Case 37-2019: A 20-Month-Old Boy with Severe Anemia

Katie Douglas, Ryan Pandya, Sabrina Sundin, and Angela Xu
Chief Complaint

A 20-month-old boy was admitted to the hospital for severe anemia.
**Patient Background**

- Mother and father have substance abuse issues, so patient is being raised with aunt and cousins in an urban area of New England.
- Has not traveled.
- No known allergies.
- Diet is varied: includes meat and vegetables, and about 0.6 liters of cow’s milk every day.
- Father has multiple cafe-au-lait macules, or flat, pigmented birthmarks.
  - Typically harmless, but may be associated with neurofibromatosis type 1 and McCune-Albright syndrome.
Patient Medical History

- Due to complex social situation, patient has not been seen by pediatrician as often as recommended
- No blood testing done
- Has not received all recommended vaccinations for his age
- Patient born at 36 weeks 5 days of gestation
- Diagnosed with neonatal abstinence syndrome at birth and treated with morphine
  - Neonatal abstinence syndrome: results when a fetus is exposed to addictive opiates while in the womb
I-clicker question 1

How many weeks gestation is considered to be full term?
A. 36 weeks
B. 38 weeks
C. 40 weeks
D. 42 weeks
E. 44 weeks
I-clicker question 1

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I-clicker question 1

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A. 36 weeks
B. 38 weeks
C. 40 weeks
D. 42 weeks
E. 44 weeks

Patient born at 36 weeks 5 days, so he is classified as premature.
Neonatal Abstinence Syndrome

- Results when a fetus is exposed to addictive opiates while in the womb
- Diagnosed by toxicology screens and a symptom scoring system
- Symptoms are extremely varied but include:
  - Diarrhea
  - Excessive crying
  - Fever
  - Irritability
  - Seizures
  - Sweating
  - Vomiting
History of Current Illness

5 days prior to admission to current hospital

- Aunt suspected patient was in pain after he began tugging his ear
- No fever, nasal congestion, runny nose, or cough
- Was taken to other hospital, diagnosed with acute otitis media, and oral amoxicillin (antibiotic) was prescribed
  - acute otitis media: inflammation and infection of the middle ear, or area behind the eardrum.
Acute Otitis Media

Most common bacterial causes
- Streptococcus pneumoniae
- Haemophilus influenzae (non-typeable)
- Moraxella catarrhalis
History of Current Illness

4 days prior to admission to current hospital

● Began vomiting

Next 3 days

● Multiple episodes of nonbloody, nonbilious emesis
● No bowel movements
● Appeared pale, was inactive, had reduced urine output
● Was fed an oral electrolyte solution
History of Current Illness

1 day prior to admission to current hospital

- Drank milk and ate pizza without vomiting
- Appeared even more pale and tired than before

Day of admission to current hospital

- Was taken to primary care pediatric clinic
At primary care pediatric clinic

- Pallor, tachycardia, and tachypnea were present

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Reference values</th>
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<tbody>
<tr>
<td>Hemoglobin level</td>
<td>2.9 g/dl</td>
<td>11-13 g/dl</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>9.0%</td>
<td>31-44%</td>
</tr>
<tr>
<td>White cell count</td>
<td>33,000/uL</td>
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Upon seeing these results, patient was then referred to the emergency department of a community hospital affiliated with this hospital.
I-clicker question 2

The hematocrit measures % by volume of...
A. plasma in the blood
B. white blood cells in the blood
C. serum in the blood
D. all cells in the blood
E. red blood cells in the blood
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This patient’s hematocrit is only about 25% of the expected value for his age. This is how we know he is severely anemic, which is the chief complaint of this patient.
Emergency Department at Community Hospital
Presentation Upon Admission at Emergency Department

- Short of breath, pale, occasional grunting
- Weight: 11.7 kg, or 27lbs (61st percentile for age, BMI not used under 2 yrs)
- Mucous membranes: pale
- Lungs: clear
- Heart: tachycardia and gallop rhythm
- Capillary refill time: less than 2 seconds (normal)
- Abdomen: distended, hepatosplenomegaly
- Rectal exam: firm stool in rectal vault
- Fecal occult blood test: negative
- Skin: Multiple cafe au lait macules present
I-clicker question 3

How is capillary refill time measured in a child?

A. Using a child-sized blood pressure cuff with stethoscope
B. Applying pressure with a finger and measuring the amount of time for color to return to the capillaries below the skin
C. Taking a finger prick and measuring time for blood droplet to form on the skin
D. Running blood sample from child through capillary polymer matrix and measuring speed
E. None of the above
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Capillary refill time is a normal assessment for unwell children. A physician will press an area of skin with moderate pressure for five seconds and measures time for color to return to skin. Capillary refill time of greater than 3 seconds is a warning sign.
# Vitals at Emergency Department

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<td>97.4-99.6</td>
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<td>150 bpm</td>
<td>70-120 bpm</td>
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<td>Blood Pressure</td>
<td>84/59 bpm</td>
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<td>44 breaths per minute</td>
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<td>Oxygen Saturation</td>
<td>100%</td>
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Intervention at Emergency Department

- Based on examination and vitals, there is obvious difficulty breathing
- Supplemental oxygen given via nasal cannula at 3L/min
- Peripheral IV catheter inserted
Labs at Emergency Department

- White blood cells
- Platelets
- Hemoglobin
- Hematocrit
- Red blood cells
Primary Care Clinic v. Emergency Department Values

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Imaging at Emergency Department - Chest X Rays

- Hyperinflation
- Cardiomegaly
- Enlargement of the central pulmonary vessels
- No pleural effusion
I-clicker question 4

Which of the following is not a possible cause of cardiomegaly?
A. COPD
B. Vitamin B1 toxicity
C. Hyperthyroidism
D. Radiation
E. Viral infection
I-clicker question 4

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B is incorrect. A vitamin B1 deficiency, or beriberi, is a cause of cardiomegaly because it leads to a high output state.
Imaging at Emergency Department - EKG

- Sinus tachycardia (155 bpm)
- Left ventricular hypertrophy, nonspecific T-wave abnormalities
- QRS axis of depolarization was 54 degrees (normal: 30-180 degrees)
- QTc interval was 404 ms (normal <440 ms)
Pediatric Intensive Care Unit at Massachusetts General Hospital
Presentation upon Admission at Mass Gen PICU

- Whimpering, appeared ill and pale
- Hands and feet were cool
- Heart: tachycardia, gallop rhythm, systolic murmur (grade 4/6), hyperdynamic precordium
- Capillary refill time: less than 2 seconds (normal)
- Skin: multiple café au lait macules, inguinal freckling and a hemangioma on the right buttock (1 cm in diameter)
Presentation at Mass Gen PICU continued

- Signs of labored breathing: tachypnea, nasal flaring, abdominal breathing, mild subcostal retractions
- Lungs: soft crackles occasionally
- Abdomen: distended, splenohepatomegaly
  - Spleen extended 6 cm below the left costal margin
  - Liver extended 5 cm below the right costal margin
# Vitals at Mass Gen PICU vs. Emergency Department

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Imaging at Mass Gen PICU - Chest X-Ray

- Hyperinflation
- Severe cardiomegaly
- Enlarged central pulmonary vessels
- Mild interstitial pulmonary edema
Imaging at Mass Gen PICU - Echocardiogram

- Patent foramen ovale and left-to-right blood flow
- B: left ventricle dilated (preserved systolic function); mildly enlarged atria
- C: mitral regurgitation
- D, parasternal long-axis view: confirms findings of B/C
- E, parasternal short-axis view: left ventricular dilation and trivial pericardial effusion (arrow)
The foramen ovale is a small hole located between the two atria present at birth. At what age should the foramen ovale close?

A. 2 weeks  
B. 1 month  
C. 2-3 months  
D. 6 months  
E. 18 months
I-clicker question 5

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D. 6 months  
E. 18 months

It is typically considered safe if the foramen ovale closes within 6 months of birth. However, approximately 25% of people have a patent foramen ovale after this time.
Differential Diagnosis
The Clinical Symptoms

● Signs of biventricular heart failure:
  ○ Gastrointestinal symptoms
  ○ Tachycardia (abnormally rapid heart rate)
  ○ Tachypnea (abnormally rapid breathing)
  ○ Crackles in breathing
  ○ Hepatosplenomegaly
  ○ Cool hands and feet
  ○ Gallop rhythm
  ○ Grade 4/6 systolic murmur
Given what we already know about the patient’s condition and the knowledge that a grade 4/6 systolic murmur is labeled as loud with thrill, what can be inferred about a grade 6/6 systolic murmur?

A. The murmur sound is faint
B. The murmur could be heard without the aid of a stethoscope
C. The murmur could be heard when the stethoscope is placed half an inch away from the chest wall
D. There is no murmur
E. This grade of murmur indicates previous myocardial infarction
I-clicker question 6

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Systolic Murmurs

- Murmur: a series of vibrations originating from the heart or major vessels that are audible when a stethoscope is placed against the chest wall.

- Systolic murmur: begins after or during the first “lub” sound and ends before or during the second “dub” sound.
<table>
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<th>Basis</th>
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<tr>
<td>Grade 1</td>
<td>Faint murmur heard on careful auscultation</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Easily audible not loud</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Easily audible loud murmur but no thrill</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Murmur with thrill</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Murmur audible stethoscope audible to chest</td>
</tr>
<tr>
<td>Grade 6</td>
<td>Murmur audible half an inch from the chest. Associated with thrill.</td>
</tr>
</tbody>
</table>

GRADE 3/6 or more intensity of systolic murmur is clinically significant with few exceptions but diastolic murmur of any degree of intensity is organic in nature.
The Clinical Symptoms

- Chest radiograph: cardiomegaly
- Lab tests: low blood serum bicarbonate levels suggestive of acidosis
- Echocardiogram: left ventricular dilation with ejaculation fraction
  - Measure of the amount of blood pumped out of the ventricle with each contraction; the heart will pump out less blood than normal
- No evidence of congenital heart disease
- Increased cardiac output due to low blood oxygen levels from anemia
Initial Action

Intermediate intervention is necessary to prevent cardiac shock

- Fluid expansion
- Transfusion
- Supplemental Oxygen
Fluid Expansion

● Purpose: enhance cardiac output to relieve cardiac strain
  ○ Increase the amount of blood flow into the ventricles before contraction
  ○ Increase ventricular stroke volume

● Downfalls:
  ○ May lead to worsened cardiac function
  ○ Increased hemodilution of red blood cells
  ○ Decrease oxygen delivery

● Fluid Expansion as Supportive Therapy Trial: a higher mortality rate among anemic, compensated shock children subjected to fluid bolus vs no bolus

● Final conclusion: give with EXTREME caution
Transfusion

- Underlying symptom: low blood oxygen content
  - Impaired oxygen delivery
  - Cardiac output increase to compensate for the low oxygen
- Transfusion should be considered as one of the earliest treatment options
- Must first identify the type of anemia present (rule out hemolysis)
- Immediate transfusion is recommended
I-clicker question 7

Which of the following is NOT a risk of receiving a blood transfusion?

A. Immune attack against the newley transfused cells
B. There are no risks
C. Contracting viruses or infections such as HIV
D. Shortness of breath due to a large increase in fluid volume leading to overload
E. A, C, and D are risks
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Supplemental Oxygen

- Additional oxygen will increase the oxygen saturation leading to
  - More oxygen bound hemoglobin
  - An increase in oxygen partial pressure
- Healthy child: 15-20ml/deciliter of arterial oxygen
- Patient: 20% of normal oxygen levels
- 3 liters of oxygen via a nasal cannula will increase the levels by only 15%
- High-flow oxygen via a nonrebreather face mask can increase the levels by 65%
  - Patient will still only have a third of normal blood-oxygen levels
- Studies: increasing oxygen partial pressure can decrease heart rate
I-clicker question 8

What do you think is the cause of the patient’s anemia (lack enough healthy red blood cells)?

A. Not enough red-blood cells are being produced
B. Red-blood cells are being destroyed
C. Red-blood cells are being lost
D. All of the above
E. None of the above
Severe Anemia

Need to determine whether red blood cells are being lost, being destroyed, not being produced, or a mixture of all three.
Blood Loss

In children, severe anemia typically results from...

- Trauma - most common type is birth trauma (damage of tissues and organs of newly delivered child)
- Bleeding from the gastrointestinal tract or menses
- Bleeding disorders - Hemophilia, Von Willebrand Disease
I-clicker question 9

What could be a symptom of GI bleeding?

A. Rapid weight gain
B. Blood in the stool
C. Trouble breathing
D. Frequent urination
E. None of the above
I-clicker question 9

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I-clicker question 10

What is related to Von Willebrand disease?

A. Missing/defective clotting factor  
B. Muscle fatigue  
C. Cold sores  
D. Seizures  
E. Excessive gluconeogenesis
I-clicker question 10

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Blood Loss continued

- No history of blood in the stool. A guaiac stool test was still performed and the results came back negative
- Child’s family has no history of bleeding disorders, could be mutation resulting in a coagulation disorder
- No known history of trauma
Red-Cell Destruction

Can be caused by

- Antibody-mediated & acquired during infection, or caused by exposure to a drug/toxin
- Red-cell membranopathies, such as spherocytosis & elliptocytosis, can lead to rapid red-cell destruction
- Hemoglobinopathies, such as sickle cell anemia & thalassemia, may also lead to shortened red-cell life span
- Deficiency in Glucose-6-phosphate dehydrogenase (G6PD), caused by defect on X chromosome, results in accumulation of oxidative species & hemolysis
Red Cell Destruction continued

- Male patient had a recent ear infection and exposure to amoxicillin, explains hemolysis, elevated LDH, & splenomegaly.
  - Absence of icterus & elevated bilirubin make hemolysis unlikely
- Patient has no exposure to food/medication that would suggest hemolysis from G6PD deficiency unlikely (fava beans or sulfa drugs)
- Recommended a Coombs’ test, peripheral-blood smear, blood typing, and screening to further assess if hemolysis is contributing to patient’s condition
Decreased Red-Cell Production

- Parvovirus B19 infection - causes fifth disease (slapped cheek rash)
- Conditions that result in ineffective erythropoiesis - iron deficiency, vitamin B12 deficiency, folate deficiency, and toxic effects from lead
Decreased Red-Cell Production continued

- Patient does not have microcytosis, is consistent with iron deficiency
- Diamond-Blackfan anemia - patients typically have normal white-cell & platelet count and characteristic facial features
- Hemophagocytic lymphohistiocytosis - expect elevated liver function and cytopenia
- Leukemia can cause pancytopenia and also elevated white-cell count
Decreased Red-Cell Production continued

- Appears that anemia due to decreased red-cell production is the most likely cause of the illness
  - Elevated white-cell count, presence of thrombocytosis, elevated prothrombin time, & elevated uric acid and LDH levels suggest high cell turnover, pointing to cancer
- No evidence of bleeding or hemolysis
- Lab evaluation not diagnostic for iron deficiency

Severity of presentation suggest a more serious disorder
Neurofibromatosis Type I & Severe Anemia due to Leukemia

- Patient has multiple cafe-au-lait macules on his body, similar to father
  - Can be caused by McCune-Albright syndrome, or more commonly by Neurofibromatosis type I (due to young age)
- Neurofibromatosis type I is associated with high risk of leukemia

Final Diagnosis
Treatment

Only treatment is allogeneic stem cell transplantation (bone marrow)

Without transplantation, median survival is less than 2 years. With transplantation, patients who survive and are disease free is estimated to be around 50%

No established role for intensive chemotherapy before transplantation is performed
Resolution

Patient received a blood transfusion and splenectomy.

Patient underwent transplantation approximately 2.5 months after initial presentation.

Although the patient has had a complicated post-transplantation course, he has had full bone marrow engraftment and no evidence of recurrent disease.