Clinical Utility of Immature Cell Indices
Beyond the Routine CBC
DISCLOSURE

I am a Clinical Specialist employed by Sysmex America, Inc.
OBJECTIVES

- Describe two novel hematology parameters and their derivation
- Explore evidence that demonstrates their clinical utility
- Discuss how this new information can be applied to patient care
DISCUSSION POINTS

- The significance of hematological immature cell indices
- Clinical applications of the parameters for wellness, prevention, and chronic disease management
- Cost of care implications for parameter utilization
DISCUSSION POINTS

- Importance of hematological immature cell indices

- Investigate the evidence for clinical utility:
  - Reticulocyte indices in management of ID and IDA
  - IPF in understanding causes of thrombocytopenia
  - IG as part of expanded WBC differential

- Understand how new information can be applied to patient care
HEALTHCARE REFORM
PAYMENT MODEL EXPERIMENTS

Quality-based Payment Models

- **Care Processes**
  - Bonus pay for higher compliance with SCIP protocols and other care processes.

- **Error Penalties**
  - Reduced payment for hospitals with high rates of SSI’s, blood clots, retained objects, etc.

- **Readmission Penalties**
  - Reduced payment for hospitals with high 30-day readmission rates, by diagnosis.

- **Patient Satisfaction**
  - Hospital score on HCAHPS survey; a component of many quality-based pay programs.

- **Shared Savings**
  - Providers share savings from lower complications and readmissions, greater efficiency.

- **Clinical Outcomes**
  - Payment linked to patient outcomes, achievement of quality and utilization goals.

Source: Surgical Directions
HEMATOPOIESIS: FORMATION OF BLOOD CELLS IN THE BONE MARROW

Immature cell count data can be used with mature cell counts to assess pathophysiological mechanisms

- Leukopoiesis (IG) White Blood Cells
- Erythropoiesis (RET-He) Red Cell Hemoglobinization
- Thrombopoiesis (IPF) Platelets
HEMATOLOGICAL CHALLENGES

- Infection/Inflammation Management
- Iron Deficiency/Anemia Management
- Thrombocytopenia Management
ANEMIA MANAGEMENT
ANEMIA PREVALENCE

- 3.4 million people in US; 2 billion people globally (1/3 of population)
- Iron deficiency (ID) is the most common cause of anemia (> 600 million people).
- Leading causes:
  - Gastrointestinal blood loss
  - Dietary iron deficiency (poor nutrition, malabsorption)
  - Infectious disease, cancer treatment
- Rapid diagnosis and treatment of iron deficiency can prevent anemia.

National Anemia Action Council, 2006
ANEMIA OVERVIEW

- Indication of underlying disorders
- Underrecognized and undertreated
- Increased morbidity and mortality
- Contributes to overutilization of blood transfusions
PATIENTS AT RISK FOR ANEMIA

Pediatrics

Chronic Illness

Pre-surgical
DIAGNOSIS OF IRON DEFICIENCY

Biochemical Parameters

- Transferrin, Transferrin saturation (TSAT)
- Ferritin
- Serum iron
- Hepcidin

Hematological Parameters

- Based on RBC:
  - Hgb, MCV, RDW
- Based on Reticulocytes
  - Retic # and %
  - IRF
  - RET-He

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## CONDITIONS AFFECTING TEST RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Falsely Increased Results</th>
<th>Falsely Decreased Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Iron</td>
<td>- Infection/Inflammation&lt;br&gt;- Sample late in the day&lt;br&gt;- Meal iron intake&lt;br&gt;- Supplement iron intake&lt;br&gt;- Hemolysis</td>
<td>Diurnal variation</td>
</tr>
<tr>
<td>Transferrin Saturation</td>
<td>- Oral contraceptive</td>
<td>- Infection/Inflammation</td>
</tr>
<tr>
<td>Serum Ferritin</td>
<td>- Infection/Inflammation&lt;br&gt;- Hyperthyroidism&lt;br&gt;- Aging&lt;br&gt;- Liver disease (HCV)&lt;br&gt;- Malignancy&lt;br&gt;- Alcohol consumption&lt;br&gt;- Oral contraceptives</td>
<td>- Vitamin C deficiency&lt;br&gt;- Hypothyroidism&lt;br&gt;- Exercise</td>
</tr>
</tbody>
</table>
RET CHANNEL
SCATTERGRAM ON NORMAL PATTERN
RETICULOCYTE PARAMETERS

- Reticulocytes
  - # and %
- Immature Reticulocyte Fraction (IRF)
  - Measure of erythropoiesis
- Reticulocyte Hemoglobin (RET-He)
  - Measure of hemoglobin content
  - Snapshot of iron availability
RETICULOCYTE HEMOGLOBIN

Ret-He/CHr

- Measured at cellular level
- Monitors acute changes in reticulocyte hemoglobin
- More sensitive than indirect chemical measurements
- Detects non-responders to ESA/functional iron deficiency
CLINICAL APPLICATIONS OF RET-He
INPATIENT & OUTPATIENT SETTINGS

- **Wellness:**
  - Pediatrics

- **Prevention:**
  - Surgical patients

- **Chronic Disease Management:**
  - End-stage renal disease
  - Congestive heart failure
  - Cancer
WELLNESS MANAGEMENT:
SCREENING AND PREVENTION
ANEMIA MANAGEMENT IN PRE-SURGICAL PATIENTS

- Increased morbidity and mortality
- Anemia screening 4 – 6 weeks prior to surgery
- Determine etiology/type of anemia
- Therapy to correct anemia before surgery
LABORATORY TESTING ALGORITHM FOR ANEMIA
SABM WEBSITE (IRWIN GROSS, MD)

Flow Diagram: Inclusion of RET-He in algorithm

1. Hgb is less than 13 gm/dl
   - MCV less than or equal to 105
     - If TSAT greater than 20% and ferritin greater than 100 ng/ml and MCV less than 80 consider thalassemia or hemoglobinopathy
     - Reticulocyte count, RET-He, iron, iron binding capacity, ferritin, creatinine
     - Ferritin less than 100 ng/ml?
     - Add testing for vitamin B12 if MCV greater than or equal to 90
AABB TRANSFUSION RECOMMENDATIONS

Don't transfuse more units of blood than absolutely necessary.

Each unit of blood in a crisis situation should be used for the red cell components of three patients. If blood components are not available, platelet concentrates should be used for the red cell components of four patients. Don’t transfuse more than one unit of blood without the blood component being known.

Don’t transfuse red blood cells for iron deficiency without hemodynamic instability.

Blood transfusion has become a routine medical response despite cheaper and safer alternatives in some settings. Pre-operative patients with iron deficiency and patients with chronic iron deficiency without hemodynamic instability (even with low hemoglobin levels) should be given oral and/or intravenous iron.

Don't routinely use blood products to reverse warfarin.

Patients requiring reversal of warfarin can often be reversed with vitamin K alone. Remember complex concentrates or plasma should only be used for patients with serious bleeding or requiring emergency surgery.

Don't perform serial blood counts on clinically stable patients.

Transfusion of red blood cells or platelets should be based on the first laboratory value of the day unless the patient is bleeding or otherwise unstable. Multiple blood draws to recheck whether a patient’s parameter has fallen below the transfusion threshold for unnecessary blood draws for other laboratory tests can lead to excessive phlebotomy and unnecessary transfusions.

Don’t transfuse O negative blood except to O negative patients and in emergencies for women of childbearing potential with unknown blood group.

O negative blood units are in chronic short supply due to in part to overutilization for patients who are not O negative. O negative red blood cells should be restricted to: (1) O negative patients or (2) women of childbearing potential with unknown blood group who require emergency transfusion before blood group testing can be performed.

CHRONIC DISEASE MANAGEMENT:
FOR IRON DEFICIENCY AND ANEMIA
WHAT IS FUNCTIONAL IRON DEFICIENCY?

- Human Recombinant Erythropoietin (ESA)
- Used in 80% of dialysis patients
- Primary cause of suboptimal response to ESA therapy
- Iron supplementation prescribed with ESA
- Serum iron studies are unreliable
- Challenges with ESA and Iron treatment
CHr TO DETECT FUNCTIONAL IRON DEFICIENCY

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHr &lt; 26pg</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>Serum Ferritin &lt; 100 ng/mL</td>
<td>71.4%</td>
<td>60%</td>
</tr>
<tr>
<td>Transferrin Sat &lt; 20%</td>
<td>57.1%</td>
<td>80%</td>
</tr>
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</table>

(N=164)

VARIATIONS IN IRON TESTS

Source and Magnitude of Variation

<table>
<thead>
<tr>
<th>Variation</th>
<th>RET-He</th>
<th>Hgb</th>
<th>Hct</th>
<th>TSAT</th>
<th>Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7.2%</td>
<td>6.0%</td>
<td>6.2%</td>
<td>40.9%</td>
<td>22.0%</td>
</tr>
</tbody>
</table>

(N=30)

RET-He, Hgb, and Hct, but not TSAT or Ferritin are useful to guide ESA and iron therapy

OUTCOME STUDY IN HEMODIALYSIS PATIENTS

- ESRD patients randomized into 2 groups:
  - Group 1 (N=32) - Iron management based on serum ferritin (SF) and TSAT
  - Group 2 (N=25) - Iron management based on CHr < 29 pg

- Study Outcome: Iron utilization:
  - Group 1 - 83.6% received IV iron
  - Group 2 - 43.2% received IV iron

KDOQI GUIDELINES FOR ANEMIA EVALUATION

Initial Anemia Evaluation

- **Cellular Assessment**
  - Hgb < 12g/dL
  - RBC indices
  - Absolute Retic
  - WBC & Diff
  - PLC

- **Iron Assessment**
  - Serum
  - Serum TSAT or CHr

Iron Assessment Indices

- **HD-CKD Target**
  - Ferritin > 200 ng/ml and
  - TSAT > 20% or CHr > 29 pg

Reference:
ANEMIA IN PATIENTS WITH CANCER

- **Complex etiology**
  - Chronic disease/inflammation
  - Treatment side effects
  - Nutritional deficiencies

- **Conventional biochemical markers inaccurate**

- **Management**
  - RBC transfusions, ESA, Iron

- **2012 recommendations**
  - Investigate patients with Hgb < 11g/dl
PERFORMANCE OF RET-H_{e} IN CANCER

- Rapid rule out of iron deficiency anemia
- Reduced unnecessary testing
- Cost savings for laboratory and health care system

Patient Screening With RET-H_{e}  
N=200

RET-H_{e} <32 pg  
And  
Hgb <11 g/dL  
NPV – 98.5%

Reduced Iron Studies by 80%

SUMMARY: RETICULOCYTE HEMOGLOBIN (RET-He)

- Measured at cellular level
- Estimates real-time bone marrow iron
- Monitors acute hemoglobinization changes
- Provides less variation than acute phase reactants
- Sensitive for early detection of ID
- May improve care of patients in wellness, prevention and chronic disease settings
- May contribute to cost effectiveness of complex anemia care
THROMBOPOIESIS
PLATELET PARAMETERS ON SYSMEX HEMATOLOGY ANALYZERS

- **Platelet Count (PLT)**
  - Normal PLT 150,000 – 450,000/µL
  - Thrombocytopenia  PLT<150,000/µL

- **Mean Platelet Volume (MPV)**
  - Normal MPV 9-12 fL

- **Immature Platelet Fraction (IPF%)**
  - Percent of immature platelets in peripheral blood

- **Cellular measurement of thrombopoiesis**
  - ↓ Plts Normal/↓ IPF = ↓ Production
  - ↓ Plts ↑ IPF = ↑ Destruction
Clinical Challenge in Thrombocytopenia

- What is the cause of the thrombocytopenia?
- Is this a disorder of decreased production?
  - Aplastic Anemia, Leukemia, BM suppression, drugs…
- Is platelet destruction increased?
  - ITP, TTP, DIC, drugs…
- Is patient’s bone marrow recovering without intervention?
POSSIBLE CAUSES OF THROMBOCYTOPENIA

Production Disorders
- Myeloablative Therapy
- Bone Marrow Transplant
- Acute Myeloid Leukemia
- Neoplasia

Destruction Disorders
- ITP/TTP
- Hepatitis C
- DIC
- Splenomegaly
- Autoimmune Disease
- Bacteremia/Sepsis
- HIT/DIT
- Pregnancy
There is no single hematologic or biochemical test that is conclusive for a given mechanism of thrombocytopenia.
DIFFERENTIATE PHYSIOLOGICAL MECHANISMS

- Low PLT + Normal/Low IPF (Consistent with production disorder)
- Normal
- Low PLT+ High IPF (Consistent with destruction disorders)
IPF IN DIFFERENTIAL DIAGNOSIS

**In thrombocytopenia**
- Does IPF help differentiate between consumptive and aplastic causes?

**In thrombocytopenia**
- Does regular monitoring of IPF provide valuable information for treatment decisions?

IPF IN DIFFERENTIAL DIAGNOSIS

IPF% is a supportive diagnostic test for ITP

- IPF% and RP% highly correlated
- Significantly increased in ITP patients
- Low values in AA+CIT

ITP – Immune Thrombocytopenia (N=47)
AA + CIT - Aplastic Anemia (AA, N=18) or chemotherapy-induced thrombocytopenia (CIT, N=10)

IMMATURE PLATELET FRACTION TO ASSESS BONE MARROW RECOVERY

Study Objective
How well can IPF help the clinician predict bone marrow recovery following peripheral blood HPC transplantation? (N=50)

“A persistently low IPF in this setting would suggest failure of thrombopoietic recovery.”

SUMMARY: IMMATURE PLATELET FRACTION (IPF)

- Cellular measurement of thrombopoiesis
- May assist in differential diagnosis of thrombocytopenia
  - Platelet production vs platelet destruction
- Earlier indicator of bone marrow recovery
THANK YOU!

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