The Internists Approach to Polycythemia and Implications of Uncontrolled Disease

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Disclosures

NONE
Overview

1. Objectives
2. Case Study
3. Diagnosis of polycythemia
4. Risk factors of polycythemia
5. Treatment strategies
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Objectives

- Identification of S & S
- Definition
- Identification of risk factors in hospitalized patient
- Identification of treatment plans in hospitalized patient
- Identification of factors to consider for post op follow up care
Case Study

- 48 yo cau male presented for outpatient cholecystectomy.
- CBC pre op revealed WBC 13,000 Hb 17.1 HCT 51
- Pre Surg clearance requested
- EMR revealed ultrasound of abd hepatocellular dysfunction with partial obstruction of biliary duct and splenomegaly (mild)
History

- ETOH and cocaine abuse-rehabilitated
- Hypertension
- Smoker 2 packs/d
- No hx of DVT
- Works as lawn maintenance
- Degenerative disc disease of lumbar spine
- Pruritus-thinks may be allergies
Diagnosis of Polycythemia

- Definition: Hct > 50
- Primary versus Secondary
- Primary: PRV and implications
- Secondary: chronic hypoxic conditions excess erythropoietin production such as paraneoplastic
Signs & Symptoms

- Fatigue
- Itching
- Headache and blurred vision
- Sweating, numbness of hands and feet
- Excess bleeding from minor cuts
- Bone pain
Polycythemia Rubra Vera
PV is a trilineage myeloproliferative neoplasm\textsuperscript{1-4}

- Characterized by clonal expansion of abnormal hematopoietic stem cells or progenitor cells driven by JAK pathway overstimulation.

In PV, chronic unregulated proliferation may occur in ≥1 myeloid cell line, including erythrocytes, platelets, and sometimes granulocytes\textsuperscript{4,5}

Polycythemia Rubra Vera
Overactive JAK pathway signaling is a key driver of pathogenesis leading to overproduction of RBCs, WBCs, and platelets.


**JAK**, Janus-associated kinase; **RBC**, red blood cell; **WBC**, white blood cell.
Polycythemia Rubra Vera
PV diagnosis\(^1\) and risk assessment\(^2\)

- PV diagnosis requires meeting all 3 major criteria or the first 2 major criteria and the minor criterion

### WHO Major Diagnostic Criteria

1. Hb >16.5 g/dL in men, >16.0 g/dL in women or Hct >49% in men, >48% in women, or increased red cell mass >25% above mean normal predicted value
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of \(JAK2V617F\) or \(JAK2\) exon 12 mutation

### WHO Minor Diagnostic Criterion

Subnormal serum erythropoietin level

### High-risk stratification criteria that may call for cytoreductive therapy in PV\(^2\)

- History of thrombosis (arterial or venous thrombosis; microcirculatory disturbances)
- Age >60 years

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Hb, hemoglobin; Hct, hematocrit; JAK, Janus-associated kinases; PV, polycythemia vera; WHO, World Health Organization.

Risk Factors of Uncontrolled Disease
Elevated Hct levels increased risk of cardiovascular death or major thrombosis

Probability of Remaining Event Free¹

![Graph showing probability of remaining event free over months with hazard ratios for low and high Hct levels.]

- Low Hct (<45%) (n = 182) (Median Hct, 44.4%)
- High Hct (45%-50%) (n = 183) (Median Hct, 47.5%)

P = 0.004 by log-rank test

Hazard ratio
- Low Hct: 5/182 (2.7%) 1.00
- High Hct: 18/183 (9.8%) 3.91 (95% CI, 1.45-10.53)

Patients with an Hct target of 45% to 50% had a 4-fold higher incidence of cardiovascular death or major thrombosis than patients with an Hct target <45%¹

Elevated WBC counts were associated with increased risk of thrombosis

Time-Dependent Multivariate Analysis on the Risk of Major Thrombosis in CYTO-PV study (N=365)\(^a\)

<table>
<thead>
<tr>
<th>WBC Count (x 10(^9)/L)</th>
<th>Events/Pts (%)</th>
<th>Hazard Ratio (95% CI), (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.0</td>
<td>4/100 (4.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>7.0–8.4</td>
<td>4/84 (4.8)</td>
<td>1.58 (0.39-6.43), 0.52</td>
</tr>
<tr>
<td>8.5–11.0</td>
<td>8/88 (9.1)</td>
<td>2.69 (0.80-9.05), 0.11</td>
</tr>
<tr>
<td>≥11.0</td>
<td>12/93 (12.9)</td>
<td>3.90 (1.24-12.3), 0.02</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for age, gender, cardiovascular risk factors, previous thrombosis, and Hct levels.

In this study, the results indicate the risk of thrombosis was increased in patients with a WBC count >7 x 10\(^9\)/L (ie, HR >1), becoming statistically significant at WBC >11 x 10\(^9\)/L

CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HR, hazard ratio; pts, patients; WBC, white blood cell.

## PV diagnosis\(^1\) and risk assessment\(^2\)

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**References:**

### Original CHADS<sub>2</sub> Score

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension (&gt;140/90mmHg)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age &gt; 75</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Prior TIA or stroke</td>
<td>2</td>
</tr>
</tbody>
</table>
ACCF/AHA/ESC 2006 Guidelines and 2011 Focused Update

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>• Aspirin (81-325 mg daily) or no therapy</td>
</tr>
<tr>
<td>1 moderate risk factor</td>
<td>• Aspirin (81-325 mg daily) or warfarin</td>
</tr>
<tr>
<td></td>
<td>• Alternative dabigatran (nonvalvular AF)</td>
</tr>
<tr>
<td>Any high risk factor or &gt;1 moderate risk factor</td>
<td>• Warfarin</td>
</tr>
<tr>
<td></td>
<td>• Alternative dabigatran (nonvalvular AF)</td>
</tr>
</tbody>
</table>

The European guidelines recommend anticoagulation over aspirin for most patients with a CHA₂DS₂-VASc score of ≥1 for nonvalvular AFib

<table>
<thead>
<tr>
<th>Less validated/weaker risk factors¹</th>
<th>Moderate-risk factors¹</th>
<th>High-risk factors¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Female sex</td>
<td>• Age ≥75 years</td>
<td>• Previous stroke, TIA, or embolism</td>
</tr>
<tr>
<td>• Age 65 to 74 years</td>
<td>• Hypertension</td>
<td>• Mitral stenosis</td>
</tr>
<tr>
<td>• Coronary artery disease</td>
<td>• Heart failure</td>
<td>• Prosthetic heart valve*</td>
</tr>
<tr>
<td>• Thyrotoxicosis</td>
<td>• LVEF ≤35%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ESC = European Society of Cardiology; HRS = Heart Rhythm Society; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

*Dabigatran is an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function).

(For references, see text.)
Treatment Strategies

- Consider thrombotic risk factors & rec
- Consider effects of elevated WBC & rec
- Consider effects of elevated HCT & rec
Summary

- Consider each case evaluated
- Weigh benefit/risk odds
- Counsel on lifestyle
- Share concern of potential underlying etiology
  - Don’t be afraid to phlebotimize if needed after hydration
Questions?