Use of Reticulocyte Hemoglobin in Anemia Assessment

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Disclosure

- I am receiving an honorarium from Sysmex for today’s presentation.
Presentation Objectives

• Identify strategies to better assist clinicians in understanding wellness, prevention and chronic disease management by using RET-He

• Discuss the RET-He threshold for defining iron availability

• Demonstrate the value of RET-He in monitoring iron deficiency (ID), iron deficiency anemia (IDA), and Erythropoietin Stimulating (ESA) therapy

• Understand the impact of successful laboratory utilization control on financial performance

Anemia Background

• Is a sign of a wide range of underlying disorders

• Anemia is often under recognized and undertreated

• Associated with morbidity and increased risk of mortality

• Contributes to over utilization of blood transfusions
Anemia Prevalence

- 2 billion people globally (1/3 of population)
- 3.4 million people in United States
- Types of Anemia:
  - Iron deficiency (IDA)
  - Anemia of Chronic Disease (ACD)
  - Vitamin Deficiency Anemia
  - Aplastic Anemia
  - Hemolytic Anemia
  - Sickle Cell Anemia … and many others

National Anemia Action Council, 2006

Leading Causes of Anemia

- Abnormal iron metabolism
- Cancer
- Cancer treatment
- Deficiency in certain vitamins or minerals
- Blood loss
- Major organ problems (severe heart, lung, kidney, or liver disease)
Patients at Highest Risk of Anemia

• Women
• Infants and Young Children
• Critically Ill
• Surgical Patients
• Chronic Kidney Disease Patients
• Congestive Heart Failure Patients
• Cancer Patients

Iron Distribution in the Body

• Iron is an essential trace element
• Iron ions circulate bound to plasma transferrin
• Iron is stored in hepatocytes and reticulo-endothelial macrophages
• Use of blood tests as a proxy for stored iron content
Hepcidin – Regulating Iron Mobilization

• Secreted by the liver in response to iron loading and inflammation
• Regulates iron recycling through the macrophages
• Decreases basolateral iron transfer and thus dietary iron absorption
• Decreased in anemia and hypoxemia
• Increased in inflammation, iron indigestion, with transfusion, with parenteral iron

Iron Deficiency

• Iron deficiency
  − TSAT < 20% and Ferritin < 100 ng/mL

• Functional Iron Deficiency (FID)
  − Iron stores are present but cannot be mobilized rapidly enough to maintain maximal erythropoietin-driven erythropoiesis
  − Described with r-HuEPO therapy in subjects with normal iron stores
Laboratory Anemia Work-up
Diagnosis of Iron Deficiency

• Biochemical parameters
  – Serum iron
  – Ferritin
  – Transferrin
  – Transferrin saturation (TSAT)
  – Hepcidin

Laboratory Anemia Work-up
Hematology Parameters

• Based on entire RBC population
  – Hgb
  – HCT
  – MCH
  – MCV
  – RDW

• Based on reticulocyte population
  – Reticulocyte Hemoglobin (RET-He/CHr)
What is Reticulocyte Hemoglobin? (RET–He/CHr)

- Measured at cellular level
- Early detection of iron deficiency
- Monitors acute changes in hemoglobin incorporation into the erythron
- More sensitive than indirect chemical measurements
- Detects non-responders to ESA (Functional Iron Deficiency)

Reference Range for RET-He

- RET-He > 28 pg/cell indicates that sufficient iron is available for incorporation into the red cell
- RET-He < 28 pg/cell indicates that not enough iron is available to produce healthy RBC’s

Reference Range

Adults: 28.2 – 36.6 pg/cell
Clinical Utility of RET-He In High Risk Populations

Iron Deficiency in Infants and Toddlers

• 2.1 – 4.1% of infants and toddlers in the US have iron deficiency anemia

• 10% have iron deficiency without anemia
Iron Deficiency in Infants and Toddlers

- Adverse consequences of iron deficiency in pediatrics:
  - Increased lead absorption
  - Impaired immunity
  - Anemia
  - Impaired neuro-cognitive development

Analytical Performance for ID/IDA

<table>
<thead>
<tr>
<th>For Iron Deficiency</th>
<th>CHr Cutoff of 26pg</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>70%</td>
<td>78%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>For Iron Deficiency Anemia</th>
<th>CHr Cutoff of 26pg</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>83%</td>
<td>75%</td>
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Screening Infants and Toddlers for ID Using Hemoglobin

AAP and CDC recommendations:

• Hb traditionally used - available, inexpensive, familiar
• But, relying on Hgb alone is problematic
  − In NHANES III, Hg < 11 g/dL had a sensitivity of 30% for detecting ID (as defined by biochemical parameters)
  − Of 321 infants undergoing iron deficiency screening, anemia (Hct <33%) failed to detect any of the 51 (16%) iron-deficient infants (as defined by ferritin <10 µg/L)
• Children with CHr > 29 pg have virtually zero probability of being iron deficient.

White, K. Pediatrics 2005;115:315
Kazal, L. J., Family Practice 2006;42:237

Recommendations for Wellness Screening

• “For infants with Hgb <11.0 mg/dL or with significant risk of ID or IDA
  Serum Ferritin and CRP levels or CHr levels should also be measured to increase the sensitivity and specificity of the diagnosis.”
• “A low CHr concentration has been shown to be the strongest predictor of ID in children.”

Baker, R., Greer, F. and The Committee on Nutrition. Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in and Infants and Young Children (0 - 3 Years of Age). Pediatrics 2010;126;1040-1050.
Anemia (i.e. hgb levels < 11–12 g/dL) is an universal feature of patients with end-stage renal disease (ESRD) on dialysis.

Largely the result of insufficient production of Erythropoietin by non-functioning kidney.

Especially true in hemodialysis, due to the coupling of accelerated erythropoiesis (rhu-EPO) and dialysis-related blood losses, including frequent laboratory testing.

IDA in ESRD Patients

Finding Balance in Anemia Management Decisions: Iron or EPO?

Challenges

• How to balance dosage and timing of iron therapy?
• What is the best assessment to balance ESA and Iron therapy?
• What is the best assessment of iron stores?
• Shouldn’t we measure changes on the cellular level?
Reticulocyte Hemoglobin in the Diagnosis of IDA

**Cutoff**
- 27.2 pg

**Sensitivity**
- 93.3%

**Specificity**
- 82.3%

### Iron Deficiency Anemia Diagnostic Criteria:

<table>
<thead>
<tr>
<th>Test</th>
<th>Criterion</th>
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<tbody>
<tr>
<td>Fe</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Tsat</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Ferritin</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Hgb</td>
<td>&lt;11</td>
</tr>
</tbody>
</table>

* For patients on maintenance hemodialysis

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### Outcome Study in Hemodialysis Patients

139 hemodialysis patients from 3 dialysis centers

Patients were randomized into 2 groups:

**Group 1**: Iron management based on serum ferritin (SF) and TSAT.
- Patients were dosed with IV iron if SF<100 ng/ml or TSAT <20%

**Group 2**: Iron management based on CHr, with dosing based on a CHr < 29 pg/cell.

**Study Outcome**

**Iron utilization:**
- 83.6% of Patients in Group 1 received treatment with I.V. Iron
- 43.2% of Patients in Group 2 received treatment with I.V. Iron

Variations in Tests of Anemia and Iron Status

<table>
<thead>
<tr>
<th>Source and Magnitude of Variation</th>
<th>RET-He</th>
<th>TSAT</th>
<th>Ferritin</th>
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<tbody>
<tr>
<td>Total</td>
<td>7.2%</td>
<td>40.9%</td>
<td>22.0%</td>
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Hgb, Hct, and RET-He, but not TSAT or Ferritin are useful analytes to guide dose adjustment for ESA or IV iron.


KDOQI Guidelines for Evaluation of Anemia

**Initial Anemia Evaluation**
- **Cellular Assessment**
  - Hgb < 12 g/dL
  - RBC indices
  - Absolute Retic
  - WBC & Diff
  - Platelet
- **Iron Assessment**
  - Serum Ferritin
  - Serum TSAT or Chr

**Iron Assessment Indices**
- **HD-CKD Target**
  - Ferritin > 200 ng/ml and
  - Tsat > 20% or Chr > 29 pg/cell

Anemia in Patients with Cancer

• Complex etiology
  − Chronic disease/inflammation
  − Chemotherapy
  − Bone marrow failure
  − Bleeding
  − Nutritional deficiencies
  − Iron deficiency

• Conventional markers such as Serum Iron, Transferrin Saturation and Ferritin are disturbed during an acute phase response and in the presence of severe diseases

Clinical interpretation of results is challenging

Iron Deficiency Anemia in Patients with Cancer

• Important Diagnosis
  − RBC transfusion
  − Use of erythropoiesis-stimulating agents
  − Available treatment
    Oral or IV iron

• Recommendation for Oncology Patients
  − Investigate patients with Hgb < 11g/dl
    (Steinmetz HT, Therap Adv in Hematol 2012)
Clinical Effectiveness of RET-He in the Cancer Patients

- This study examined the use of the RET-He to rule out ID, as defined by serum iron studies
- Anemia was defined by:
  - Transferrin Saturation <20%
  - Serum iron <40 µg/dL
  - Ferritin <100 ng/mL
- In an unselected cancer patient population with test requests for CBC and serum iron studies


Diagnostic Performance of RET-He in the Evaluation of Anemia in Cancer Patients

Patient Screening using RET-He
n=209

- RET-He <32 pg and Hgb <11 g/dl
n=43
NPV- 98%

- Rapid rule out of iron deficiency anemia
- Reduce unnecessary testing
- Cost Savings for Laboratory and Health Care System

Iron Deficiency is Common in Patients with Congestive Heart Failure (CHF)

- 37% of 546 CHF patients were iron deficient
- Iron deficiency (ID) was a strong, independent predictor of unfavorable outcome
- 3-year survival rate was 66.7% in patients without ID vs. 53.6% in patients with ID

Figure 2. Kaplan-Meier curves reflecting 3-year event-free survival rates in patients with systolic chronic heart failure with vs. without iron deficiency.


Screening and Prevention of Iron Deficiency and Anemia
Prevention

- Resolving anemia before surgery or initiating therapy
  - Improves outcomes
  - Maximizes patient reserves
  - Promotes blood product management
  - Makes the patient feel better

Anemia Management in Pre-surgical Patients

- Increased morbidity after surgery
  - Increased rates of post-operative complications
  - Increased length of stay
- Anemia screening 4 – 6 weeks prior to surgery
- Identify presence of anemia
- Determine etiology/type of anemia
- Therapy to correct anemia before surgery
  - I.V. iron (less expensive than ESA, effective even in inflammation, fewer adverse events)
Prevention - Early Identification for Appropriate Intervention

- The course of 2 clinical parameters during preoperative epoetin treatment
- There is a clear difference between responders and non-responders
- The haemoglobinisation level of reticulocytes is an early detector of FID due to epoetin injections

Reticulocyte Hemoglobin (RET–He/CHr) Summary

- Measured at cellular level
- Monitor acute changes in hemoglobin incorporation into the red cell
  - Real-time estimate of iron availability in bone marrow
- Shown to be a more sensitive tool for early detection of iron deficiency
  - Changes rapidly, more sensitive screen than Hgb
  - Less variation than acute phase reactants
- Provides additional information for managing iron requirements for rHuEPO therapy
- RET-He results should be interpreted in conjunction with other tests and clinical picture of the patient
THANK YOU

Questions?

Acknowledgements: Rebecca Rossi