Blood Day for Primary Care

Not small adults: Diagnosis of anemia in children

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Disclosures

1. No disclosures relevant to this presentation
Objectives

At the completion of this talk you will be aware that:

1. The definition of anemia is age-dependent
2. The causes of anemia differ in frequency across the age continuum
3. Congenital causes of anemia should be considered when investigating children
Referral to Pediatric Hematology

“Dear Pediatric Hematologist:

Please see this 20 month old boy for investigation of persistent anemia: HGB 107 g/L, MCV 72 fL.”

Does this child have anemia?

a) YES
b) NO
c) NOT SURE
<table>
<thead>
<tr>
<th>Age</th>
<th>HGB g/L Mean</th>
<th>HGB g/L -2SD</th>
<th>MCV fL Mean</th>
<th>MCV fL -2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT Newborn</td>
<td>165</td>
<td>135</td>
<td>108</td>
<td>98</td>
</tr>
<tr>
<td>1-3 days</td>
<td>185</td>
<td>145</td>
<td>108</td>
<td>95</td>
</tr>
<tr>
<td>2 weeks</td>
<td>166</td>
<td>134</td>
<td>105</td>
<td>88</td>
</tr>
<tr>
<td>1 month</td>
<td>139</td>
<td>107</td>
<td>101</td>
<td>91</td>
</tr>
<tr>
<td>6 months</td>
<td>126</td>
<td>111</td>
<td>76</td>
<td>68</td>
</tr>
<tr>
<td>6 mo-2 yrs</td>
<td>120</td>
<td>105</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>2-6 years</td>
<td>125</td>
<td>115</td>
<td>81</td>
<td>75</td>
</tr>
<tr>
<td>6-12 years</td>
<td>135</td>
<td>115</td>
<td>86</td>
<td>77</td>
</tr>
<tr>
<td>12-18 years (M)</td>
<td>145</td>
<td>130</td>
<td>88</td>
<td>78</td>
</tr>
<tr>
<td>12-18 years (F)</td>
<td>140</td>
<td>120</td>
<td>90</td>
<td>78</td>
</tr>
<tr>
<td>Adults (M)</td>
<td>155</td>
<td>135</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Adults (F)</td>
<td>140</td>
<td>120</td>
<td>90</td>
<td>80</td>
</tr>
</tbody>
</table>
Tip #1: Age-dependent reference ranges

- Normal ranges for hemoglobin, hematocrit, and RBC indices (other CBC parameter, too) are age-dependent from infancy to late teen years.

- Does your laboratory provide you with age-dependent reference ranges on the CBC report?
Is it just anemia?

- Are other cell lines normal, or are you actually dealing with more than one cytopenia?
  - Anemia and thrombocytopenia
  - Anemia and neutropenia
  - Pancytopenia

Tip #2: Be alert to multiple cytopenias

- The differential diagnosis of multiple cytopenias is not the same as for isolated anemia: investigations may be different, particularly if the child is acutely ill.
Tip #3: Know what is common in children

- CBC, RBC indices and reticulocyte count are the most useful initial tests.
- The frequency of specific diagnoses differ from adults and by age, gender and ethnic background.
- Frequency:
  
  microcytic anemias >> normocytic anemias >> macrocytic anemias
Dear Pediatric Hematologist:

Please see this 13 year old girl with chronic Fe deficiency anemia. Hb 108-110, indices suggest iron deficiency.

Irregular periods. Has been on iron supplementation for three months, but not compliant. May have an eating disorder.

Mother died of colon cancer at age 29 years.

Unable to obtain stool O.B. on daughter.

Referral to Pediatric Hematology
# Referral to Pediatric Hematology

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Ref. Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC x 10⁹/L</strong></td>
<td>7.34</td>
<td>5.0-15.0</td>
</tr>
<tr>
<td><strong>HGB (g/L)</strong></td>
<td>109</td>
<td>120-160</td>
</tr>
<tr>
<td><strong>RBC x 10¹²/L</strong></td>
<td>5.34</td>
<td>4.1-5.3</td>
</tr>
<tr>
<td><strong>MCV (fL)</strong></td>
<td>65</td>
<td>80-98</td>
</tr>
<tr>
<td><strong>MCH (pg)</strong></td>
<td>20.4</td>
<td>25-35</td>
</tr>
<tr>
<td><strong>RDW (%)</strong></td>
<td>17.3</td>
<td>11.4-14.4</td>
</tr>
<tr>
<td><strong>Retic. x 10⁹/L</strong></td>
<td>59</td>
<td>20-75</td>
</tr>
<tr>
<td><strong>Platelets x 10⁹/L</strong></td>
<td>240</td>
<td>150-500</td>
</tr>
<tr>
<td><strong>Blood film</strong></td>
<td></td>
<td>microcytosis, anisocytosis</td>
</tr>
<tr>
<td><strong>Ferritin (ug/L)</strong></td>
<td>45</td>
<td>20-140</td>
</tr>
</tbody>
</table>
What is the most likely cause of anemia in this girl?

1. Iron deficiency anemia
2. Anemia of chronic disease
3. Thalassemia trait
4. Folate deficiency
Referral to Pediatric Hematology

Hgb electrophoresis
Hgb A 90.2% (96-98%)
Hgb F 7.2% (<0.5%)
Hgb A_2 2.6% (2.1-3.2%)

Molecular studies
Heterozygous for a partial deletion of the beta-globin gene cluster, removing the delta and beta genes.
Dx: Delta-beta thalassemia

http://sickle.bwh.harvard.edu/thal_inheritance.html
Tip #4: Microcytic anemia is not always iron deficiency

- Microcytic anemias are common
- Iron deficiency may be the most common diagnosis but not the only diagnosis
- RBC count, RBC indices, Reticulocyte count and blood film provided additional information.
- A limited trial of oral iron (1 month) is reasonable if age, history and laboratory screening support iron deficiency as the most likely diagnosis. If there is an inadequate response, broaden the differential diagnosis.
Work-up of MICROCYTIC ANEMIA in CHILDREN

1. Low hemoglobin
   - Age specific reference ranges
   - Is it only anemia?
     - CBC
       - RBC indices
       - Retic. count
         - More than one cell line affected
           - Refer to Hematology
         - Is this pancytopenia?
           - Microcytic
             - Are history and indices consistent with iron deficiency?
               - Yes. Trial of oral iron.
                 - Response. Continue iron supplementation for a total of three months.
               - No response
             - Normocytic
             - Macrocytic
               - Isolated anemia MCV?
                 - No.
                   - Iron studies, Hgb electrophoresis, investigate for chronic disease
                 - No cause found.
                   - Refer to Hematology
                   - Anemia of chronic/inflammatory disease
                   - Hemoglobinopathy: thalassemia
                   - Iron refractory iron deficiency
Tip #5: Microcytic anemia: is it thalassemia?

• The prevalence of alpha and beta thalassemia syndromes is increasing, as demographics shift in Manitoba.

• Hemoglobin electrophoresis is most useful when patient is not also iron deficient.

• Why confirm the diagnosis?
  • Avoid prolonged iron therapy
  • Genetic counseling

http://sickle.bwh.harvard.edu/thal_inheritance.html
“Dear Pediatric Hematologist:

Please see this 3 year old girl with three documented episodes of sudden worsening of anemia and jaundice, associated with progressive splenomegaly. Anemia has responded to courses of prednisone, but spleen continues to enlarge.

She had prolonged neonatal jaundice, treated with phototherapy. She has been on iron supplementation for 3 years.

On examination, is pale and jaundiced. Her spleen is palpable 6 cm below left costal margin.”
Referral to Pediatric Hematology

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<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Ref. Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC x 10⁹/L</td>
<td>9.5</td>
<td>5.0-15.0</td>
</tr>
<tr>
<td>HGB (g/L)</td>
<td>77</td>
<td>115-135</td>
</tr>
<tr>
<td>RBC x 10¹²/L</td>
<td>2.8</td>
<td>3.9-5.3</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>78</td>
<td>75-87</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>30.3</td>
<td>11.4-14.4</td>
</tr>
<tr>
<td>Retic. x 10⁹/L</td>
<td>307</td>
<td>20-75</td>
</tr>
<tr>
<td>Platelets x 10⁹/L</td>
<td>330</td>
<td>150-500</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>643</td>
<td>190-400</td>
</tr>
<tr>
<td>Bilirubin (mmol/L)</td>
<td>185</td>
<td>3-18</td>
</tr>
<tr>
<td>Ferritin (ug/L)</td>
<td>247</td>
<td>21-310</td>
</tr>
<tr>
<td>DAT</td>
<td>negative</td>
<td></td>
</tr>
</tbody>
</table>
What is the most likely cause of this girl’s anemia?

1. Autoimmune hemolytic anemia
2. Hereditary spherocytosis
3. Anemia of chronic inflammation
4. Drug-induced hemolysis
Referral to Pediatric Hematology

- RBC osmotic fragility: increased
  - Dx: Hereditary spherocytosis
  - Sensitivity 85%

- EMA-binding test: Flow cytometric method using a fluorescent probe, eosin-5’-maleimide, which binds to protein band 3 complex.
  - Sensitivity 95%
Hereditary Spherocytosis
Tip #6: Consider congenital hemolytic anemia

- In addition to the CBC, reticulocyte count, bilirubin and review of the blood smear are the most useful tests.

- Hemolytic anemias in children are often congenital/hereditary. Clues to a congenital hemolytic anemia:
  - Direct antiglobulin test: negative
  - Prolonged or severe neonatal jaundice
  - Exacerbation by inter-current viral illnesses
  - Progressive splenomegaly

- Transient bone marrow hypoplasia may cause dramatic fall in Hgb and reticulocyte count
Work-up of HEMOLYTIC ANEMIAS in CHILDREN

1. Increased reticulocytes, increased unconjugated bilirubin
   - Hemolytic anemia?
     - Direct antiglobulin test
       - Positive: immune hemolysis
         - Neonate: Rh/ABO incompatibility
           - Primary or secondary
         - Autoimmune hemolytic anemia
       - Spherocytes, elliptocytes
         - HS, HE, AIHA
       - Target/sickle cells
         - Hb variants
       - RBC fragmentation
         - Sepsis, HPP
       - Normal
         - G6PD deficiency
         - Other Enzymopathies

   - Negative
     - Blood smear: RBC morphology

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.
Neonates are a special case

Work-up of NEONATAL ANEMIAS

- Hemolysis
  - congenital hemolytic anemias
  - allo-immune hemolytic anemias
  - secondary causes of hemolysis
- Decreased RBC production
  - congenital marrow hypoplasia
  - secondary causes of bone marrow failure
- Blood loss
  - prenatal events
  - extrauterine
- Anemia

- HS, HE, G6PD def, hemoglobinopathies
- ABO and Rh incompatibility
- Sepsis, drugs
- DBA and SDA
- Congenital or acquired infection; asphyxia
- Twin-twin transfusion, fetal maternal transfusion, cord rupture
- ICH, gastrointestinal hemorrhage, congenital or acquired bleeding disorders

Pathways are subject to clinical judgment and actual practice patterns may not always follow the proposed steps in this pathway.

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When to consider referral to Pediatric Hematology

- Cytopenias affecting more than one cell line
- RBC parameters suggesting bone marrow hypofunction/failure: decreased reticulocyte count, normocytic/macrocytic indices
- Persistent anemia severe enough consider transfusion
- Iron refractory iron deficiency anemia
- When you are concerned, please call us. We can often make some initial recommendations by phone
Key points:

1. Use age-dependent normal ranges when considering CBC results in a child.

2. Microcytic anemias are common in childhood. Consider alternative etiologies to iron deficiency, including hemoglobinopathies.

A useful reference

Practical Algorithms in Pediatric Hematology/Oncology (Sills, Ed.):


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