To Transfuse Or Not To Transfuse For Patients with Sickle Cell Disease

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Pre Question 1 – Select the correct response

A. Sickle cell patients on chronic transfusions are not at high risk for iron overload
B. Transfusion triggers are the same for patients with or without sickle cell disease
C. The risk of delayed hemolytic transfusion reactions is decreased if phenotypically matched blood is provided
D. Units for transfusion should be irradiated
E. Alloantibody development occurs rarely in the transfused sickle cell patient

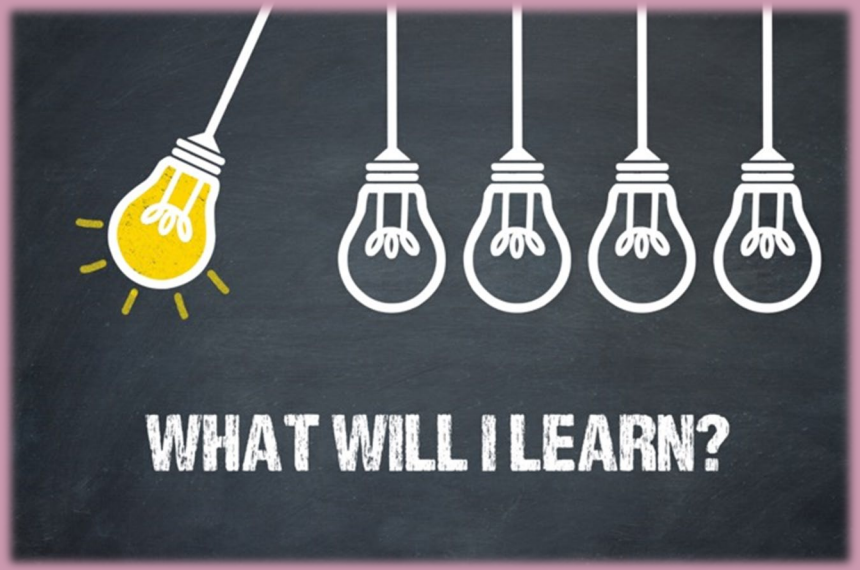
Pre Question 2 – Select the correct response

In the absence of symptoms of inadequate tissue oxygen delivery, at what hemoglobin range should you first consider a red cell transfusion?

A. Less than 50 g/L
B. When between 50 g/L – 60 g/L
C. Whenever it's less than 70 g/L
D. When between 70 g/L – 80 g/L
E. Based on patient's request for transfusion

Pre Question 3 – True or False

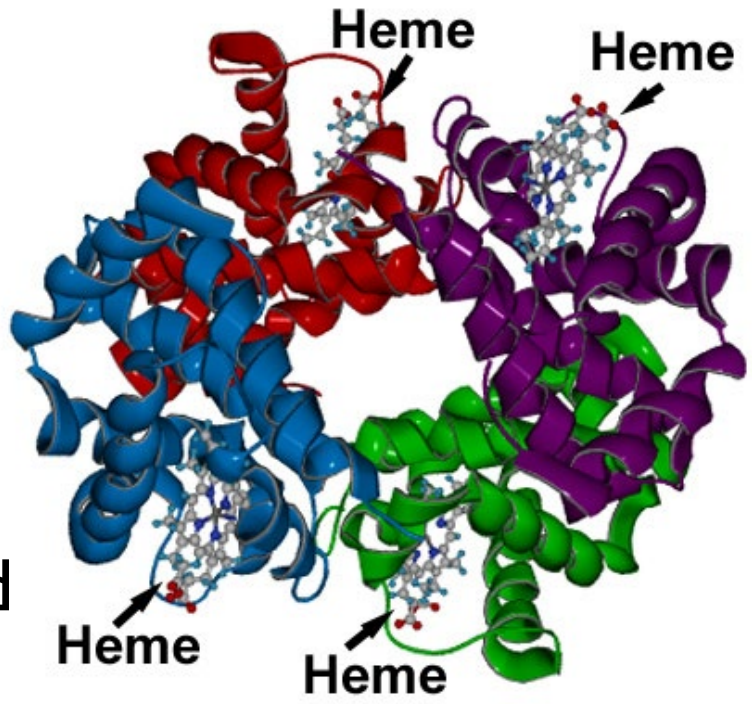
When a patient with sickle cell disease arrives to the emergency department with an uncomplicated vaso-occlusive pain crisis, transfusions are one of the recommended treatments to help reduce pain and improve bioavailability of oxygen.



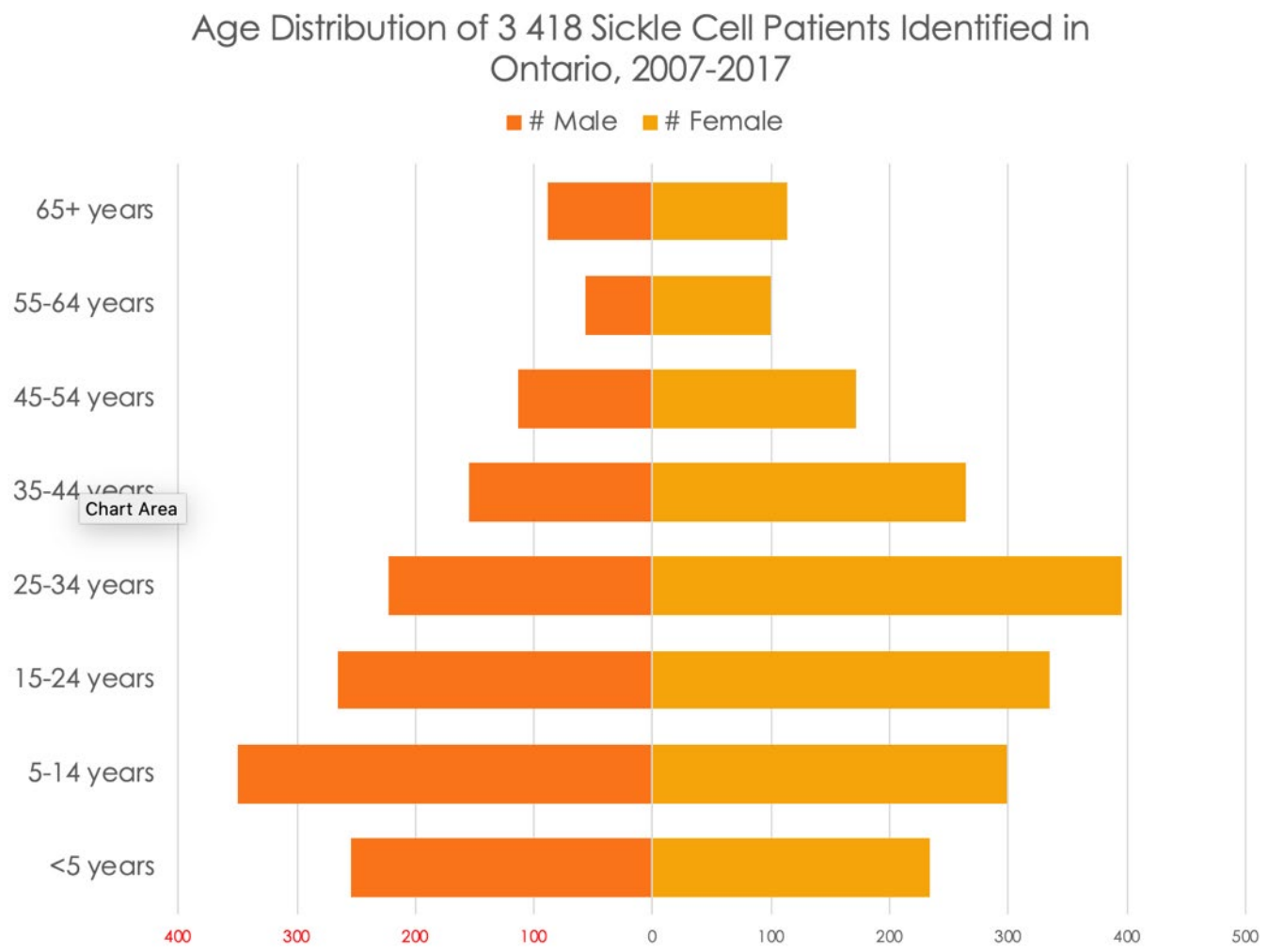
- Review the conditions under which transfusions are a safe option for patients with Sickle Cell Disease (SCD)
- Identify barriers to care for patients with SCD
- Discuss transfusion complications such as aplastic crisis and hyperhemolysis
- Appreciate the psychosocial, emotional, and physical impact of chronic conditions, such as Sickle Cell Disease, for racialized patients

Sickle Cell Disease: Pathophysiology

- Inherited red blood cell disorder that is autosomal recessive
- Due to specific point mutation in sixth codon of ß-globin gene
- Resulting HgbS has a hydrophobic domain which predisposes to precipitation when deoxygenated
- HgbS polymerization results in formation of elongated fibres which stretch and deform the erythrocyte
- Membrane damage results in cellular dehydration, rigidity, adhesiveness/thrombogenicity
- Net result: **hemolysis, vaso-occlusion**

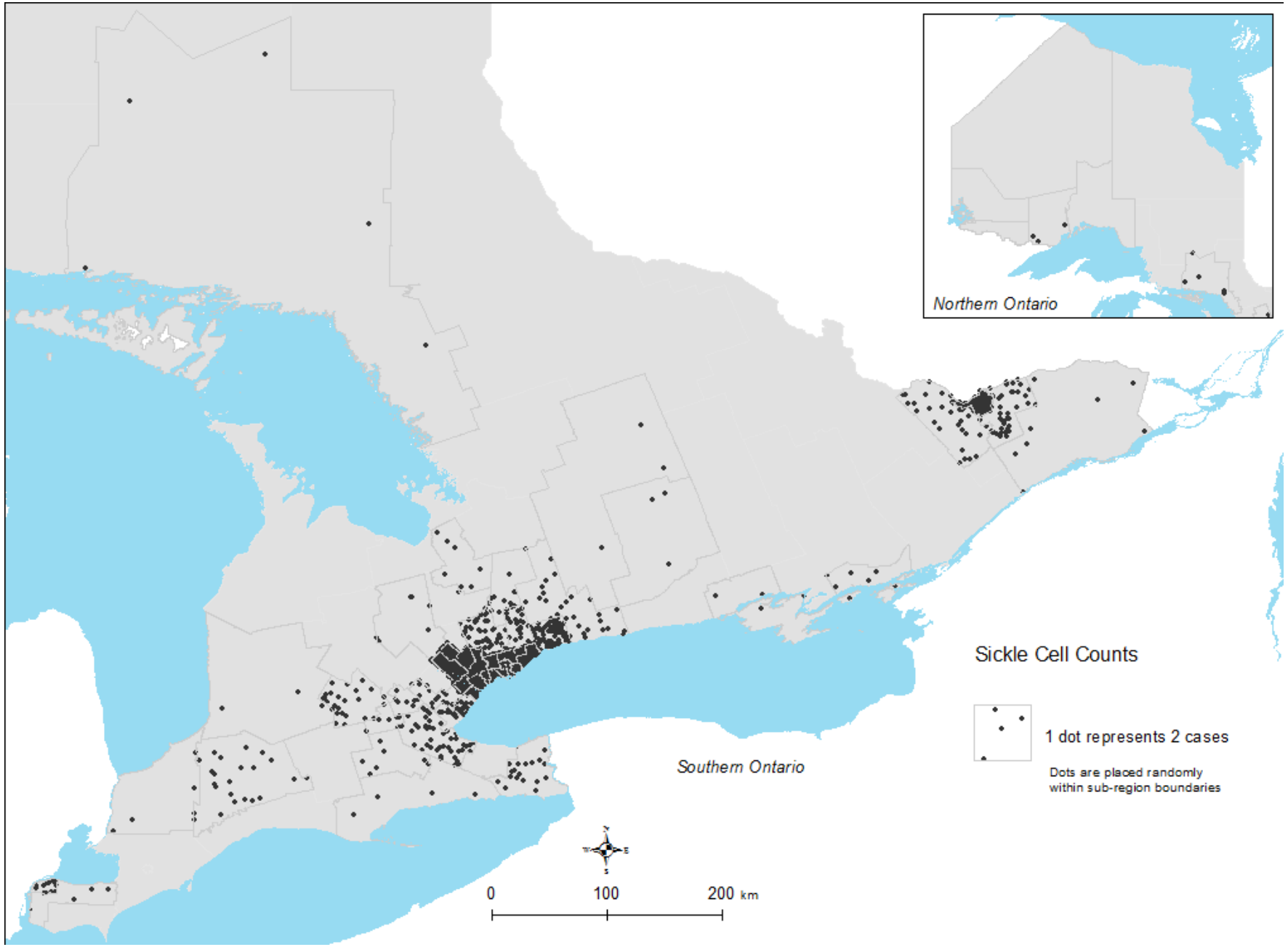


~3500 Patients with Sickle Cell Disease in Ontario



- *56% female*
- *Median age = 24*
- *One third ≤ 14 years*
- *~ 30-40 children born with sickle cell disease in Ontario every year*
- *Does not include patients without OHIP (eg., patients with UHIP, IFH, private or no coverage)*

Pendergrast J, CMAJ Open. 2023;11:E725



- Median of 1 hospitalization (IQR 1-5) and 2 ER visits (IQR 1-7) per patient, but data skewed by small number of “superusers”
- Majority reside in urban areas, mostly Toronto and Ottawa, but can be found in all areas of the province
- 38.9%% lived in neighbourhoods with lowest median national income quintile

Pendergrast J, CMAJ Open. 2023;11:E725

Ontario Health Quality Standards for Sickle Cell Disease (Released January 2023)

Quality Statement 1: Racism and Anti-Black Racism

People with sickle cell disease (and their families and caregivers) experience care from health care providers within a health care system that is free from racism and anti-Black racism, discrimination, and stigma. Health care providers promote a culture that is compassionate, trauma informed, and respectful of people's racial/ethnic and cultural backgrounds. They build trust with people with sickle cell disease (and their families and caregivers), work to remove barriers to accessing care, and provide care equitably.

Quality Statement 3: Vaso-occlusive Acute Pain Episodes

People with sickle cell disease who present to an emergency department or hospital with a vaso-occlusive acute pain episode receive a timely pain assessment and clinical assessment. Their treatment begins within 30 minutes of triage or 60 minutes of presentation. Before discharge, they are involved in the development of a plan for continuing to manage their acute pain episode at home. This plan includes symptom management strategies and information on how to access follow-up care and support from health care providers, as needed.

Quality Statement 4: Life-Threatening Acute Complications

People who present to an emergency department or hospital with a potentially life-threatening acute complication of sickle cell disease have their condition and its severity identified through a prompt clinical assessment. Their condition is managed appropriately with an individualized treatment and monitoring plan.

Case Introduction – Patient History

- Adesola is a 22 year-old woman with HgbSS sickle cell disease
- Originally from Nigeria, she has been living on her own in Toronto for the past year, attending university on a student VISA
- While her symptoms are normally well-controlled with hydroxyurea, her first Canadian winter has triggered a severe vaso-occlusive pain crisis
- She has tried to manage her pain at home, but the pain is to severe and she heads to the Emergency Department

Arrival to ED – Triage Assessment

- At triage, she has a low grade fever, but her other vitals are normal, with an oxygen level of 98% on room air
- Despite reported symptoms of severe pain in her lower back and right leg, she is noted to be ambulating without difficulty and has no visible trauma
- She is assigned CTAS level 3

CTAS Scores		
		See patient:
CTAS 1	Resuscitation	Immediate
CTAS 2	Emergent	≤ 15 minutes
CTAS 3	Urgent	≤ 30 minutes
CTAS 4	Less Urgent	≤ 60 minutes
CTAS 5	Non Urgent	≤ 120 minutes

What should the CTAS score be for a patient with sickle cell disease presenting to the Emergency Department with a vaso-occlusive episode?

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What is a CTAS Score and Why Does It Matter?

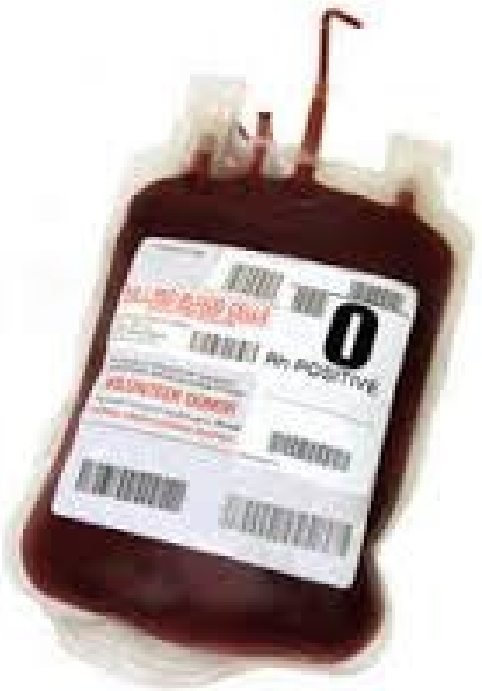
- The Canadian Emergency Department and Triage Acuity Scale is used by triage nurses to determine in a 2 to 5 minute assessment how quickly a patient needs to be seen by a physician on arrival at the ED
- CTAS level is a guide and compliance with adhering to time frames is relative to the CTAS levels of other patients in the ED. The highest CTAS is level 1 and the patient must be seen immediately.
- **Level 2 is for patients who are considered 'emergent' and the expected time to physician assessment is less than or equal to 15 minutes**; the 15 minute interval also guides the frequency with which a nursing reassessment should occur while awaiting physician assessment if there is a delay.

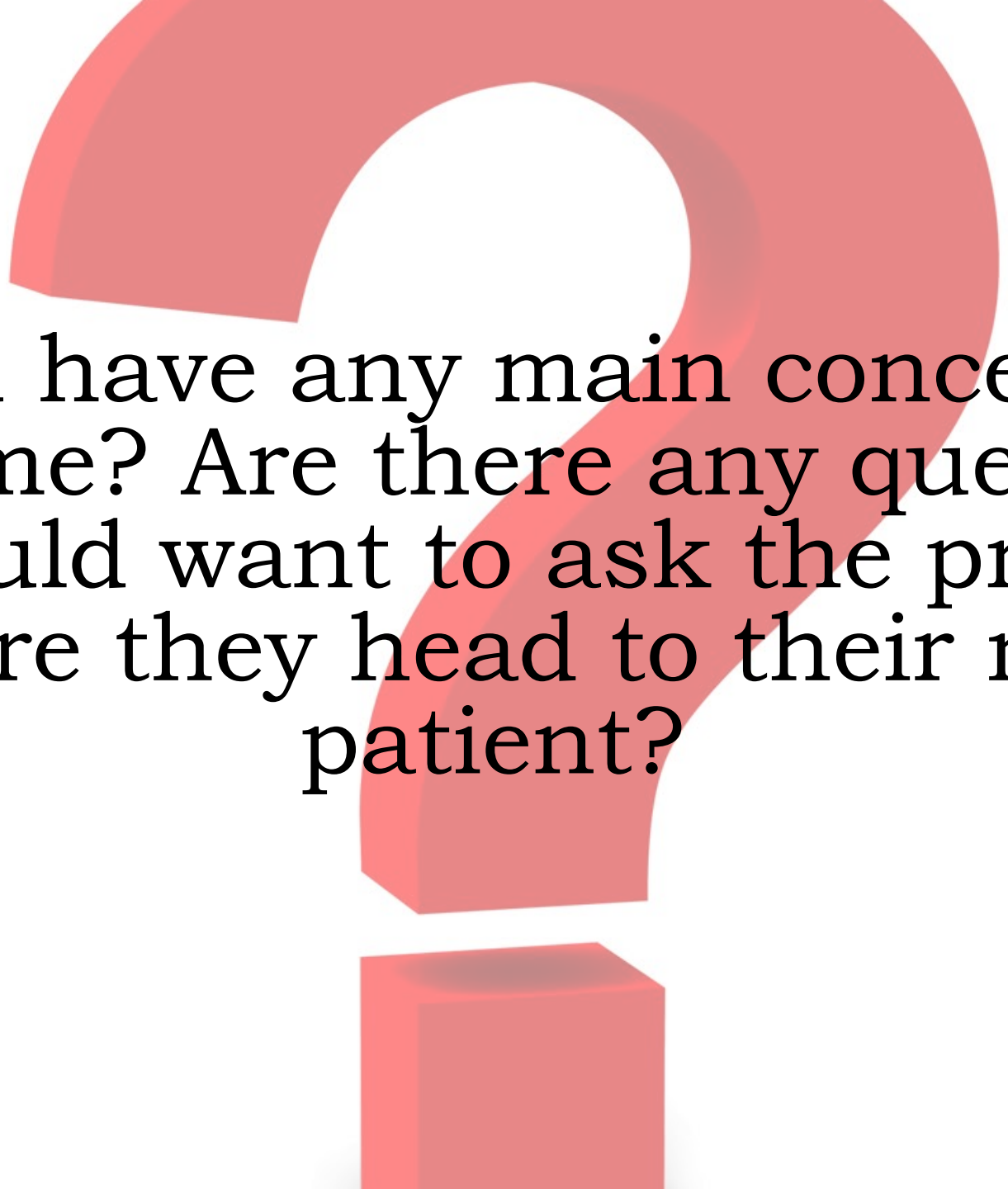
ER Physician Assessment

- She is assessed by the ER physician 2 hours after initial presentation, who orders the following:
  - Morphine 10 mg IV q4h with 2 mg IV q1h prn for breakthrough
  - 0.9% NS at 250 mL/hr
  - CBC, electrolytes, creatinine, liver enzymes, bilirubin
- One hour later, despite receiving her first breakthrough dose of morphine, she reports pain that is still poorly controlled, and requests an additional dose
- Due to concerns with the possibility of drug-seeking behaviour, the ER physician attempts to contact a hematologist for guidance and orders an x-ray of the patient's back to identify a structural lesion as a cause for the pain

Critical Result

- While waiting for hematology to call back, the laboratory calls with an urgent result: **Hgb is 62 g/L**
- Due to an unplanned downtime, it is not possible to review her previous laboratory investigations through ConnectingOntario
- However, patient reports that her hemoglobin is usually in the range of 75-85 g/L, and that she had been transfused 3 weeks earlier at another hospital, where she had also presented with a pain crisis
- She reports her pain is now much more severe
- An order for a 2 unit RBC transfusion is written





Do you have any main concerns at this time? Are there any questions you would want to ask the provider, before they head to their next patient?

Barriers to Care for SCD Patients

Barriers	Details
Social Isolation	Patients with sickle cell disease are more likely to seek medical assistance for acute care if: • lack of medical home • inadequate social supports (friends, family) • feelings of fear/helplessness
Fragmented Care	Medical records from other countries where care received (eg., previous complications and treatments) and other Ontario hospitals (eg., lab results) not easily accessible.
Implicit Bias	Unwarranted suspicion of drug-seeking behaviour, desire to seek external party validation of reported symptoms Not engaged in their care, lazy, uneducated
Knowledge Gap of Healthcare Providers	Many caregivers unaware of the role and risks of RBC transfusion that are specific to patients with sickle cell disease Many unaware of what sickle cell disease is and acute nature of situation

Key Considerations for Transfusions in SCD Patients

- Individuals with SCD naturally have higher blood viscosity.
- This makes blood flow more sluggish. Therefore patients with SCD should never be transfused to a hemoglobin **exceeding 100 to 110 g/L**.
- The best means of achieving improved oxygen delivery in SCD is to ***decrease the Hgb%*** rather than simply *increase the total hemoglobin*.
- In some situations, increasing the hematocrit may actually worsen oxygen delivery because of viscosity effects.
- Transfusions should be considered when the hemoglobin (Hb) is less than 50 g/L, or has fallen by more than 20 g/L in the absence of hemodilution.

Transfusion Support in SCD

Simple Transfusion

Only an option if Hgb < 90g/L

Possible goals:

1. Decreasing HgbS in setting of organ failure (eg., acute chest syndrome) or prior to surgery. Two unit top-up typically decreases HgbS from to 60%

2. Increasing total Hgb in setting of severe anemia (eg., Hgb < 50 g/L)

Partial Manual Exchange

An option if Hgb > 90 g/L

Goal is to decrease HgbS in setting of organ failure (eg., acute chest syndrome) or prior to surgery

Process is manual phlebotomy followed by transfusion (2 out/2 in typically achieves HgbS of 60%)

Automated Exchange

Can achieve rapid reduction of HgbS to <30%

Requires specialized equipment and personnel

Usually reserved for very high risk patients (eg., admitted to ICU, history of stroke)

Overview of Transfusion Indications for SCD

Generally Accepted	Possibly Effective	Not Indicated
• Acute cerebrovascular accident • Primary and secondary stroke prevention • Retinal artery occlusion • Acute and recurrent splenic sequestration • Intrahepatic cholestasis • Acute chest syndrome • Aplastic crisis • Pre-operative for moderate to high-risk procedure • Hemorrhage (eg splenic rupture) • Prevention of pain crises	• Recurrent or persistent priapism • Pulmonary hypertension • Progressive renal failure • Pregnancy with exacerbation of anemia or evidence of placental insufficiency • Severe sepsis	• Compensated anemia • Infections other than aplastic crisis or acute chest syndrome • Treatment of uncomplicated pain crisis • Pre-operative for minor procedures • Non-surgical management of avascular necrosis • Uncomplicated pregnancy

Frequent cause of inappropriate transfusions!

In general, a hematology consultation should always be sought before transfusing a patient with sickle cell disease

Adapted from Wanko, Hem Onc Clinics of NA 2005;19:803

Alert, alert, alert!

- Due to differences in RBC expression in SCD patients and typical blood donors (ie., mismatched ethnicity), and the tendency of sickle cell patients to mount immune responses to foreign antigens, extra care is required in matching for RBC antigens.
- Failure to provide this extended antigen matching places SCD patients at **high risk for transfusion reactions**, which in some cases can be **life threatening**.
- Transfusion medicine staff need sufficient time to prepare specialized blood products for individuals with SCD.
- If you have information related to previous transfusions (e.g. - the names of other hospitals patient has received care at), provide this information to the blood bank as well).

Let's get back to the case…

Does Adesola need a transfusion?

- Current presentation consistent with a simple acute pain crisis (no organ dysfunction)
- Current hemoglobin = 62 g/L and no reports of severe fatigue or dyspnea

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No transfusion Needed

Change in Patient Condition

- Patient is admitted to internal medicine ward for further pain management
- The next day, Adesola tells you that she is feeling more tired and her pain is still 8 out of 10
- Reports that when she went to the bathroom, she noticed her urine was very dark red
- Vitals signs are stable aside from low-grade fever, but she looks very pale
- You inform the MD and they order a stat CBC and crossmatch

To Transfuse or Not?

- 30 minutes later, the lab calls with a critical result =

Hgb is 45 g/L

- Blood bank reports they have detected a new anti-C antibody from her recent transfusion

What type of transfusion should be considered for this patient, at this point?

A. Simple transfusion
B. Partial manual exchange
C. Automated red cell exchange
D. Transfusion should be avoided in this situation

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Hgb < 50 in SCD: What should I be looking for?

Aplastic Crisis	• Signs of erythrovirus (parvovirus B19) infection: erythematous rash and arthropathy • Reticulocytopenia with preserved WBC and platelets
Sequestration Crisis	• Splenic (children): LUQ pain with hypovolemic shock • Hepatic (adults): RUQ pain with transanimitis • Reticulocytosis with fall in all 3 cell lines
Hyperhemolysis	• Pain crisis within 1 month of transfusion • *Normal reticulocyte count* with fall in hemoglobin below pre-transfusion levels

Hgb < 50 in SCD: What are the risks

Aplastic Crisis	• Volume overload • Patients have normalized their blood volume by the time they present • Transfuse small volumes and reassess
Sequestration Crisis	• Polycythemia • Sequestered RBCs can be released back into circulation (autotransfusion) • Transfuse small volumes and reassess
Hyperhemolysis	• Worsening anemia • Transfusions may accelerate hemolysis of both transfused and the patient's own RBCs • Avoid transfusions and start immunosuppression

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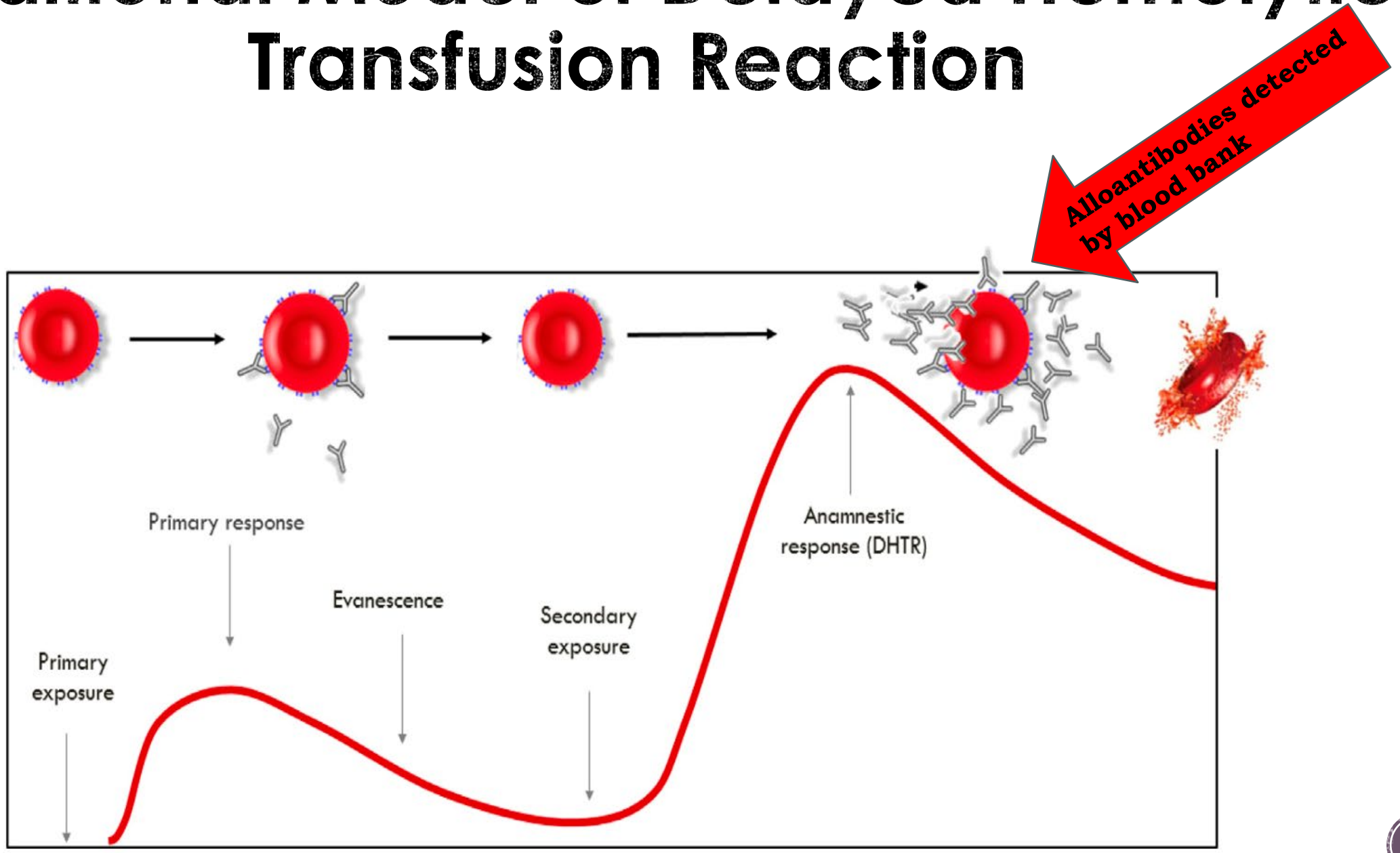
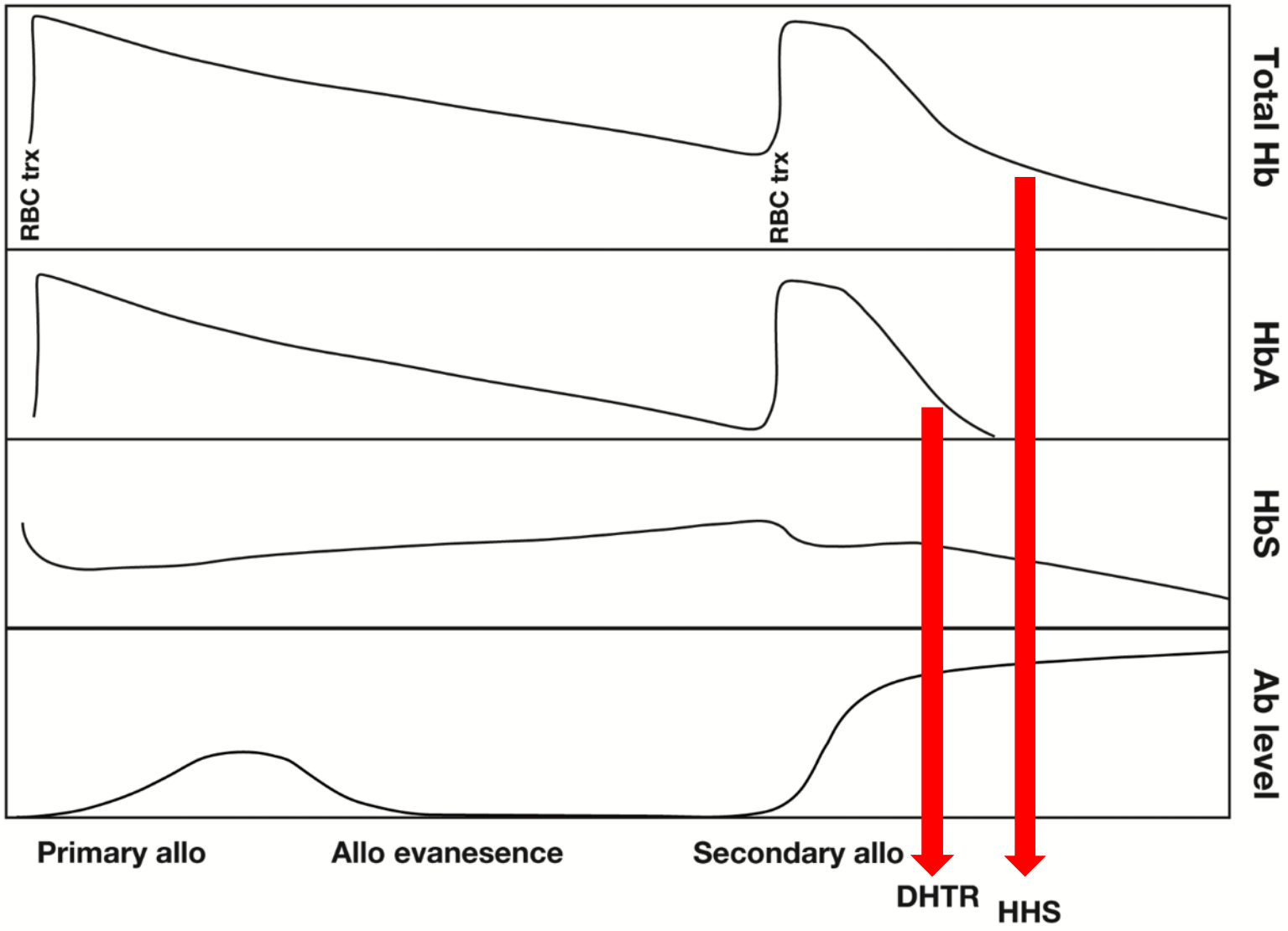
Traditional Model of Delayed Hemolytic Transfusion Reaction





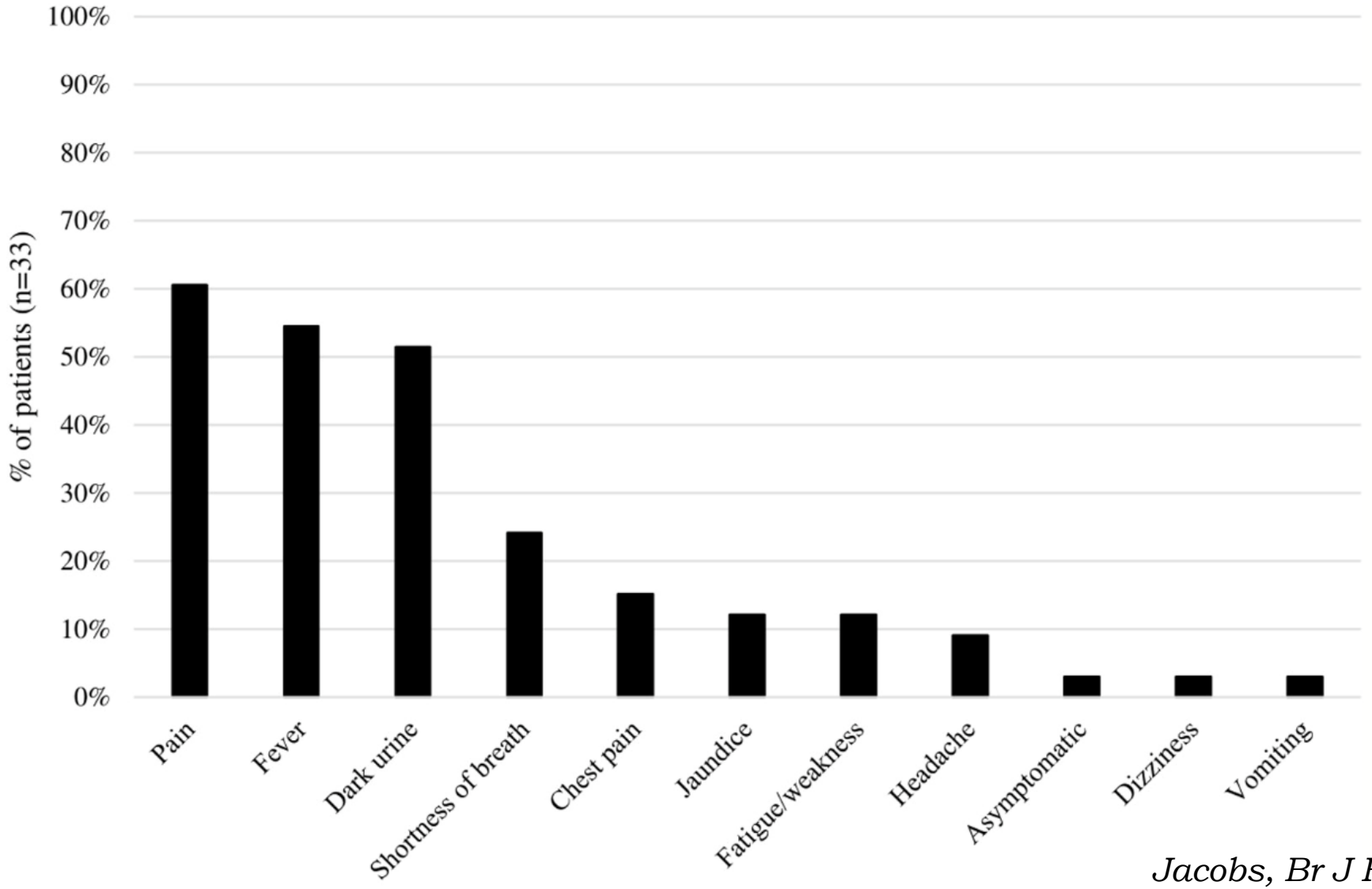
When **total** hemoglobin falls below pre-transfusion levels, suggests an accompanying fall in patient's own cells, indicating <u>hyperhemolysis</u>

Delayed hemolytic transfusion reaction in sickle cell indicated by rapid fall in HgbA cells

In either case, antibodies not always observed

Thein, Haematologica 2020;105:539

Most common presenting signs/symptoms in HHS (patients can have more than 1)



Median onset from time of last transfusion = 6 days (range 0 –21)

Median Hgb nadir of 39 g/L occurred at median of 10 days post-transfusion

Jacobs, Br J Haematol. 2023;201:1025

To Transfuse or Not?

With hyperhemolysis further transfusions will only worsen anemia and may be fatal!

- Hematology consulted, who recommend:
  - Increasing oxygen delivery via patient plasma rather than hemoglobin: patient placed on 100% FiO2 by face-mask despite SpO2 of 100%
  - Avoid worsening anemia with unnecessary blood draws
  - Driving the reticulocyte count to > 250 with erythropoietin 40 000 units daily
  - Shutting down hemolysis with high-dose steroids and IVIG
  - Preparing for rescue therapy with eculizumab and/or rituximab

Outcome

- Over the following week, Adesola's hemoglobin recovers to 65 g/L
- Erythropoietin and oxygen therapy discontinued
- Patient advised that there is a very high risk of recurrence, future transfusion should be avoided at all costs.

Which sickle cell patient (HbSS) warrants an exchange transfusion?

A. 28 yr old female, 25 weeks pregnant, G1P0, Hb 70g/L
B. 45 yr old female with Hb 34g/L with an aplastic crisis
C. 21 yr old female with vaso-occlusive crisis and Hb 70g/L
D. 20 month old girl going for cholecystectomy with Hb 80g/L
E. 38 yr old female with acute chest syndrome requiring mechanical ventilation

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Summary

- Tranfusing patients with sickle cell disease requires careful consideration, patient's past transfusion history, resources available for support, and knowledge of care providers. **A hematology consult is strongly advised before transfusing patients with SCD.**

- Simple, partial manual, and red cell exchange transfusions all have different purposes and are selected based on need to reduce HbS% or increasing hemoglobin to increase oxygen available.

- Uncomplicated vaso-occlusive episodes are not a reason for transfusion and are often ordered due to lack of knowledge/awareness of the considerations in ordering transfusion for SCD patients

Post Question 1 – Select the correct response

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THANK YOU