Educational Case: Granulocyte Transfusion

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.¹

Keywords
pathology competencies, diagnostic medicine, concepts of transfusion, blood components, transfusion medicine, transfusion reactions, granulocyte transfusion

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Primary Objective
Objective TM1.1: Blood Components. Define the blood components and blood component substitutes available for clinical use; the evidence-based indications and dosing of transfusion of these components; and how the efficacy of transfusion may be monitored.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic: (TM) Transfusion medicine; Learning Goal 1: Concepts of Blood Transfusion.

Secondary Objective
Objective TM1.2: Transfusion reactions. Compare and contrast the pathophysiology, presentations, prophylaxis, and acute management of the different types of transfusion reactions.

Competency 3: Diagnostic Medicine and Therapeutic Pathology; Topic: (TM) Transfusion medicine; Learning Goal 1: Concepts of Blood Transfusion.

Patient Presentation, Part 1
A 25-year-old male presented to his primary care physician with 3 weeks of fatigue and intermittent low-grade fevers. Last year, he recalls being able to run 3 miles easily, but now he becomes short of breath going up a flight of stairs. Otherwise, the patient’s past medical history was unremarkable. A complete blood count (CBC) with differential showed atypical cells consistent with blasts. A bone marrow biopsy was performed along with flow cytometric analysis, confirming a diagnosis of acute lymphoblastic leukemia.

Diagnostic Findings, Part 1
During his admission for induction chemotherapy, he developed high-grade fever (103°F), tachycardia, hypoxia, and hypotension. Otherwise, his physical examination was unremarkable.

Questions/Discussion Points, Part 1
What Is the Differential Diagnosis for Fever in This Patient and What Initial Diagnostic Studies Should Be Performed?
Fever is common in patients with cancer. It can be associated with infectious or noninfectious causes such as chemotherapy, radiation, tumor-associated inflammation, and venous

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thromboembolism. Since these patients are usually immunocompromised, it is important to initially rule out infection. Complete blood count, blood and urine culture, and chest X-ray were performed.

**Diagnostic Findings, Part 2**

Chest X-ray was unremarkable. Urine analysis was negative for leukocyte esterase, and no organisms were seen. A urine culture was negative. Complete blood count results are shown in Table 1. Blood culture was positive, and the Gram stain from the blood culture bottle showed gram-negative rods (Figure 1), which were identified as *Escherichia coli*. The organism was susceptible to piperacillin/tazobactam. Despite appropriate antibiotic therapy for 3 days, the patient continued to have fevers and positive blood cultures.

**Questions/Discussion Points, Part 2**

*What Is the Clinical Significance of the Patient’s Complete Blood Count Results?*

The patient’s CBC shows low hemoglobin (anemia), low platelet (thrombocytopenia), low white blood cells (leukopenia), and severe neutropenia. Leukopenia and in particular neutropenia predispose patients to fungal and bacterial infections. Anemia (hemoglobin <7 g/dL) can lead to tissue hypoxia, altered mental status, and cardiac arrest. Thrombocytopenia increases the chance of bleeding. Patients who are stable and not bleeding can typically tolerate a platelet count above 10/\text{µL}. Patients who are bleeding or undergoing invasive procedures are often transfused to maintain a higher platelet count (up to 100/\text{µL} for neurosurgical procedures).

*What Are the Common Types of Blood Products Used for Transfusion?*

Common types of blood products are summarized in Table 2. The efficacy of blood product transfusion can be monitored directly (eg, rise in posttransfusion count, coagulation test results) or by assessing efficacy (eg, bleeding assessment, survival).

For example, one unit of apheresis platelets should raise the patient’s platelet count by 30 000 to 50 000/\text{µL} within 1 hour of transfusion; however, the actual increase will also depend on the recipient blood volume and the platelet content of the unit, among other factors. The platelet count may fail to rise after platelet transfusion either due to antibody-mediated (typically anti-human leukocyte antigen [HLA]) clearance of platelets in circulation, increased consumption of platelets in the setting of clotting, or splenic sequestration as a consequence of splenomegaly.

*What Are Granulocytes?*

Granulocytes are white blood cells, specifically those with prominent intracytoplasmic granules visible by microscopy (neutrophils, eosinophils, and basophils). Neutrophils are the most abundant granulocyte and play an important role in combating bacterial and fungal infections.

**Review the Indications for Granulocyte Transfusions**

The purpose of granulocyte transfusion is to provide functional neutrophils to combat bacterial or fungal infections. The following are the generally accepted clinical indications of granulocyte transfusion:

- Neutropenia, absolute neutrophil count <0.5 x 10^3/\text{µL}.
- Fungal or bacterial infection unresponsive to appropriate therapy for at least 24 to 48 hours.
- Expectation of neutrophil recovery.

| Component     | Value       | Reference Range and Units             |
|---------------|-------------|---------------------------------------|
| WBC           | 2.8         | 4.0-10.0 x 10^3/\text{µL}             |
| RBC           | 3.1         | 4.30-5.90 x 10^3/\text{µL}            |
| Hemoglobin    | 11.01       | 13.0-17.0 g/dL                        |
| HCT           | 30.3        | 39.0%-51.0%                           |
| MCV           | 77          | 81.0-99.0 CU Microns                  |
| MCH           | 28.1        | 27.0-33.0 pg                          |
| MCHC          | 36.4        | 32.5-36.5 g/dL                       |
| RDW           | 13.4        | 11.6%-14.8%                           |
| Platelet count| 27          | 150-400 x 10^3/\text{µL}              |
| Lymphocytes   | 32          | 12%-40%                               |
| Monocytes     | 0           | 4%-12%                                |
| Segmented neutrophils | 4 | 40%-74%                             |
| Absolute neutrophil count (ANC) | 0.3 | 1.5-8.0 x 10^3/\text{µL}              |
| Eosinophils   | 1           | 0%-8%                                 |
| Myelocytes    | 1           | 0%-0%                                 |
| Blast         | 7           | 0%-0%                                 |

Abbreviations: HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.

* The results show pancytopenia with severe neutropenia.
Describe Donor Selection for Granulocyte Transfusion

- Granulocyte products contain a significant number of red blood cells (RBCs); therefore, they should be ABO/RhD compatible with the recipient and not react with any significant RBC alloantibodies currently or previously detected in the recipient’s plasma.
- Cytomegalovirus (CMV) seronegative patients should receive granulocytes from CMV seronegative donors.5
- Routine donor infectious disease testing takes at least 24 to 48 hours to complete. However, granulocytes begin to lose function within 6 to 8 hours and the product’s shelf life is 24 hours. Therefore, granulocytes must be transfused before the results of donor testing collected at the time of granulocyte donation are available (ie, emergency release).4,6

Diagnostic Findings, Part 3

Three days after the first positive blood culture, the patient remained febrile and was transfused with a granulocyte product. He also received a unit of apheresis collected platelets and a unit of packed RBCs earlier that day. One hour after the granulocyte transfusion, he developed worsening hypoxia requiring intubation. Otherwise, his vital signs and physical examination findings were unremarkable.

Questions/Discussion Points, Part 3

What Is the Differential for This Worsening Hypoxia in the Setting of Transfusion?

Hypoxia is defined as oxygen saturation less than 90% on room air. Symptoms of acute hypoxia during or after the cessation of transfusion should raise concern for a transfusion reaction. Common transfusion reactions are summarized in Table 3.12,13 Since, this patient had hypoxia prior to transfusion, it might also be due to their underlying medical condition (ie, sepsis in the setting of neutropenia).

What Are the Common Transfusion Reactions Associated With Granulocyte Transfusion in Particular?

Granulocyte transfusion can cause an increase in cytokines and chemokines and the development of granulocyte-reactive antibodies, which can cause transfusion-related acute lung injury.

### Table 2. Blood Products

| Component            | Indication                              | Typical Storage                      | Dosage (Typical Adult Dosing) | Monitoring Efficacy                                      |
|----------------------|-----------------------------------------|--------------------------------------|-------------------------------|----------------------------------------------------------|
| Whole blood          | Acute blood loss                        | 4°C                                  | Based on clinical condition and estimated blood loss | Blood hemoglobin, coagulation tests, bleeding assessment, and measures of improved tissue oxygenation |
| Red blood cells (RBCs) | Anemia                                  | 4°C                                  | 10-20 mL/kg                   | Blood hemoglobin, measures of improved tissue oxygenation |
| Platelets            | Thrombocytopenia                        | Room temperature with agitation      | One apheresis collected platelet product | Platelet count, bleeding assessment                      |
| Plasma               | Coagulation factor replacement          | Frozen, then 4°C after thaw          | 12-15 mL/kg                   | Coagulation tests, bleeding assessment                    |
| Cryoprecipitate      | Replacement of Factors II, VIII, XIII, VWF | Frozen                              | One unit per 5-19 kg body weight | Coagulation tests, bleeding assessment                    |
| Granulocytes         | Transient neutropenia plus infection (fungal or bacterial) | Room temperature, without agitation | 1-10 × 10^10 cells per dose | Patient survival, microbial response                      |

* This table shows the common indications, storage conditions, dosing, and methods of monitoring efficacy for the commonly used blood products.
Also, granulocyte products contain T-lymphocytes in addition to granulocytes and can cause transfusion-associated graft-versus-host disease (TA-GVHD). Due to the risk of TA-GVHD, all granulocyte products should be irradiated to prevent T-cell duplication in the recipient. Transfusion reactions that are seen with other blood products can also be caused by granulocyte transfusion including febrile nonhemolytic, hemolytic, allergic, and septic reactions in addition to transfusion-associated circulatory overload (TACO).

### What Diagnostic Studies Should Be Performed?

If transfusion reaction is suspected, transfusion should be stopped immediately and the blood bank should be notified. The blood bank investigation of a suspected transfusion reaction should include the following:\[13,16\]

- **Clerical check to confirm correct labeling of the product and patient identification.**
- **Visual inspection of the returned blood product bag and tubing.**
- **Visual inspection of the recipient’s plasma to look for signs of hemolysis (color change).**
- **Repeat ABO Rh typing to confirm previous results.**
- **Direct antiglobulin test, also known as the Coombs test, to detect antibodies or complements bound to red blood cells in the patient’s circulation.**
- **If a septic reaction is suspected: bacterial culture of residual blood product.**
- **If TRALI is suspected: notification of blood supplier and look back to determine whether the blood donor for this product has caused other potential TRALI reactions in the past.**

In consultation with the blood bank, clinical evaluation of a suspected transfusion reaction should include the following:

- **Posttransfusion vital signs.**
- **To assess for hemolysis: haptoglobin, direct and indirect bilirubin, lactate dehydrogenase (LDH), plasma-free hemoglobin, and urine hemoglobin.**

### Table 3. Transfusion Reactions.\[12,13\]

| Reaction                      | Pathophysiology                                                                 | Presentation                                      | Prophylaxis                                      | Acute Management                                      |
|------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------|-------------------------------------------------------|
| Febrile nonhemolytic         | Cytokine release from WBCs in blood product                                   | Rise in temperature, chills/rigors               | Prestorage leukoreduction, premedication         | Antipyretics                                          |
| Allergic/anaphylactic        | Possibly hypersensitivity reaction to antigens in donor plasma                | Varies from itching/ hives to anaphylaxis       | Decrease plasma content of product (eg, platelet   | Epinephrine, diphenhydramine, steroids, and/or bronchodilators |
| Transfusion-associated       | Pulmonary edema due to volume overload                                        | Hypoxia                                          | Avoid volume overload, volume-reduced products   | Diuresis and supportive measures                      |
| circulatory overload         |                                                                                  |                                                  |                                                   |                                                       |
| (TACO)                       |                                                                                  |                                                  |                                                   |                                                       |
| Transfusion-related          | Pulmonary edema due to anti-HLA antibodies/cytokine release                    | Hypoxia                                          | Avoid plasma from donors with anti-HLA antibodies | Supportive measures, donor look back                   |
| acute lung injury            |                                                                                  |                                                  |                                                   |                                                       |
| (TRALI)                      |                                                                                  |                                                  |                                                   |                                                       |
| Transfusion-associated       | Unknown                                                                         | Respiratory distress                              | Unknown                                          | Supportive measures                                   |
| dyspnea                      |                                                                                  |                                                  |                                                   |                                                       |
| Hypotensive                  | Cytokine release                                                                | Significant drop in blood pressure               | None                                             | Supportive measures                                   |
| Acute hemolytic              | Preformed antibody causes hemolysis                                             | Allantoibody and hemolysis                       | Crossmatch, antigen matching donor and recipient | Monitor hemoglobin, maintain adequate urine output    |
| Delayed hemolytic            | Antibody mediated hemolysis                                                    | Allantoibody and hemolysis                       | Antigen matching donor and recipient             | Monitor hemoglobin                                    |
| Delayed serologic            | Antibody mediated hemolysis                                                    | Allantoibody                                     | Antigen matching donor and recipient             | Monitor hemoglobin, test for signs of hemolysis       |
| Transfusion-associated       | Donor T cells attack recipient                                                 | Pancytopenia, gastrointestinal symptoms etc      | Irradiated blood products                       | Supportive measures if severe                         |
| graft-versus-host disease    |                                                                                  |                                                  |                                                   |                                                       |
| Transfusion transmitted      | Failure of donor screening/testing                                             | Varies                                           | Pathogen inactivated blood products             | Varies by infectious agent, notify blood supplier     |
| infection                    |                                                                                  |                                                  |                                                   | IVIG, plasma exchange (if IVIG doesn’t work)         |
| Posttransfusion purpura      | Immune-mediated clearance of donor and recipient platelets (often anti-HPA-1a) | Thrombocytopenia                                 | Washed RBCs, HPA-1a-negative donor              |                                                       |

**Abbreviations:** anti-HLA, anti-human leukocyte antigen; IVIG, intravenous immunoglobulin; WBC, white blood cell.

\[ This table summarizes the commonly recognized transfusion reactions and provides a brief description of their pathophysiology and presentation. The most common prophylaxis and initial management approaches also listed. In the United States, all fatalities that may have been due to transfusion are reportable directly to the US Food and Drug Administration (FDA).\]
• If septic reaction is suspected: blood culture drawn from the patient.
• If respiratory symptoms are present: chest X-ray to assess for pulmonary edema or other causes of respiratory symptoms.
• If fluid overload is suspected: brain natriuretic peptide (BNP) and the record of fluid balance.

Diagnostic Findings, Part 4
The blood bank investigation revealed no clerical or testing errors, and there was no evidence of hemolysis on visual inspection. Direct antiglobulin test was negative. Chest X-ray showed diffuse bilateral infiltrates. A BNP was elevated (2000 pg/mL, reference range <100 pg/mL), and the chart showed evidence of net positive fluid balance (positive 2 L in the previous 24 hours).

Questions/Discussion Points, Part 4
What Is the Likely Diagnosis for This Patient’s Sudden Hypoxia After Transfusion?
The patient’s reaction could be due to TRALI or TACO. The history of positive net fluid balance and elevated BNP supports a diagnosis of TACO.

How Should This Patient Be Acutely Managed?
Hypoxia associated with TACO should improve with diuresis. In the meantime, oxygen saturation should be maintained with supplemental oxygen as necessary and additional fluid administered should be minimized.

What Should Be Done Prior to Future Blood Product Transfusions?
Transfusion-associated circulatory overload reactions might be prevented in the future by avoiding fluid overload, diuresis, transfusing slowly, and transfusing volume reduced or split blood products (so that lower volumes are administered).15

Patient Follow-Up
After receiving 3 daily granulocyte transfusions, the patient became afebrile, showed an increase in neutrophil count, and blood cultures became negative. At this point, granulocyte transfusions were stopped. The patient successfully completed the chemotherapy.

Teaching Points
Granulocyte transfusion is indicated in severe neutropenic patients with bacterial or fungal infection unresponsive to appropriate antimicrobial therapy.
• Granulocyte transfusion cannot be used indefinitely and should not be used if a patient’s own neutrophil production is not expected to recover.
• Blood products are life-saving therapeutics that replace whole blood or specific blood components (eg, platelets, RBCs, coagulation factors).
• All blood products are associated with transfusion reactions that can mimic a patient’s underlying medical condition.
• Prompt recognition and investigation of a possible transfusion reaction is essential for acute management and future prophylaxis.

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