e.g. symptomatic treatment) required but lack of such would not result in permanent damage or impairment of a body function.

**Grade 2 (Severe):** Inpatient hospitalization or prolongation of hospitalization directly attributable to the event and/or:

- Persistent or significant disability or incapacity

OR

- **A medical or surgical intervention that is necessary to preclude permanent damage or impairment of a body function.**

**Grade 3 (Life-threatening):** Major intervention required following the transfusion (vasopressors, intubation, transfer to intensive care) to prevent death.

**Grade 4 (Death):** The recipient died following an adverse transfusion reaction.

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### Slide 49 – Case 8: TACO Severity Grade

The severity grade for case #8 is classified as 2 because without medical intervention (furosemide), she would likely have developed further respiratory distress and may have required intubation.



## Case 8 – TACO Imputability



**Definite:** Meets definitive protocol criterion and no other cause of volume overload.

**Probable:** Judgment call by the attending physician. Patients received other fluids, and transfusion is likely contributory to volume overload.

**Possible:** For patients with pre-existing cardiac insufficiency, imputability should not be classified higher than “possible”.

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### Slide 50 – Case 8: TACO Imputability

The imputability of the transfusion to the fluid overload is definite as it meets the definitive case criterion and no other cause of volume overload was identified during the investigation.



## Case 9



Demographics	76 y/o M (DOB: 07/10/1932). Admitting diagnosis: Elevated INR of unknown etiology.
Pre-transfusion Vital Signs	BP 155/75, P 90, RR 20, T 37.2
08/30/2008 13:00 – 14:30 15:00 - 2 FFP	Plasma administered prior to diagnostic percutaneous liver biopsy. First FFP unit transfused over 90 min without difficulty. Second FFP started at 15:00.
08/30/2008 15:15	Halfway through second FFP unit (same rate), patient became agitated. Oxygen saturation decreased from 94% before transfusions to 90%. One dose of furosemide administered with little effect.
Laboratory/Radiology	Transfusion reaction investigation negative for evidence of hemolysis. Chest x-ray – Slightly increased interstitial markings in LLL and increased cardiac size.

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### Slide 51 – Case 9

Please read case #9 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



# Case 9 - Transfusion Associated Dyspnea Investigation Results



Diagnosis :	Transfusion Associated Dyspnea
Case Definition Criteria:	Definitive
Severity: (standard)	Grade 1 Non-severe
Imputability:	Probable

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## Slide 52 – Case 9: Transfusion Associated Dyspnea Investigation Results

Transfusion associated dyspnea is a transfusion reaction characterized by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction. Case #9 is a definitive transfusion associated dyspnea (TAD) transfusion reaction with a severity grade 2 and probable imputability.



## Case 9 – Transfusion Associated Dyspnea Signs & Symptoms



**Definition:** Characterized by respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO, or allergic reaction.

**Definitive:**

- **Acute respiratory distress AND**
- **Occurs within 24 hours of transfusion AND**
- **TRALI, TACO, allergic reaction and patient's underlying condition ruled out.**

**Probable:** N/A

**Possible:** N/A

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### Slide 53 – Case 9: TAD Signs & Symptoms

TAD only has a definitive case definition and this scenario meets all the criteria. The patient had acute respiratory distress that occurred within 24 hours of the transfusions. TRALI was excluded as O<sub>2</sub> saturation did not decrease below 90% and no infiltrates were seen on CXR. TACO was excluded when furosemide did not improve respiratory status. The patient did not meet the case criteria for allergic reaction and he no known underlying conditions that could explain his respiratory distress.

The severity grade for this case is classified as 1 or non-severe. The patient improved without medical intervention; the furosemide had little effect.



## Case 9 – TAD Imputability



**Definite:** Meets **definitive** protocol criterion and the patient has no other conditions that could explain symptoms.

**Probable:** Other conditions that could explain fever/chills are unlikely but not fully excluded.

**Possible:** Other conditions are present or were present before the transfusion that could explain the symptoms.

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### Slide 54 – Case 9: TAD Imputability

TAD is a diagnosis of exclusion for cases that do not meet definition of other respiratory complications of transfusion like TACO, TRALI, allergic reaction and that are not caused by the patient's underlying condition. The imputability a judgment call based on the results of the transfusion reaction investigation. The general criteria of imputability in Appendix C of the NHSN Hemovigilance Module protocol should be used.

The imputability of the transfusion to the transfusion associated dyspnea is definite. For this case there was no evidence this reaction was related to TACO, TRALI, allergic reaction, it was not caused by the patient's underlying condition, and there is evidence beyond reasonable doubt that the adverse event can be attributed to the transfusion.



## Case 10



Demographics PMH	2 y/o M (DOB: 01/10/2006) This young patient was under treatment for neuroblastoma with multi-agent chemotherapy but required no transfusion during four hospitalizations.
Pre-transfusion Vital Signs	BP 95/60, P 110, RR 25, T 37.2
03/06/2008 03/13/2008 2 AS-1 leukoreduced RBC (not irradiated)	Subsequently, at his community hospital, the patient received portions of two different units of RBCs (non-irradiated) for persistent, symptomatic anemia
04/14/2008	Approximately four weeks after the second transfusion, the child was admitted for an erythematous rash, hepatic dysfunction, diarrhea and pancytopenia. The admitting team was not aware at the time that he had been transfused at an outside hospital.
04/21/2008	The child died one week later. An autopsy was refused by the parents. No samples from the child were available for HLA phenotyping, and the parents declined to be phenotyped.

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### Slide 55 – Case 10

Please read case #10 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 10 – Transfusion Associated-Graft Versus Host Disease Investigation Results



Diagnosis :	Transfusion Associated - Graft Vs. Host Disease
Case Definition Criteria:	Possible
Severity:	Grade 4 Death
Imputability:	Possible

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### **Slide 56 – Case 10: Transfusion Associated-Graft versus Host Disease Investigation Results**

Transfusion associated-graft versus host disease (TA-GVHD) occurs when immunocompetent allogeneic lymphocytes of donor origin are transfused into a susceptible host where they engraft, proliferate, and destroy host cells.

Case #10 is a possible transfusion associated-graft vs. host disease (TA-GVHD) with a severity grade 4 and possible imputability.



# Case 10 – TA-GVHD Signs & Symptoms



**Definition:** The introduction of immunocompetent lymphocytes into susceptible hosts. The allogeneic lymphocytes engraft, proliferate, and destroy host cells.

**Definitive:** A clinical syndrome occurring from 2 days to 6 weeks following transfusion characterized by symptoms of:

- Fever
- Characteristic rash
- Hepatomegaly
- Diarrhea
- Liver dysfunction
- Pancytopenia
- WBC chimerism
- Characteristic histological appearances on skin biopsy or liver biopsy.

**Probable:**

- Clinical presentation of TA-GVHD with biopsy confirmation.
- No confirmation by chimerism studies (not done or negative).

**Possible: Clinical presentation without confirmation by biopsy or chimerism (not done or negative) studies.**

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## Slide 57 – Case 10: TA-GVHD Signs & Symptoms

The clinical presentation is consistent with TA-GVHD; however the diagnosis was not confirmed by biopsy or chimerism studies, so this is only a possible case of TA-GVHD. A probable case requires conformation by characteristic histological appearances on skin or liver biopsy. A definitive case requires conformation by biopsy and WBC chimerism.



## Case 10 – TA-GVHD Severity Grade



**Grade 1:** N/A

**Grade 2:** Patient had marked symptoms, responded to treatment.

**Grade 3:** Patient alive due to treatment (e.g. immunosuppression).

**Grade 4:** Patient died from TA-GVHD.

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### **Slide 58 – Case 10: TA-GVHD Severity Grade**

The severity grade is classified as 4 because the patient's death is believed possibly related to TA-GVHD.



## Case 10 – TA-GVHD Imputability



### **Definite:**

- Meets definitive protocol criterion and related to blood donor
- Matching chimeric alleles in donor and recipient.

**Probable:** Presentation consistent with TA-GVHD; however, chimerism demonstrated in recipient but matching alleles could not be tested in the donor.

**Possible:** **Apparent TA-GVHD** when alternative explanations of cause are likely **but TA-GVHD cannot be confirmed** (i.e., negative chimerism studies, in the setting of allogeneic solid organ transplantation).

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### **Slide 59 – Case 10: TA-GVHD Imputability**

The imputability of the transfusion to TA-GVHD is only possible because TA-GVHD cannot be confirmed by biopsy or chimerism studies.



# Case 11



Demographics PMH	21 y/o M (DOB: 06/21/1987) Blood type O+ Patient multiply transfused due to aplastic anemia.
Pre-transfusion Vital Signs	110/60, P 60, RR 18, T 37.0
07/20/2008 14:00 Leukoreduced AS-1 RBCs O+.	<p>Five minutes into an outpatient transfusion, patient noted that he "did not feel well." Vital signs were unchanged from pre-transfusion at that point. At 10 min into transfusion, the patient began to cough and transfusion terminated.</p> <p>Oxygen saturation at that point was noted to be 88%. (No pre-transfusion value.) Patient coughed intermittently for 30 min, then began to feel better. Oxygen saturation climbed to 98%.</p> <p>No additional therapy required. Discharged to home. Returned for uneventful two-unit transfusion the following day.</p>
Laboratory/radiology	<p>Chest x-ray revealed bilateral infiltrates. Transfusion reaction investigation negative for evidence of hemolysis.</p> <p>Patient known to be HLA-A3 (+). Plasma from segment later shown to have strong anti-HLA-A3.</p>

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## Slide 60 – Case 11

Please read case #11 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



# Case 11 – Transfusion-related Acute Lung Injury Investigation Results



Diagnosis :	Transfusion Related Acute Lung Injury
Case Definition Criteria:	Definitive
Severity:	Grade 1 Non-severe
Imputability:	Definite

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## **Slide 61 – Case 11: Transfusion-related Acute Lung Injury Investigation Results**

Transfusion-related acute lung injury is characterized by acute hypoxemia combined with chest x-ray showing bilateral infiltrates in the absence of left atrial hypertension (i.e., circulatory overload). Case #11 is a definitive transfusion related acute lung injury (TRALI) with a grade 1 severity and a definite imputability.



# Case 11 – TRALI Signs & Symptoms



**Definition:** Acute hypoxemia (FIO<sub>2</sub> ratio <300 mm Hg) combined with chest x-ray showing bilateral infiltrates in the absence of left atrial hypertension (i.e., circulatory overload).

**Definitive:**

- No evidence of prior acute lung injury (ALI) to transfusion AND
- **Acute onset of ALI during or within 6 hours of transfusion AND**
- Hypoxemia
  - ◆ PaO<sub>2</sub> / FiO<sub>2</sub> ≤ 300 mm Hg OR
  - ◆ **Oxygen saturation is < 90% on room air** OR
  - ◆ Other clinical evidence

**AND**

- No evidence of left atrial hypertension (i.e. circulatory overload) AND
- No temporal relationship to an alternative risk factor for ALI during or within 6 hours of completion of transfusion AND
- Bilateral infiltrates on chest x-ray.

**Probable:** Same as definitive.

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## Slide 62 – Case 11: TRALI Signs & Symptoms

This case presentation meets the definitive criteria for TRALI. There was no evidence of prior acute lung injury (ALI) to transfusion and no alternative risk factor for ALI. The acute onset of ALI was within 6 hours of transfusion, hypoxemia was documented by oxygen saturation < 90% on room air, bilateral infiltrates are seen on CXR, and there is no evidence of left atrial hypertension (i.e., circulatory overload).

There is not a probable case criterion for TRALI.



# Case 11 - TRALI Signs & Symptoms



## ■ Possible:

- ◆ Same as definitive **EXCEPT** there is a temporal relationship to one of the following alternate risk factors:
  - ✧ 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

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### Slide 63 – Case 11: TRALI Signs & Symptoms

This slide show the alternative risk factors for direct an indirect lung injury that, if present, would make the case only a possible TRALI transfusion reaction.



## Case 11 – TRALI Imputability



If protocol criterion = **Definitive** then  
relationship is **Definite**

If protocol criterion = **Possible** then  
relationship is **Possible**

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### **Slide 64 – Case 11: TRALI Imputability**

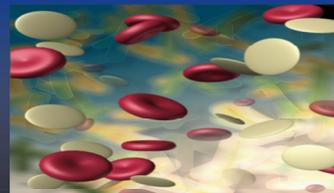
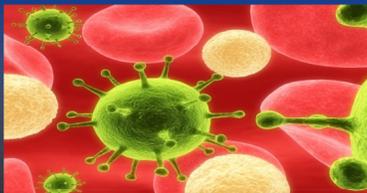
For TRALI adverse reactions, if the case definition meets the definitive criteria then the imputability is classified as definite, if not then the imputability can be only possible. There is no probable imputability category for TRALI.



# Infection-related Adverse Reactions



- Any infectious organism is available from the pathogen list in NHSN. The pathogens in the table on the next slide will appear at the top of the pathogen drop down list in NHSN because:
  - ◆ They have public health significance for hemovigilance
  - ◆ Are common bloodstream infection pathogens AND/OR
  - ◆ Are routinely screened in blood donors.



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## Slide 65 – Infection-related adverse reactions

Before we move on to infection-related adverse reaction cases, we will provide a brief introduction to this category. Any infectious organisms that can be found in the bloodstream could be transmitted through blood products. All known infectious organisms are available from the pathogen drop down list in the NHSN hemovigilance module.



# Infection-related adverse reactions



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

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## Slide 66 – Infection-related adverse reactions (continued)

The pathogens listed in the table on this slide will appear at the top of the pathogen drop down list in the NHSN hemovigilance module because:

- They have public health significance for hemovigilance,
- Are common bloodstream infection pathogens and/or,
- Are routinely screened in blood donors.

These are the ones you will use most often. If the suspected pathogen isn't one of the ones listed here, you will need to continue to scroll down the list to find the pathogen. They are in alphabetical order following the list of more common pathogens.



# Infection Investigation Triggers



- Investigation triggers for infections thought to be transfusion-transmitted:
  - ◆ 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
  - ◆ 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
  - ◆ 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
  - ◆ Any of the above laboratory findings in the recipient unit upon residual testing.

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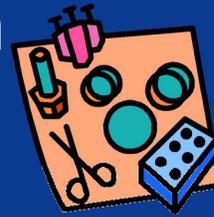
## Slide 67 – Infection Investigation Triggers

The decision to initiate a transfusion transmitted disease investigation can be triggered by several different laboratory findings or clinical signs/symptoms and may occur weeks to months after the implicated transfusion event. Some laboratory triggers are listed here. They include identification of an unexpected bacterial, mycobacterial, fungal, viral or parasitic organism in a recipient within the time period from exposure (i.e., transfusion) to onset of infection appropriate for the suspected pathogen. Tests commonly used to identify bacterial, mycobacterial, and fungal infections include gram stain, other smear/staining, and culture. Viral infections are usually identified using culture, direct fluorescent antibody or polymerase chain reaction (PCR) techniques. Parasitic infections are often identified by blood smear, histopathology, or stool testing for ova/parasites.

The finding of a bacterial, mycobacterial, fungal, viral or parasitic organism in the recipient unit upon residual testing would also trigger a transfusion transmitted disease investigation.



# Infection Investigation Triggers



- Investigation triggers (cont.)
  - ◆ Unexplained clinical events occurring after transfusion that are consistent with transfusion-transmitted disease, such as:
    - Encephalitis, meningitis, or other unexplained central nervous system abnormalities
    - Sepsis with or without multi-system organ failure
    - Recipient death
  - ◆ In addition, for infections routinely screened in the blood donor, any infection in the recipient occurring within 6 months after transfusion if:
    - The index donation testing was negative and
    - The donor was subsequently found to be infected, but
    - The recipient had no pre-transfusion history of the same infection.

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## Slide 68 – Infection Investigation Triggers (continued)

Unexplained clinical events may also trigger a transfusion transmitted disease investigation. These include, but not limited to:

1. Encephalitis, meningitis, or other unexplained central nervous system abnormalities,
2. Sepsis with or without multi-system organ failure and/or,
3. Recipient death.

In addition, for infections routinely screened in the blood donor (e.g., HBV, HCV, HIV), any infection in the recipient occurring within 6 months after transfusion if:

1. The index donation testing was negative,
2. The donor was subsequently found to be infected, and
3. The recipient had no pre-transfusion history of the same infection.



# Infection and Imputability



For a decision on imputability, the following evidence is considered:

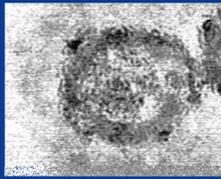
- 1) Evidence of contamination of the recipient unit upon residual testing
- 2) Pre- and post-transfusion infection status (e.g., seroconversion) in the recipient
- 3) Evidence of other recipients with infection from the same organism who received blood from the same donor
- 4) Evidence of donor infection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

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## Slide 69 – Infection and Imputability

The case definition criteria for an infection related adverse event is a little different than the other adverse event because the potential organism has already been identified. The real question is the likelihood the infection was transmitted due to the transfusion of a blood product. For a decision on imputability, the following evidence is considered:

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, and
4. Evidence of donor infection with the same organism.



## Case 12



Demographics PMH	45 y/o M (DOB: 01/02/1963) The patient was chronically transfused because of his sickle cell anemia which had resulted in multiple pain and pulmonary sequestration crises.
Pre-transfusion Vital Signs	BP 153/84, P 60, RR 20, T37.0
01/10/2008 2 RBCs	On 4/02/2008, the patient presented with increasing jaundice and elevated liver function tests.
Laboratory/ Radiology	Anti-HCV positive with a viral load > 100,000 GEU/mL. Creatinine was mildly elevated, and his ejection fraction (by cardiac echo) was 45%. A transcutaneous liver biopsy revealed moderate periportal necrosis (grade 2) and no fibrosis (grade 0). Iron staining was intense. HCV antibody test was negative on pre-BMT work-up 12/30/2007.

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### Slide 70 – Case 12

Please read case #12 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 12 – Infection Investigation Results



Diagnosis : Infection – Hepatitis C Virus

Case Definition Criteria: Definitive

Severity: Grade 1 Non-severe

Imputability: Possible

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### Slide 71 – Case 12: Infection Investigation Results

This patient definitely has hepatitis C virus (HCV) infection as demonstrated by a positive HCV serology and detection of HCV in blood by PCR. Case #12 is a definitive HCV infection. The severity grade is 1 as no medical intervention is required.

The question is how likely this infection is related to a blood product transfusion he received.



## Case 12 – Infection Imputability



### Definite:

- An investigation trigger with laboratory evidence of the suspected organism in the recipient  
**AND**
- Laboratory evidence that the same recipient was negative for this organism prior to transfusion  
**AND**
- Laboratory evidence of the same organism in the donor (Note: for bacterial cases, identification of the organism in the unit upon residual testing is equivalent to laboratory evidence of the same organism in the donor)  
**AND EITHER**
- Laboratory evidence of the same organism in any other recipients from the same donor as the initial case recipient **OR**
- Laboratory evidence of the same organism in the recipient unit upon residual testing.

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### Slide 72 – Case 12: Infection Imputability

This slide shows the definite imputability criteria. In this case an investigation was triggered by laboratory evidence of HCV in the recipient and there is laboratory evidence that the same recipient was negative for HCV infection 4 months earlier. However, we don't have laboratory evidence of the same organism in the blood donor nor do we have evidence of the same organism in recipients from the same donor as the initial case recipient or laboratory evidence of the same organism in the recipient unit upon residual testing. So, this case does not meet criteria for definite imputability.



## Case 12 – Infection Imputability



### Probable:

- An investigation trigger with laboratory evidence of the suspected organism in the recipient

### Plus any two of the following:

- Laboratory evidence that the same recipient was negative for this organism prior to transfusion OR
- Laboratory evidence of the same organism in other recipients (if any) from the same donor as the initial case recipient OR
- Laboratory evidence of the same organism infecting the donor OR
- Laboratory evidence of the same organism in the recipient unit upon residual testing.

### Possible:

- **An investigation trigger**
- **Information essential for confirming or ruling out a case is missing, not available, or cannot be obtained**
- **Case fails to meet definition for definite, probable or ruled out.**

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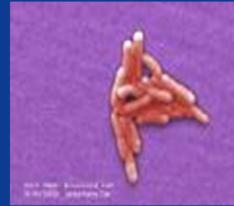
### Slide 73 – Case 12: Infection Imputability (con't)

This slide shows the probable and possible infection imputability criteria. Again because we don't have laboratory evidence of the same organism in the blood donor nor do we have evidence of the same organism in recipients from the same donor as the initial case recipient or laboratory evidence of the same organism in the recipient unit upon residual testing, this case doesn't meet criteria for probable HCV transmission.

This case does meet the possible imputability criteria because an investigation was triggered; however, information essential for confirming or ruling out the case is missing, not available, or cannot be obtained and the case fails to meet definition for definite, probable or ruled out.



# Case 13



Demographics	61 y/o M (DOB: 06/21/1947)
Pre-transfusion Vital Signs	T 145/80, P 95, RR 20, T 37.3
08/16/2008 09:50 – 10:20 1 apheresis platelet	<p>Patient was receiving apheresis platelets in an outpatient transfusion center when he desaturated to 68% and was placed on an oxygen mask. He desaturated a second time and was placed on a re-breather mask; he felt much better with O2 saturation up to 94%.</p> <p>The patient was admitted to hospital at 14:30 with BP of 84/59 that did not respond to fluid bolus. He also experienced fever, chills, nausea, and vomiting. He was transferred to the ICU and started on Imipenem and Vancomycin for presumed sepsis.</p>
Laboratory	<p>Within an hour of admission to ICU the micro lab called to say that the platelets were highly contaminated with bacteria.</p> <p>Final results from the hospital lab confirmed that both patient's blood and the apheresis platelets were positive for the same type of salmonella: <i>Salmonella choleraesuis</i>.</p>
08/25/2008	Patient's blood counts improved quickly and he was discharged.

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### Slide 74 – Case 13

Please read case #13 and determine type of adverse reaction and indicate how well case matches definitions (i.e., definitive, probable, or possible), case severity, and imputability grade.



## Case 13 – Infection Investigation Results



Diagnosis :	Infection - Bacterial
Case Definition Criteria:	Definitive
Severity:	Grade 3 Life Threatening
Imputability:	Definite

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### Slide 75 – Case 13: Infection Investigation Results

This case definitely had a salmonella blood stream infection as document by positive blood cultures. Case #13 is a definite bacterial (*Salmonella choleraesuis*) infection. The patient was admitted to the ICU in septic shock which makes this a grade 3 or life threatening severity.



## Case 13 – Infection Imputability



### Definite:

- An investigation trigger with laboratory evidence of the suspected organism in the recipient  
**AND**
- Laboratory evidence that the same recipient was negative for this organism prior to transfusion  
**AND**
- Laboratory evidence of the same organism in the donor (Note: for bacterial cases, identification of the organism in the unit upon residual testing is equivalent to laboratory evidence of the same organism in the donor)  
**AND EITHER**
- Laboratory evidence of the same organism in any other recipients from the same donor as the initial case recipient **OR**
- Laboratory evidence of the same organism in the recipient unit upon residual testing.

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### Slide 76 – Case 13: Infection Imputability

This slide shows the definite infection imputability criteria. In this case an investigation was triggered by sepsis occurring after transfusion that was possibly related to the platelet transfusion. We have laboratory evidence of the same organism in the recipient unit on residual testing and for bacterial cases identification of the organism on residual testing is the equivalent to finding it in the donor. However, we don't have laboratory evidence the recipient was negative for the organism prior to transfusion. So, this case does not meet criteria for definite imputability.



## Case 13 – Infection Imputability



### Probable:

- **An investigation trigger with laboratory evidence of the suspected organism in the recipient**

### Plus any two of the following:

- Laboratory evidence that the same recipient was negative for this organism prior to transfusion
- Laboratory evidence of the same organism in other recipients (if any) from the same donor as the initial case recipient
- **Laboratory evidence of the same organism infecting the donor**
- **Laboratory evidence of the same organism in the recipient unit upon residual testing.**

### Possible:

- An investigation trigger
- Information essential for confirming or ruling out a case is missing, not available, or cannot be obtained
- Case fails to meet definition for **definite, probable** or ruled out.

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### Slide 77 – Case 13: Infection Imputability

This slide shows the probable and possible infection imputability criteria. An investigation was triggered by sepsis. We have laboratory evidence of the same organism in the recipient unit on residual testing and for bacterial cases identification of the organism on residual testing is the equivalent to finding it in the donor. So this case meets the case definition for a probable bacterial transmission.



# Questions or Need Help?



Send an e-mail NHSN User Support  
at [NHSN@cdc.gov](mailto:NHSN@cdc.gov)

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**Slide 78** – This concludes our Biovigilance Component Adverse Reactions – Case Definition training. For questions or user assistance send an email to [NHSN@cdc.gov](mailto:NHSN@cdc.gov).