Hemolytic Anemia in Children

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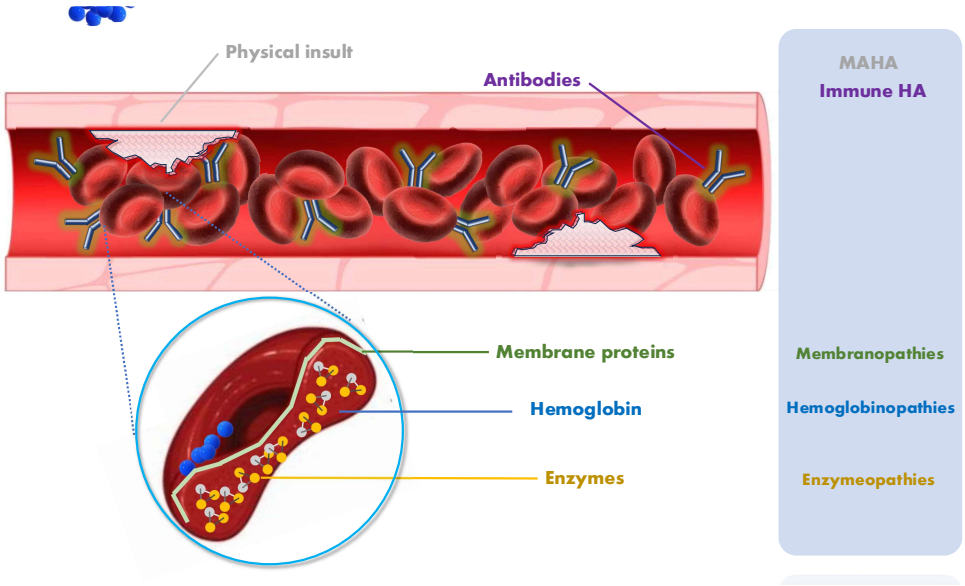
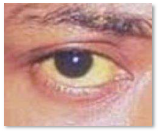
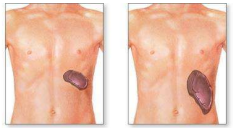


General Clinical and Laboratory Findings


Pallor


Hemoglobinuria


Jaundice

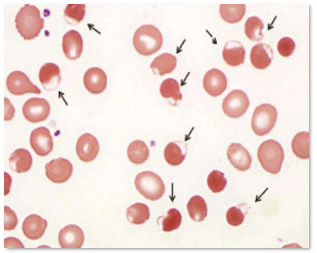

Splenomegaly

- CBC mostly indicates anemia, which is generally **normocytic** but can be microcytic or macrocytic
- **Bilirubin, predominantly unconjugated,** and **LDH** are generally increased
- **Reticulocyte count** is almost always appropriately elevated, except rare occasions in some severe cases
- **Peripheral blood smear** is generally diagnostic
- **Splenomegaly** can be present depending on the underlying Dx

Case 1

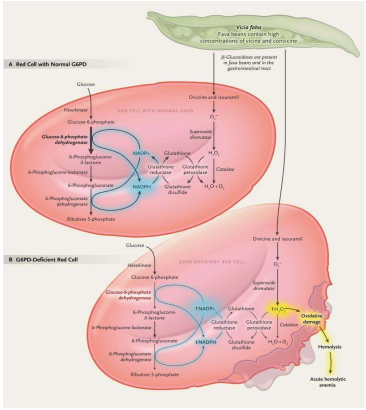
- Pranav is 12-year-old male who was born in Canada to South Asian parents.
- He had neonatal jaundice requiring phototherapy but no hemolytic anemia as a neonate. He had a normal CBC 3 years ago.
- Presents with mild jaundice and pallor for 2 days. He is slightly fatigued. Otherwise well. Reports slightly dark urine.
- Exam is normal except mild pallor and jaundice. Vital signs are normal, and he is afebrile.
- No recent travel. No recent infection. His grandmother is visiting from India and has been cooking delicious traditional Indian food.

- **Hb 89** g/L (normal 120-160 g/L)
- **MCV 91** (normal 75-95 fL)
- MCH 29 (normal 26-32 pg)
- **Platelet count: 282** x 10e9/L
- **WBC: 7.7** x 10e9/L
- **Differentials: all normal**
- **Reticulocyte count 242** x 10e/L (normal 20-90)
- **Bilirubin, Unconjugated: 42** (normal < 17 ug/L)
- **DAT negative**


bite cells and blister cells

Enzymopathies: G6PD Deficiency

- Depletion or absence of red blood cell enzymes required either for ATP generation or as deoxidant.
- In G6PD deficiency, most patient don't have ongoing hemolysis, but can develop **acute hemolysis**, sometime quite brisk and severe, with exposure to certain food and medications.
- Is **X-linked**, but 10-15% of people with G6PD deficiency are females.
- Presumed to confer evolutionary protection against severe malaria.
- Hemolysis happens both intra-vascularly and extra-vascularly (in the spleen). **Splenomegaly is not common** in mild cases, but in severe cases, it can be appreciated.
- Diagnosis is through **G6PD assay** or enzyme activity.

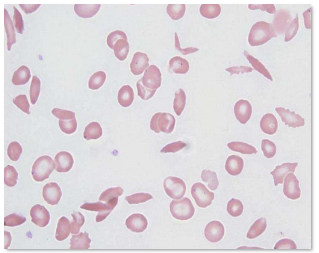


Luzzatto L and Arese P. NEJM, 2018

Case 2

- Mikah is a 4-year-old girl who has recently moved to Canada from Cameroon with a student via. He was previously healthy. Pregancy and delivery was unremarkable.
- He presented to ER with a 3-day history of fever, URTI symptoms, dehydration and vomiting.
- The child is dehydrated (5%), looks tired. He has a left otitis media and is noted to be jaundiced. No organomegaly and the rest of exam is unremarkable.
- He has had vaccination catch up as per BC guidelines

- **Hb 89** g/L (normal 105-135 g/L)
- **MCV 85** (normal 75-87 fL)
- MCH 29 (normal 24-30 pg)
- **Platelet count: 615** x 10e9/L
- **WBC: 18.1** x 10e9/L
- **Differentials: neutrophil 10.3**
- **Total bilirubin 48** (<17 ug/L)
- **LDH 1670** (normal < 800)
- **Reticulocyte count 322** x 10e/L (normal 20-90)
- **DAT: negative**



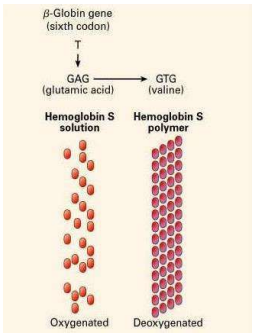
Sickel Cells

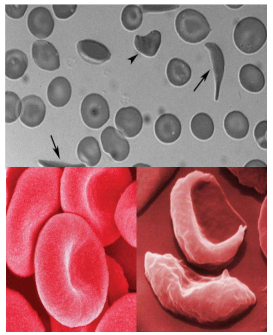
G6PD-Deficieny: Management

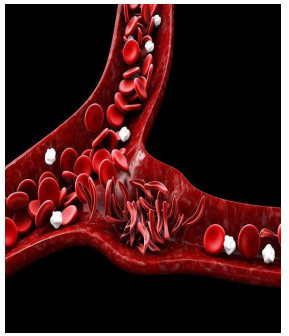
- In mild cases, prompt hydration, short-interval follow up, and symptomatic treatment will suffice.
- More severe cases warrant hospitalization and **blood transfusion**. **Hydration** to prevent acute kidney injury.
- Once diagnosed (now on newborn screening) **counselling** is warranted:
  - signs and symptoms of hemolysis and avoidance of triggers:
  - fava beans, moth balls
  - Certain medications.
  - Some antimalarial agents
- **Referral to hematology NOT REQUIRED**

- AboutKidsHealth.ca
- BCChildrens.ca

Hemoglobinopathies: Sickle Cell Disease



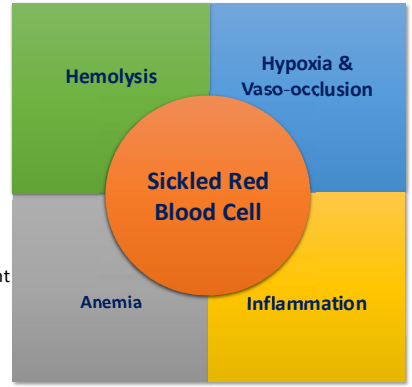




Sickle Cell Disease: Complex Pathophysiology

- Hyperbilirubinemia
- Gall stone
- Stroke
- Pulmonary hypertension
- Priapism
- Thrombosis

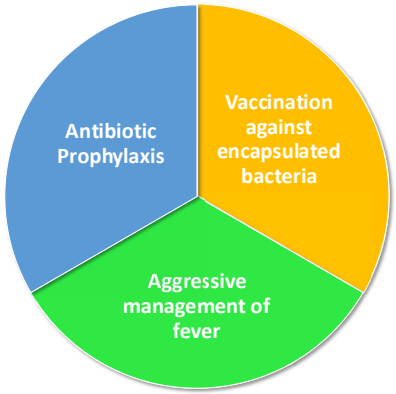
- Renal dysfunction
- Cardiac dysfunction
- Poor Growth/Development
- Bone abnormalities
- Endocrine dysfunction



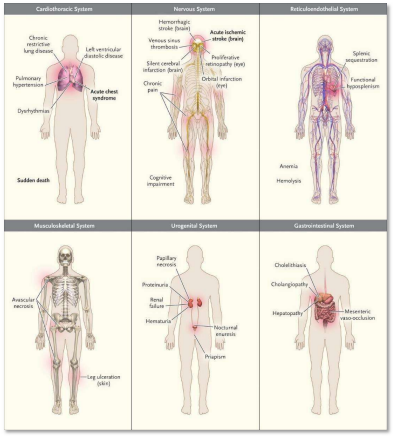
- Pain
- Silent ischemic infarcts
- Multi-organ dysfunction
- Asplenia
- Avascular necrosis
- Acute chest syndrome

- Asthma
- Tonsillar Hypertrophy/OSA
- Thrombosis
- Pain

Management of Infection in SCD



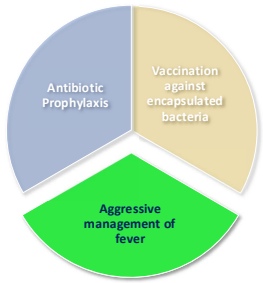
SCD Causes Multi-Organ Dysfunction



- Children with SCD often have a variety of clinical complications as well as issues with growth and development.
- while all types of SCD are closely monitored in Hematology Clinic for their SCD, **the role of primary care pediatricians is invaluable in the care children with SCD**

Piel FB et al, NEJM 2017

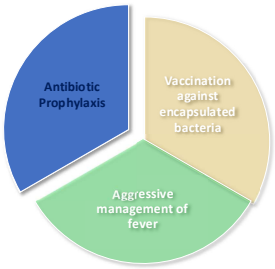
Aggressive Management of Fever



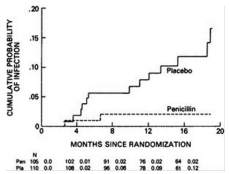
- **Any SCD patient with fever should be started on antibiotics against encapsulated bacteria and salmonella until cultures are negative**
- Certain patients can be managed as outpatient.
  - unwell child
  - a temperature above 40.0 °C
  - a white-cell count > 30 or < 5 x10e9/L
  - a platelet count below 100,000 x10e9/L
  - a history of pneumococcal sepsis
  - children with signs or symptoms associated with complications of sickle cell like severe pain, lung infiltration or dyspnea, splenic sequestration
  - a hemoglobin level < 50 g/L
  - those allergic to penicillin or cephalosporins.
  - Inability to ensure compliance or access to care

Wilimas JA et al, NEJM 1993

Antibiotic Prophylaxis with Penicillin



- All children with SCD should be started on prophylaxis antibiotics

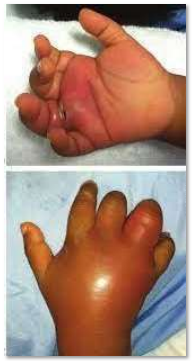


- Antibiotics can be stopped in vaccination patients who did not have a history of bacteremia at age 5 years.

Gaston MH et al. NEJM 1986. Falletta JM et al J Peds 1995

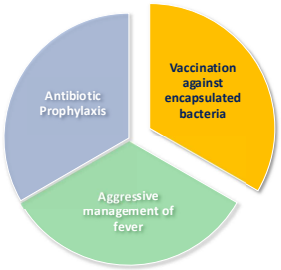
Acute Vaso-occlusive Event

- The pathophysiology of pain in SCD is complex
  - Tissue ischemia.
  - activation of inflammatory cascades,
  - ongoing damage to endothelium
  - neuroplasticity
- The most common cause of hospital admission in patients with SCD
- Affects the quality of life of children the most
- In general, patients with HbSC and HbSβ+ have less painful episodes than those with HbSS or HbSβ0, but individual patients may have severe and frequent painful episodes regardless of their genotype.



Gill FM et al Blood 1995

Vaccination against encapsulated bacteria



- SCD patients should be vaccinated as per guideline for patients with asplenia


Government of Canada | Gouvernement du Canada

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MENU

Canada.ca › Health › Healthy living › Vaccines and immunization › Canadian Immunization Guide › Part 3 - Vaccination of Specific Populations

Immunization of persons with chronic diseases: Canadian Immunization Guide

For health professionals

Management of Pain

No pain	Outpatient	Emergency	Inpatient	Post discharge
•Prevention strategies - Avoid extremes of ambient temperature - Hydration - Infection prevention •HbF induction and WBC reduction -hydroxyurea •Chronic Transfusions •Education •Spleen exam by family •Surveillance for disease related complications	•Early, outpatients' analgesics, targeted to severity of pain •Provide clear instructions •Provide support by phone •Consider non-pharmacologic interventions •Hydration	•Immediate initiation of treatment with regular intravenous or continuous opioids + NSAIDs/ acetaminophen •Rehydration	•IV opioids (regular boluses or patient/nurse-controlled analgesia) - Bolus doses for break-through. Short acting preferred - Frequent assessment and adjustment if necessary •Non-opioid alternatives •Hydration •Adjuvant support for potential analgesics' side effects (pruritus, constipation) •Close monitoring for serious side effects (hypoventilation, acute chest syndrome, seizure,), Treat as appropriate. • Incentive spirometry, encourage mobilization if possible. •Consider less common etiologies (osteomyelitis, avascular necrosis) •Provide multidisciplinary, social and family centered support •House staff education of patients' treatment requirement	•Continue analgesics. Regular short acting preferred •Clear discharge instructions •Close follow-up •Adjust medications/doses as appropriate •Provide education, review strategies for future •Social support •Encourage activities, back to school

The pain in children with SCD is often underappreciated or ignored
Need for high doses of opioids should not be disregarded

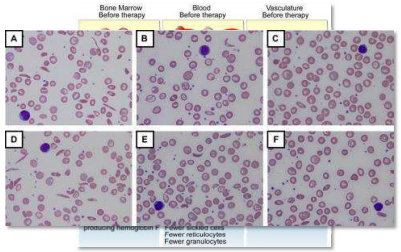
Disease Modifying and Curative Therapy

Disease modifying therapies

- Hydroxyurea
- Regular transfusion
- Novel medications

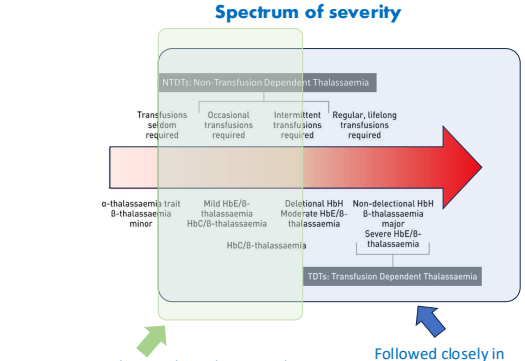
Curative therapies

- Stem Cell Transplant
- Gene therapy / editing



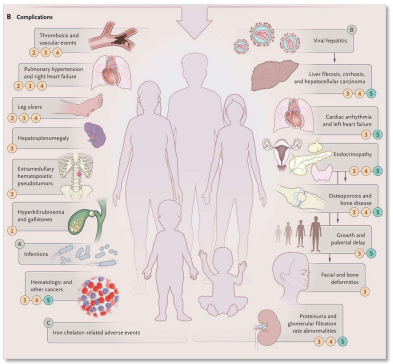
Ware R, Blood 2010

Thalassemia



May present with acute hemolysis or aplasia, and complications of chronic anemia

Followed closely in hematology clinic

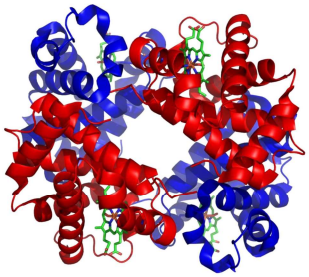


Complications of anemia and iron overload

Taher AT et al. NEJM, 2021

Hemoglobinopathies: Thalassemia

- Results from **imbalance production of alpha globin and beta globin chains** of hemoglobin tetramers.
- Carriers are healthy and have mild microcytosis/hypochromia +/- anemia
- ***Beta thalassemia*** leads to destruction of erythroblast, very early on, in the bone marrow (**ineffective erythropoiesis**).
- ***Alpha thalassemia*** cause **hemolysis** in the circulation. Quite similar to G6PD deficiency
- CBC showed microcytosis, hypochromia, and inappropriate (low) reticulocytosis (in beta-thalassemia)
- **Splenomegaly** and hepatomegaly (extramedullary hematopoiesis).
- **Hemolytic markers** are moderately increased.
- Severe forms (**thalassemia major**) are transfusion dependent.
- Those with intermediate severity (**thalassemia intermedia**) do not require regular transfusion for survival



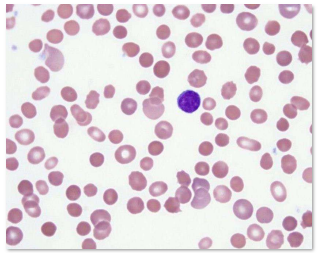
Thalassemia Intermedia

- **Non transfusion dependent thalassemia can experience:**
  - Thalassemia bone changes
  - Symptoms and complications of chronic anemia,
  - Complications of chronic hemolysis (jaundice, cholelithiasis)
  - Present with acute hemolysis or aplastic event, requiring transfusion
  - May have splenomegaly with abdominal pain and poor appetite
  - Poor growth
  - Poor school performance
  - Complications of iron overload even without transfusions (due to increase GI absorption)
  - Complications of extramedullary hematopoiesis (rare in Canada)
  - Should enjoy all foods, but do not offer extra iron.
  - Folic acid and vitamin D supplementation

Case 3

- Oakley is a 2-year-old male who is born to a mother with hereditary spherocytosis.
- Oakley is healthy. Normal growth and development.
- Mother was diagnosed at the age of 34 yr, following diagnosis of cholecystitis.
- Physical exam is normal, including no pallor or jaundice. No splenomegaly. No abdominal tenderness.
- You do a blood work to see if Oakley has also inherited the spherocytosis.

- **Hb 116** g/L (normal 105-135 g/L)
- **MCV 82** (normal 75-87 fL)
- MCH 29 (normal 24-30 pg)
- **Platelet count: 312** x 10e9/L
- **WBC: 7.5** x 10e9/L
- **Differentials: all normal**
- **Total bilirubin 13** (<17 ug/L)
- **Reticulocyte count 122** x 10e/L (normal 20-90)



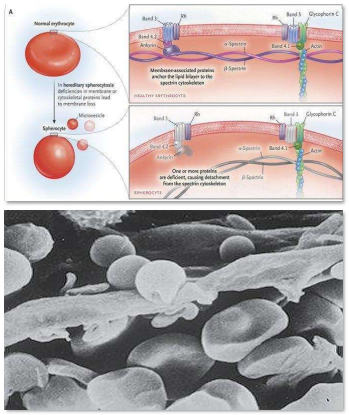
spherocytes

Hereditary Spherocytosis: Management

- **Monitoring** of Hb / bilirubin / reticulocyte count. Generally, may have more hemolysis as neonate/early infancy.
- Monitoring for **symptomatic cholelithiasis**
  - I reserve ultrasound for those with symptoms.
- **Transfusion** for severe or progressive hemolytic anemia or acute aplastic event
  - Similar to G6PD deficiency, needs hydration to prevent AKI.
- Consider **extended vaccination against encapsulated bacteria**, in preparation of possible future splenectomy
- **Splenectomy is curative** in great majority of cases.
  - reserved for patients who require multiple transfusions or had a severe episode. Consider splenectomy if cholecystectomy is needed.
  - laparoscopic or through laparotomy, Partial or complete.
  - Post splenectomy, requires antibiotics against encapsulated bacteremia (? duration). Urgent assessment for fevers
  - Post splenectomy, may have some thrombocytosis and erythrocytosis
- **Mild cases may be managed by primary care physician**

Membranopathies: Hereditary Spherocytosis

- Due to defect in the membrane proteins leading to deformity of red blood cells.
- Red cells are functionally normal but are cleared in the spleen. **Purely extravascular hemolysis**.
- Wide spectrum of hemolytic anemia.
- Blood work shows anemia (can be normocytic or microcytic), increased reticulocyte count, increased hemolytic markers, and spherocytes on smear.
- Signs and symptoms of **chronic hemolysis** (jaundice, **cholelithiasis**) with episodes of **acute hemolysis** (with physiological stress like fever, infections, surgery) or **aplastic events** (viral infections)
- Symptoms of **splenomegaly** (abdominal pain, early satiety)
- **Confirmatory diagnosis is peripheral blood smear.** Eosin-5-Maleimide (EMA) which is a fluorescent dye that binds membrane proteins and show decrease of fluorescence intensity in HS is not recommended for all cases – only equivocal cases.

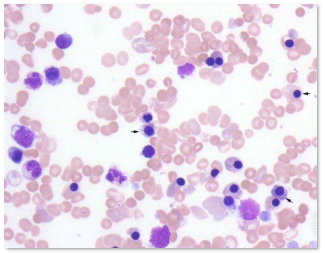


Rencic J at al. NEJM, 2017

Case 4

- A term newborn was noted to have hyperbilirubinemia, requiring phototherapy.
- Baby is born to a mother, recently arrived from Syria at 7 months gestation. She had one pregnancy in the past, but the baby passed away after birth due to sepsis.
- Pregnancy was unremarkable including normal ultrasounds. GBS positive. Received antibiotics.
- Delivery was vaginal and uncomplicated.

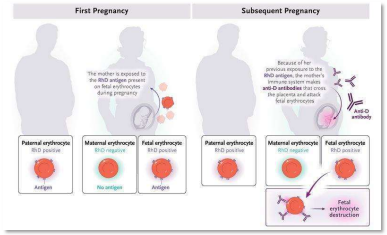
- **Hb 80** g/L (normal 105-135 g/L)
- **MCV 104** (normal 85-105 fL)
- MCH 29 (normal 24-30 pg)
- **Platelet count: 125** x 10e9/L
- **WBC: 22** x 10e9/L
- **Differentials: all normal**
- **Reticulocyte count 322** x 10e/L (normal 40-110)
- **Bilirubin 310 ug/dL** (Above phototherapy curve)
- **DAT: strongly positive**
- **Baby's BG: A+**
- **Mother's BG: A-**



Erythroblastosis

IHA: Hemolytic Disease of the Newborn

- Transplacental passage of alloimmune IgG antibodies from mother with **Ag(-)** (ABO – RhD – Other) to the fetus with Ag(+)
- Leading to variable degree of **hemolytic anemia** and **neonatal jaudince**
- Can start early *in utero* leading to **hydrops fetalis**, or mild postnatal jaundice
- Severity depends on antigen type (RhD, Rhc and K antigens, etc.), antibody dose, host factors
- Hemolysis is extravascular. **Splenomegaly** is common. Hepatomegaly may be noted. Features of hydrops in severe cases
- **DAT and blood antigen incompatibility are diagnostic**
- **Marked reticulocytosis**, unless mother received intrauterine transfusions
- Spontaneous resolution with antibody clearance (1-3 months)

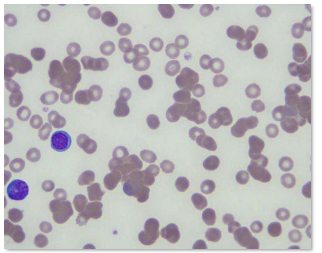


Maisonneuve E, at al. NEJM, 2024

Case 5

- Emily is a 6-yr-old, previously healthy, who is seen in your office for new-onset jaundice, pallor and fatigue. This is after a recent viral infection in the family.
- Mother noticed a dark urine since yesterday.
- On exam she is noted to have Raynaud's and acrocyanosis. There is no lymphadenopathy or hepatosplenomegaly.
- Past medical history of unremarkable.

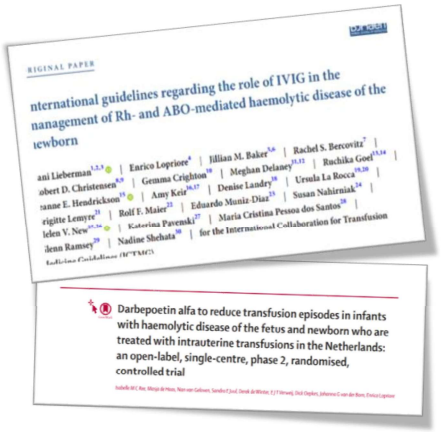
- **Hb 87** g/L (normal 105-135 g/L)
- **MCV 98** (normal 78-95 fL)
- MCH 29 (normal 24-30 pg)
- **Platelet count: 171** x 10e9/L
- **WBC: 4.1** x 10e9/L
- **Differentials: mild neutropenia**
- **Reticulocyte count 322** x 10e/L (normal 40-110)
- **Bilirubin 70 ug/dL** (<17)
- **DAT: Strong positive for C3b**



hemagglutination

HDN: Management

- Pregnancy care
  - RhoGam (preventative)
  - Intrauterine transfusion
  - IVIg
  - Nipocalimab, an anti–neonatal Fc receptor blocker, inhibits transplacental IgG transfer
- **Monitoring** of the hemolysis and anemia is the key, until stability or improvement is noted.
- Depending on the severity, neonates may require:
  - **intensive phototherapy** +/- **exchange transfusions** for management of hyperbilirubinemia
  - **Blood transfusions** for management of anemia
  - Management of hydrops fetalis complications
  - **Role of IVIG is not clear but can be considered**
  - **Darbopoetin** can be considered if robust reticulocytosis is not observed.
- **Referral to hematology NOT REQUIRED**


RIGINAL PAPER

nternational guidelines regarding the role of IVIG in the nanagement of Rh- and ABO-mediated haemolytic disease of the ewborn

Darbepoetin alfa to reduce transfusion episodes in infants with haemolytic disease of the fetus and newborn who are treated with intrauterine transfusions in the Netherlands: an open-label, single-centre, phase 2, randomised, controlled trial

Lieberman L et al. Br J Haem. 2022. Ree IMC et al, Lancet Haem 2023. Moise Jr KJ et al, NEJM 2024

Autoimmune Hemolytic Anemia

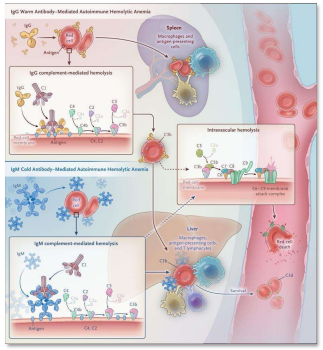
Cold Agglutinin Syndrome

- Generally, IgM-complement mediated, at low temperatures
- Antibodies mostly against "I" Ag
- RBCs cross-linked by IgM Abs which are presented to reticuloendothelial system in the liver (extravascular) or intravascularly during acute phase.
  - Splenomegaly is not common
  - hemagglutinin
- Occurs with cold exposure, mostly after cold or infections (mycoplasma, EBV).
- **Diagnosis through DAT (C3b) and cold agglutinin titer**

- ***Paroxysmal Cold Hemoglobinuria*** *is relatively similar, but Ab against "P" Ag. IgG mediated, intravascular. Diagnosis through C3b and Donath–Landsteiner test. No agglutination.*

Warm Autoimmune HA

- Mostly IgG-complement mediated.
- Antibodies are polyclonal directed against common RBC antigens
- Occur at body temperature
- Opsonized RBCs are cleared in spleen (extravascular).
  - Micro-spherocytes
  - Splenomegaly
- An underlying cause can be identified in more than 50% of cases
  - Infection (viral, bacterial)
  - Immune disorders (SLE, CVID)
  - Lymphoproliferative disorders
  - Drugs
- Can present at pancytopenia (Evans syndrome). High risk of thrombosis
- Can be brisk, life-threatening, and often difficult to treat. Low reticulocyte count can be seen in severe cases
- **Diagnosis through DAT (IgG+)**



Berentsen S and Barcellini W. NEJM, 2021

AIHA: Management

Cold Agglutinin Syndrome

- **Most patients do not require Hematology referral**
- Generally self-limiting in children. If recures, referral to hematology is indicated
- Steroid is NOT recommended
- Keep warm. Hydration. Treatment of underlying disease
- Transfusion of warmed blood (blood warmer), based on severity of symptoms
- Investigation of underlying cause in recurrent cases

Warm Autoimmune Hemolytic

- **Referral to Hematology**
- Consider urgent ER referral or very close follow up.
- Hydration to prevent AKI
- "best-matched" blood transfusion for cardiovascular compromised due to anemia. Transfuse with caution
- Steroids
- Immunosuppression/modulation
- Treatment of underlying cause
- Splenectomy
- Thromboprophylaxis

Take Home Message

CBC

Bilirubin (conjugated/unconjugated)

Reticulocyte Count

Peripheral Blood Smear

DAT (Coombs Test)

Thank you