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TRANSFUSION REACTIONS

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Introduction:

Hello everyone,

Welcome to PedsCases! My name is Bryan, and my name is Justin, and we are second-year medical students at the University of British Columbia. In this podcast, we will have a discussion on how we can approach pediatric transfusion reactions. This podcast was made in collaboration with Dr. Kate Chipperfield, the Head of the Division of Hematopathology at BC Children's Hospital.

Objectives:

After listening to this podcast, the learner should be able to:

1. Describe the incidence of transfusion reactions in pediatric patients
2. Differentiate between the types of transfusion reactions and their pathogenesis
3. Describe the different clinical presentations of transfusion reactions
4. Formulate an approach in assessing and managing a patient with an **acute** transfusion reaction

Clinical Case:

Let's start with a case:

During your call shift, you receive a page regarding Min, a 3-year-old with acute lymphocytic leukemia who has developed a fever during his transfusion. You learn that he was admitted to hospital initially for chemotherapy and had symptomatic anemia. As a result, Min received a 10 ml/kg red cell transfusion, which finished about 30 minutes ago. The nurse tells you that Min's temperature is at 38 degrees Celsius, but the rest of his vitals are within a normal range.

What is your approach in caring for this patient?

Background:

To start, we would like to highlight that pediatric patients have a unique set of clinical needs compared to that of the adult population (1). Due to differences in the physiology, drug pharmacokinetics/dynamics, blood volume, and disease pathophysiology during development, children can react differently to certain treatments than adults would.

This principle applies for transfusion reactions as well, based on the differences in the incidence between pediatric and adult patients (2). Different studies show an increased incidence of transfusion reactions within the pediatric population, in which children experience 6.4-10.7 per 1000 products transfused, compared to 2.5 per 1000 transfusions in adults (2,3). Although these differences could reflect under-reporting of transfusion reactions in adult patients (4), it is important to recognize transfusion reactions in the pediatric population to improve our ability to detect and treat these life-threatening reactions.

The most common cause of adverse transfusion reactions is due to human error. In the United Kingdom, 82% of adverse outcomes from blood transfusions in children was due to infusion of incorrect blood components (5). Most commonly, this involves failing to provide specific products such as irradiated blood. Less common, but more dangerous, scenarios include transfusing the wrong blood group or administering the blood product to the wrong patient. Other errors included over- or under- transfusion, or rapid transfusions which can increase the risk of adverse transfusion reactions (6). Furthermore, acute transfusion reactions such as allergic reactions are very common, contributing to an overall higher incidence of reactions (4). This highlights the importance of rigorous protocols and guidelines that promote hemovigilance among clinicians to prevent introducing unnecessary risk to the patients (7).

We will now discuss what the different types of transfusion reactions are in children.

Classification of transfusion reactions

Transfusion reactions can be categorized by whether the reaction is acute, occurring within 24 hours of the start of the infusion, or delayed, occurring more than 24 hours after the start of infusion (5). Once you establish the timing of the reaction in relation to the transfusion, we can categorize the reactions as infectious and non-infectious.

Infectious complication complications have greatly decreased in the last 20 years thanks to improvements in donor screening, viral inactivation procedures, and testing for various pathogens (4). However, there is still risk of new or unidentified infectious agents, or bacterial contamination from skin contamination at the time of phlebotomy (4). Infectious risks include viral infections and bacterial sepsis.

Three transfusion-transmitted viruses that have significant morbidity and mortality are human immunodeficiency virus (HIV), hepatitis B, and hepatitis C. Fortunately, the estimated risk of a potentially infectious donation being collected is low: 1 in 21.4 million donations for HIV, 1 in 12.6 million donations for hepatitis C, and 1 in 7.5 million donations for hepatitis B (8). The risk of infection, however small, is present, and may be a common concern for parents.

Different bacteria are associated with acute infection depending on the blood component being transfused. For example, Gram Negative organisms are associated with packed red blood cells, while skin flora (eg. Staphylococcus epidermis and Streptococcus species) are associated with platelets. Of note, there is a higher risk of acute infection with platelets because platelets are stored at room temperature, however the overall incidence of bacterial contamination across Canada is low, at 1 per 292,775 units transfused (9).

Non-infectious complications are now much more likely than infectious. As well, almost all fatal complications of transfusions seen currently are of non-infectious etiology (4). Within the non-infectious risks, there are immune-mediated, which generally involve antibody reactions between the donor and recipient, and non-immune-mediated, which can be caused by properties of the transfusion product (4).

So we can say then, that all non-infectious complications of transfusion will fall under one of the following categories:

1) acute immune-mediated transfusion reactions
2) acute non-immune-mediated transfusion reactions,
3) delayed immune-mediated transfusion reactions, and
4) delayed non-immune-mediated transfusion reactions (4,5).

We use this framework to classify the different transfusion reactions. However, our approach to acute transfusion reactions is based on the patient's clinical presentation.

Acute Transfusion Reactions by Clinical Presentation

There are many types of acute transfusion reactions. The most common reactions present in 3 ways: fever, allergic reaction, and dyspnea.

Transfusion reactions associated with fever include febrile non-hemolytic transfusion reactions, acute hemolytic transfusion reaction and sepsis.

1) **Febrile non-hemolytic transfusion reactions** are acute immune-mediated reactions caused by exposure to pyrogenic cytokines. Cytokine exposure may be due to activation of donor leukocytes by preformed antibodies in the recipient, by activation of recipient leukocytes and endothelial cells by transfused leukocytes or plasma contents, or by transfer of accumulated cytokines in the blood product.

   Febrile non-hemolytic transfusion reactions typically present within 1-4 hours after transfusion with:
   - Fever, chills, rigors
   - headache
   - increased diastolic blood pressure
   - and rarely nausea and vomiting (5)

   Febrile non-hemolytic transfusion reactions are benign and typically just require supportive care. Importantly – kids with FNHTR will NOT be clinically unstable with low blood pressure or oxygen saturation; fever is usually *responsive* to antipyretic.

   Febrile non-hemolytic transfusion reactions are a diagnosis of exclusion due to other possible transfusion-related causes of fever. To treat febrile non-hemolytic transfusion reactions, first consider and exclude infection and hemolysis, and provide antipyretic and supportive care.

2) **Acute hemolytic transfusion reactions** are acute immune-mediated reactions caused by ABO or other RBC antigen incompatibilities. The reaction happens because of destruction of transfused red cells by the recipient's immune system. This almost always occurs due to staff failure to follow checking and identification procedures at the time of transfusion, or at the time the pre-transfusion blood group sample was taken. It presents as:
   - fever (which is the most common sign), chills, rigors,
   - discomfort and apprehensiveness,
   - pain in lower back, flank, chest, and/or at the injection site,
   - hypotension,

- bleeding,
- laboratory signs of hemolysis disseminated intravascular coagulation,
- and/or renal failure (5).

To treat acute hemolytic transfusion reactions, patients are given supportive care with aggressive hydration and diuretics to encourage urine output (10).

3) **Sepsis** is an acute infectious complication, which is due to bacterial contamination of the blood product, leading to bacteremia. Such contamination is much more common in platelet transfusions due to storage of this product at room temperature.
It presents as:
   - Fever – often >38C and poorly responsive to antipyretic
   - Rigors, hypotension
   - and other signs of systemic inflammatory response syndrome (11).
   - Labs will be less likely to show signs of hemolysis

   To treat a septic transfusion reaction, provide supportive care. Send the product remainder to be cultured and obtain blood cultures from the patient. Start broad-spectrum antibiotic therapy based on local resistance charts.

The next clinical presentation of transfusion reactions is an allergic reaction.

4) **Allergic transfusion reactions** are acute immune-mediated reactions caused by IgE- mediated and IgE-independent mast cell activation and histamine release. It can present as anaphylaxis or other mast-cell mediated symptoms including:
   - Skin symptoms including urticaria pruritus, angioedema/facial edema
   - GI symptoms including nausea, vomiting, abdominal cramps and diarrhea
   - Respiratory Symptoms including upper airway edema causing obstruction/stridor and lower airway reactions such as bronchospasm, wheezing, chest wall retractions, and shortness of breath
   - Cardiovascular symptoms including hypotension and syncope.

   Most allergic transfusion reactions are mild and respond to antihistamine. Further treatment and more intensive monitoring would be based on the severity of reaction and may include administering epinephrine, bronchodilators and corticosteroids if the reaction is severe or anaphylactic.

The last clinical presentation of transfusion reaction is dyspnea. These reactions can be life-threatening and include transfusion-associated circulatory overload (TACO) and Transfusion-Related Acute Lung Injury.

5) **Transfusion-associated circulatory overload (TACO) are** acute non-immune mediated reactions caused by an excessive rate or volume of transfusion delivered in a susceptible patient, for example, a neonate (6).

   TACO typically occurs within 6 hours of the end of the infusion, and presents as:
   - shortness of breath, chest tightness, cough, tachypnea,
   - headache,
   - tachycardia, hypotension, and

- signs of volume overload, such as jugular venous distension, S3 heart sound, and pulmonary edema.

To treat TACO, patients are given supplemental oxygen and diuretics.

6) **Transfusion-related acute lung injury (TRALI)** is an acute immune-mediated reactions defined as an acute lung injury with a clear temporal relationship to the transfusion, occurring within 6 hours of the transfusion (4).

The proposed mechanism is not completely understood. It is thought that when alloantibodies are present, donor antibodies cause noncardiogenic pulmonary edema by attacking the white blood cells within the recipient's microcirculation. If antibodies are absent, it may be due to primed neutrophils from a previous trauma or surgery, and mediators in transfused plasma activate the neutrophils adhered to the endothelium of the lungs, causing acute lung injury (4,11).

TRALI is associated with use of products with higher amounts of plasma, such as fresh frozen plasma (4,5). TRALI has become uncommon due to blood supplier practices avoiding use of plasma from higher risk donors.

TRALI's clinical presentation is similar to respiratory distress syndrome and includes:
- shortness of breath, increased work of breath, cough, tachypnea, hypoxemia,
- tachycardia, hypotension or hypertension,
- fever, and
- bilateral pulmonary infiltrates on a CXR (4,5).

Diagnosis of TRALI requires CXR. To treat TRALI, patients are given supplemental oxygen or mechanical ventilation if needed, and a restrictive fluid strategy

Delayed Transfusion Reactions, a Brief Introduction

As mentioned above, delayed transfusion reactions occur more than 24 hours after the start of the infusion. We will briefly characterize delayed hemolytic transfusion reactions but please note that delayed transfusion reactions are less common and require a different approach than acute reactions.

1) **Delayed hemolytic transfusion reactions** are delayed immune-mediated reactions caused by previous recipient alloimmunization to red cell antigen, and antibody mediated extravascular hemolysis of the antigen-positive transfused red cells. They may be subtle and clinically mild, presenting with:
   - Unexpected anemia, usually within the first two weeks following transfusion (5).
   - Fever, chills
   - Jaundice
   - Malaise
   - Back pain

To treat delayed hemolytic transfusion reactions, symptomatic treatment (such as with antipyretics) is usually enough as the reaction is often self-resolving. It is good practice to monitor hemoglobin levels regularly to ensure the reaction is not getting worse (12). It's very important to identify the specific antibody causing this reaction, to allow better selection and matching of red cells for transfusions in the future.

A hemovigilance report from Quebec looking at the rates of transfusion reactions between 2000 and 2012 puts into perspective which types of reactions are more common in Canada.
shows that minor allergic reactions and non-hemolytic febrile reactions accounted for approximately 70% of reactions from therapeutic blood products, while "serious" reactions such as volume overload and ABO incompatibility accounted for 14% (13).

So, if your patient presented with any of the clinical presentations we listed, how would you approach the problem? We will now discuss how to formulate an approach to transfusion reactions.

Approach to Transfusion Reactions

This section will give an overview to the general approach of transfusion reactions; the details of how each specific type of transfusion reaction is managed is out of the scope of this podcast.

The following steps should be taken for all patients who are potentially having a transfusion reaction:

1. Immediately stop the transfusion to prevent worsening of the patient's complications. Secure any remaining blood product in the bag with a sterile stopper and send to the transfusion laboratory (14).

2. If not physically present with the patient, the physician should go see the patient at bedside. Given that the signs and symptoms of mild versus life-threatening complications overlap, it is appropriate for the physician to be at bedside to closely monitor and evaluate the patient with suspected transfusion reaction (15).

3. Assess the patient's vital signs, typically at 15-minute intervals (16). If the patient requires stabilization, the physician should assess the ABCs, that is, the patient's airway, breathing, and circulation, and address issues according to their findings.

4. Verify the patient's identity and the transfused blood product to confirm that the correct product was given to the patient. Check that the information on the patient's identification band, issue tag, and the blood component label are identical (17).

5. Perform a focused history and physical exam based on your patient's primary complaint. This is a crucial step as it will guide the subsequent treatment approach by refining the differential diagnosis. We reviewed the three most common presentations of transfusion reactions (16,18–20):

    a. Fevers and chills are commonly associated with FNTHR, but can also be present in sepsis, acute hemolytic transfusion reactions, or TRALI. Pay attention to blood pressure, pulse and the patient response to initial antipyretic therapy. If bacterial contamination or sepsis is suspected, culture the patient's blood as well as the blood product remnant. Fever can also be present after a recent surgery; therefore, the history is important.

    b. Presence of hives/urticaria, itching, and abdominal cramps may indicate an allergic reaction. You can also note any respiratory symptoms such as shortness of breath, or exam findings of bronchospasm or wheeze that would indicate anaphylaxis

b. Respiratory distress or dyspnea can point towards concerning reaction types such as TACO or TRALI. A chest x-ray must be done to further investigate. Check and document oxygen saturation, respiratory exam findings and signs of volume overload.

On top of the 3 most common presentations, other signs and symptoms can be associated with certain transfusion reactions:

d. Hypotension can be present in anaphylaxis, sepsis, acute hemolytic transfusion reaction, or TRALI

e. Acute hemolytic transfusion reactions may uniquely present with hemoglobinuria (red/brown, discolored urine) and back/chest pain

f. It can also be helpful to note the details of any history of transfusion reactions in the past

g. Other symptoms which appear within hours of starting transfusion which suggest a reaction are: anxiety, GI symptoms such as diarrhea, nausea, and vomiting, feeling of impending doom, tachycardia, chest pain or tightness, new on-set headache, and difficulty speaking among others.

At this point of the assessment, you should have a differential diagnosis of which transfusion reaction type the patient is mostly likely experiencing, so from here a treatment plan can be devised. In most cases, management of transfusion reactions is supportive, such as by using antipyretics for fevers, antihistamines for allergic reactions, or giving supplemental oxygen for those experiencing respiratory distress (16,18).

Revisiting the Clinical Case

Let's revisit our clinical case. Min is a 3-year-old who received RBC transfusion for his chemotherapy associated anemia and developed fever after transfusion. You promptly go in-person to assess the patient and re-measure the vitals which are: temperature of 38.2, heart rate 100, respiratory rate 28, blood pressure of 100/60, and O2sat 98%, which are all within normal limits for his age. You determine that he is stable and does not require immediate resuscitation. You also check that Min's ID band, issue tag, and the infused blood product label all match, and are reassured that he received the correct blood product. The nurse has already collected a post-reaction blood sample for the lab, so further checks of compatibility can be done.

Next, keeping in mind the differential diagnosis of febrile transfusion reactions, which include FNHTRs, sepsis, acute hemolytic transfusion reactions, or TRALI, you start your work up to find the cause of his reaction. You order a series of laboratory tests, which include CBC, blood smear, eGFR, blood culture, and a chest x-ray

- First, on general inspection, Min does not display increased work of breathing which makes TRALI/TACO unlikely. Furthermore, the chest x-ray you ordered shows clear lungs without any infiltration which points away from TRALI.

- On your focused physical exam, lung sounds are clear. Min does not have any tenderness in his lower back, or any flank pain. From this you are less worried about an acute hemolytic transfusion reaction, but you would have to see the results of his labs for signs of hemolysis, renal function or disseminated intravascular coagulation to make sure. You put acute hemolytic transfusion reactions lower on your differential.
- You are waiting on the results of the blood culture. However, as Min does not display hypotension or other systemic inflammatory syndrome conditions such as tachycardia, tachypnea, or increased WBC count, you hold the broad spectrum antibiotic therapy and put sepsis lower in your differential.

From your findings, you preliminarily diagnose Min with FNHTR by the process of exclusion. You provide supportive measures which includes antipyretics and carefully monitor the progression of his symptoms and vitals, which seem to be resolving. Later that day, the blood cultures come back negative, and the labs and blood smear. As Min continuously starts to improve, you are confident that you've adequately addressed his problems. Together with Min's nurse, you report this reaction to the Transfusion Laboratory.

Key learning points:

In conclusion, the key learning points of this podcast are:

1. Pediatric patients are more susceptible than adults to transfusion reactions, which may happen due to errors, or inappropriate ordering of product specifications, volume, or infusion rate
2. There are many types of transfusion reactions, but the clinical features can help you formulate your differential diagnosis and treatment plan
3. Always assess the patient in-person when suspecting a transfusion reaction, as the first symptoms and signs may not reliably predict the severity of the transfusion reaction
4. Most treatments of transfusion reactions are supportive

We hope that this podcast was helpful in your learning. Thank you for listening!

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