How to treat non-clonal polyglobulia: to bleed or not to bleed

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Guy’s and St Thomas’ Hospitals London, UK
Disclosures

Institutional research support: Novartis and Shire Pharmaceuticals

Speaker: Novartis, Sanofi Avensis, Shire, CTI, Prime oncology, Medscape

Consultancy work: Novartis, Sbio, YMBioscience, Cellgene, Sanofi Avensis, Gilead, CTI, NICE
Learning outcomes

■ To be able to classify erythrocytosis
■ To understand the investigation of a suspected erythrocytosis
■ To consider possible management options for a patient with an erythrocytosis…..

“To venesect or not”
Who should be investigated?

- A persistently raised venous haematocrit (>0.52 males, >0.48 in females for >2 months) should be investigated.
- A Hct above 0.60 in males and 0.56 in females can be assumed to have absolute erythrocytosis.

Caution

- Patients with iron deficient red cell indices

BCSH guidelines 2007 McMullin et al
RCM shows better correlation with HCT

Haemoglobin and red cell mass (males) shows less good correlation
Diagnostic criteria for Polycythemia Vera
WHO 2016

**Major**
- HCT > .49 (men), .48 (women) or other evidence of increased red cell mass
- JAK2 mutation
- Bone marrow biopsy showing panmyelosis

**Minor**
- Serum Epo below the normal reference range

All major or two major and one minor establishes PV
Erythrocytosis

**Apparent:** Raised haematocrit Red cell mass normal

**Absolute:** Red cell mass >125% of predicted value

**Relative:** Raised haematocrit Red cell mass normal and Reduced plasma volume
Erythrocytosis

**Apparent:**
Raised haematocrit
Red cell mass normal

**Relative:**
Raised haematocrit
Red cell mass normal and
Reduced plasma volume

**Absolute:**
Red cell mass
>125% of predicted value
- Primary erythrocytosis
  - Congenital
  - Acquired
    - Polycythemia vera
    - *LNK* mutations (congenital and acquired)

- Secondary erythrocytosis
  - Congenital
  - Acquired
    - Central hypoxic process
    - Local hypoxia
    - Pathologic EPO production
    - Exogenous EPO

- Idiopathic erythrocytosis
Congenital erythrocytosis:

- **Primary**
- **EPO receptor mutations**
- **Secondary**
  - Oxygen sensing pathway mutations
    - *VHL gene mutations*
    - *PHD2 mutations*
    - *HIF-2a mutations*
  - Bisphosphoglycerate mutase deficiency
  - High oxygen-affinity haemoglobin
  - Methaemoglobinemia
  - Hereditary ATP increase

............................................And many others now being recognised...
Diagnostic pathway

- Persistence
- History and examination
- EPO level +/- JAK2 mutation test
- CarboxyHaemoglobin
Diagnostic pathway

- History and examination
- Symptoms of hyperviscosity
- Predisposing factors
- Drugs including recreational
- Lifestyle
- Family history:
  - Vascular disease &
  - Erythrocytosis
Investigations

- Repeat confirmatory FBC
- Erythropoietin level, Carboxyhaemoglobin, JAK2 mutations

- Bone marrow biopsy
- Imaging
- Overnight oximetry
- Red Cell Mass
- $P_{50}^-$ Oxygen dissociation curve
- Haemoglobin electrophoresis
- Sequencing of known gene mutations

- NGS..... Can replace p50, electrophoresis and sequencing
Erythrocytosis

Measurement of EPO levels

Primary if low/normal (10%)

Secondary if normal/high

Defect intrinsic to erythroid cell

Erythropoietin driven
Investigations

- Repeat confirmatory FBC
- Erythropoietin level, Carboxyhaemoglobin, JAK2 mutations
- Bone marrow biopsy
- Imaging
- Overnight oximetry
- Red Cell Mass
- \( P_{50} \) - Oxygen dissociation curve
- Haemoglobin electrophoresis
- Sequencing of known gene mutations

NGS….. Can replace \( P_{50} \), electrophoresis and gene sequencing
Absolute Erythrocytosis

- SaO₂ > 92%
- SaO₂ < 92%

Acquired secondary Erythrocytosis:
- Cardiac or pulmonary disorder?
- Spleenomegaly or thrombocytosis or leukocytosis

Consider:
- Serum Epo high (or upper normal range)
- Serum Epo low (or lower normal range)

Check:
- JAK2 V617F + exon 12 sequencing
- ± bone marrow biopsy

Is there evidence to warrant genetic testing? (e.g. young onset, family history)

Erythrocytosis gene panel (FULL GENE sequencing)

- Novel variants in known-disease genes
- Known causal mutations in:
  - JAK2
  - Epo signaling pathway: EPOR, SH2B3 (LNK)
  - Oxygen-sensing pathway: VHL, EPAS1 (HIF2A), EGLN1 (PHD2)
  - Globin genes: HBB, HBA1, HBA2
  - 2,3-BPG deficiency: BPGM

Functional and/or replication studies

PV

- ECYT1
- ECYT 2-4
- Hb variant with high O₂-affinity
- 2,3-BPG deficiency
Acquired secondary erythrocytosis
Acquired: EPO mediated: Hypoxia driven

Central hypoxic process
- Chronic lung disease
- Right-to-left cardiopulmonary vascular shunts
- Carbon monoxide poisoning
- Smoker's erythrocytosis
- Hypoventilation syndromes including sleep apnoea
- High-altitude habitat

Local renal hypoxia
- Renal artery stenosis
- End stage renal disease
- Hydronephrosis
- Renal cysts (polycystic kidney disease)
- Post-renal transplant erythrocytosis
Acquired: Excess EPO

Pathologic EPO production

- Cerebellar haemangioblastoma
- Meningioma
- Parathyroid carcinoma/adenomas
- Hepatocellular carcinoma
- Renal cell cancer
- Pheochromocytoma
- Uterine leiomyomas
Management of secondary erythrocytosis:

- Venesection is NOT the mainstay
Considering PV there is clear evidence of HCT control being important..........

Relation of PCV range to number of vascular occlusive episodes per 10 patient-years
In patients with primary proliferative polycythaemia.
Risk of cerebral infarction (16 year follow up) according to antecedent hemoglobin and blood pressure status. Men and women 30-62 at entry: Framingham Study.

But if you lower the HCT does it lower the risk?

KANNEL, et al, Stroke, 1972, 3, 409-420
What about primary prevention with aspirin?

**Figure 2. Probability of Survival Free of a Thrombotic Event.**

The analysis was performed according to the intention-to-treat principle. The relative risk of a thrombotic event in the aspirin group, as compared with the placebo group, was 0.42 (95 percent confidence interval, 0.24 to 0.74; P=0.002 by the log-rank test).
Management of acquired secondary erythrocyosis

- Address the underlying cause where possible
- Many require non-haematological input eg sleep apnoea
- Standard lifestyle measures apply

- Only venesect if there is a very clear indication
- Eg very high HCT > 0.54 and symptoms or risk eg pre op
- NB this does NOT apply to cyanotic heart disease
- Aspirin only if otherwise indicated
Recent case from our clinical practice

- 34 year old man presents with episode of black out
- Shortly after arrival had an epileptic seizure, full recovery
- No relevant history, non-smoker, increasing headaches.

**FBC**
- Hb 240g/L
- HCT 0.64
- Wbc $8 \times 10^9$
- Platelets $341 \times 10^9$

**Advice?**
- Persistently abnormal
Recent case from our clinical practice

- 34 year old man presents with episode of black out
- Shortly after arrival had an epileptic seizure, full recovery
- No relevant history, non-smoker, increasing headaches.

FBC
Hb 240g/L
HCT 0.64
Wbc 8 x 10⁹
Platelets 341 x 10⁹

- Check EPO/JAK2 etc
- Get urgent imaging
- Hydrate and perform isovolaemic venesection
Brain imaging

Cerebellar abnormality

• EPO 10 IU/L
• JAK2 mutations negative

Continue venesections target <0.5 for surgery

“POLYCYTHEMIA” ASSOCIATED WITH CEREBellar HEMANGIOBLASToma

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Division of Neurosurgery, University of Washington, and Neurosurgical Service, 
Veterans Administration Hospital, Seattle, Washington

(Received for publication December 16, 1955)

In 1948, Carpenter and co-workers reported 2 cases of cerebellar hemangioblastoma with associated “polycythemia vera.” They added 3 cases from the literature. Since then, about 22 such cases have been reported in the American literature. Hemangioblastomas of the posterior fossa constitute only 2 per cent of intracranial tumors and those associated with “polycythemia” less than 20 per cent of the total number of hemangioblastomas. Thus, the association of “polycythemia” with posterior fossa hemangioblastoma is, to paraphrase Carpenter, an event of the greatest rarity.

Polycythemia rubra vera has been defined as a disease of unknown etiology, characterized by an excessive production of all marrow elements with resultant increase in red blood cell count, total red blood cell volume, white blood cell and platelet counts, and accompanied by increased blood viscosity and decreased velocity of blood flow. Since quantitative blood studies have been done in only 1 of the reported cases of cerebellar hemangioblastoma, it is difficult to determine whether polycythemia vera (as defined above) did, in fact, exist in the remainder. Possibly erythrocytosis, in which the red blood cell count is elevated with no increase in white blood cells or platelets, might be a more appropriate term to use.

We have recently studied 2 patients who had posterior fossa hemangioblastomas with associated erythrocytosis. Both patients were treated surgically, one with subtotal and the other with total removal of the tumor. We believe that the hematologic studies made in these 2 cases are more nearly complete than those reported heretofore.

It has not yet been proved that the relationship between the altered blood picture and the tumor is more than fortuitous. Although the basic physiopathology is unknown, the reduction in the degree of erythrocytosis in some cases following removal of the tumor suggests a cause-effect rela-
Primary erythrocytosis
- Congenital
  - Acquired
  - Polycythemia vera
  - LNK mutations (congenital and acquired)

Secondary erythrocytosis
- Congenital
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  - Central hypoxic process
  - Local hypoxia
  - Pathologic EPO production
  - Exogenous EPO

Idiopathic erythrocytosis
Investigation of an erythrocytosis with a low EPO level

- *EPO* receptor mutations
- *JAK2* mutations
- *LNK* mutations reported some congenital and some acquired
Erythropoietin (EPO) Receptor

EPO Signal Transduction

- EPO
- Receptor
- JAK2
- STAT5

Down modulation

- EPO
- Receptor
- JAK2
- SHP-1

Truncated EPO R

- EPO
- Receptor
- JAK2
- SHP-1

active STAT5 dimers

McMullin 2009
EPO receptor truncation mutation

- *De novo* G to A at base 6002
- Stop codon at aa 439

<table>
<thead>
<tr>
<th>Individual</th>
<th>Hb (g/dL)</th>
<th>PCV</th>
<th>WBC (x10⁹/L)</th>
<th>Platelets x10⁹/L</th>
<th>EPO Level (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teenage boy</td>
<td>20.5</td>
<td>0.60</td>
<td>4.1</td>
<td>211</td>
<td>4.4 (NR 9.1-30.8)</td>
</tr>
</tbody>
</table>

McMullin 2009
Management of patients with EPO R truncation….?

- Lack of evidence base
- Consider venesection if patients are symptomatic and HCT > 0.55
- Careful management of anaesthesia etc

- The teenage boy is now 38 years old has 2 x / year venesections
JAK2 Kinase - JH1 and JH2 Domains

active state

inactive state

JH1

JH2

Interface 1

Interface 2

V617
JAK2 mutation in Polycythaemia Vera

- Chromosome 9 exon 12
- G→T transversion at nucleotide 1849
- Resulting V617F mutation

![Diagram of JAK2 protein domain structure with V617F mutation highlighted.](image-url)
JAK2 Exon 12 mutations

Scott et al 2007
Diagnostic criteria for Polycythemia Vera
WHO 2016

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  - Bone marrow biopsy showing panmyelosis

- **Minor**
  - Serum Epo below the normal reference range

Very rare JAK2 mutation negative PV cases do exist a bone marrow biopsy if useful to detect them. Very low level JAK2 mutations may also be considered

all major or Two major and one minor establishes PV
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- NGS….. Can replace $P_{50}$, electrophoresis and gene sequencing

As directed by history, examination and clinical findings
Investigations

- Repeat confirmatory FBC
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As directed by history, examination and clinical findings

- NGS..... Can replace $P_{50}$, electrophoresis and gene sequencing
NGS based technologies can be very helpful.
Roche (NimbleGen SeqCap)- SEQCAP
Examples of genes on the erythrocytosis NGS panel

<table>
<thead>
<tr>
<th>Candidate Gene</th>
<th>Position</th>
<th>No of exons</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>Chr3:10183319-10195354</td>
<td>3</td>
</tr>
<tr>
<td>EPAS1</td>
<td>Chr2:46524541-46613842</td>
<td>16</td>
</tr>
<tr>
<td>EGLN1</td>
<td>Chr1:231499497-231560790</td>
<td>4</td>
</tr>
<tr>
<td>EPOR</td>
<td>Chr19:11487881-11495018</td>
<td>8</td>
</tr>
<tr>
<td>BPGM</td>
<td>Chr7:134331531-134364568</td>
<td>3</td>
</tr>
<tr>
<td>HBB</td>
<td>Chr11:5225464-5227071</td>
<td>3</td>
</tr>
<tr>
<td>SH2B3</td>
<td>Chr12:111405948-111451623</td>
<td>8</td>
</tr>
<tr>
<td>JAK2</td>
<td>Chr9:4985245-5128183</td>
<td>25</td>
</tr>
<tr>
<td>EGLN2</td>
<td>Chr19:41305048-41314346</td>
<td>5</td>
</tr>
<tr>
<td>HBA1</td>
<td>Chr16:22958-22749</td>
<td>3</td>
</tr>
<tr>
<td>HBA2</td>
<td>Chr16:22277-22375</td>
<td>3</td>
</tr>
</tbody>
</table>
Management of idiopathic erythrocytosis (ie everything is negative)

- Venesection to HCT target of 0.54

- If previous thrombosis or increased risk of thrombosis then consider a target of 0.45

- Cytoreductive therapy is contraindicated
# High Affinity Hemoglobins..... examples

<table>
<thead>
<tr>
<th>UPN</th>
<th>116</th>
<th>162</th>
<th>214</th>
<th>224</th>
<th>228</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>Olympia</td>
<td>Olympia</td>
<td>Pierre Benite</td>
<td>Heathrow</td>
<td>Santa Clara</td>
</tr>
<tr>
<td>Age at presentation (yrs)</td>
<td>42</td>
<td>33</td>
<td>56</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>19.2</td>
<td>18.2</td>
<td>18.1</td>
<td>15.4</td>
<td>19.1</td>
</tr>
<tr>
<td>Hct</td>
<td>0.59</td>
<td>0.53</td>
<td>0.54</td>
<td>0.48</td>
<td>0.58</td>
</tr>
<tr>
<td>WBC (x 10^9/l)</td>
<td>5.8</td>
<td>5.8</td>
<td>N/A</td>
<td>6.4</td>
<td>6.8</td>
</tr>
<tr>
<td>Pts (x10^9/l)</td>
<td>233</td>
<td>186</td>
<td>N/A</td>
<td>334</td>
<td>171</td>
</tr>
<tr>
<td>EPO (mIU/ml)</td>
<td>9.1</td>
<td>4.9</td>
<td>23</td>
<td>29.1</td>
<td>5.8</td>
</tr>
</tbody>
</table>
Recommendations: management of high (oxygen) affinity haemoglobins

- Possible indications for Venesection include:
  - Presence of symptoms such as dizziness, dyspnoea or angina, for which a raised Hct is considered to be a contributory factor.
  - One or more previous thrombotic episodes.
  - Asymptomatic individuals in whom a family member with a high oxygen affinity haemoglobin, similar haemoglobin concentration, and comparable risk factors for thrombosis has developed a thrombotic problem.

McMullin 2007 BCSH recommendations
High oxygen affinity haemoglobins

- Consideration venesection should be given for individuals with a Hct >0.60 requiring major surgery.

- Do not attempt to reduce the Hct to within the normal range. *Venesection* to maintain the Hct <0.60 has been recommended.

- When thrombosis or symptoms compatible with hyperviscosity develop at a lower Hct, a target Hct of 0.52 has been suggested.

McMullin 2007 BCSH recommendations
**VHL Mutational screen**

Normal
> 100 patients

Homozygous
C598T/Arg200Trp
9 Asian families

Data suggests single founder individual

McMullin 2009
Patient case:

- 23 year old originally from Bangladesh referred to clinic
- Had hypoplastic left heart, and transposition of great vessels corrected as baby, multiple operations.
- Good function, no exercise limitation, no hypoxia
- 15 months earlier suffered thrombotic CVA at that time (Hb 24 HCT 0.62)
Patient case

- 23 year old originally from Bangladesh referred to clinic
- Had hypoplastic left heart, and transposition of great vessels corrected as baby, multiple operations.
- Good function, no exercise limitation, no hypoxia
- 15 months earlier suffered 2 x thrombotic CVA at that time (Hb 24 HCT 0.62)
- EPO 15 IU/L

Father attends with him and mentions that he was seen at St Thomas’ Hospital 18 years before and had lots of tests for “Too much blood” Used to have vanesections, well in himself. Hb 18.8 mcv 56 HCT 0.54, EPO 20
Diagnosis?

- Father and son had a known mutation affected HIF 2A (EPAS 1 gene)

Management?

- Father needs venesection target < 0.5
- Son < 0.45 and aspirin
- Screen family members
Clinical events in erythrocytoses

- Homozygotes with Chuvash polycythaemia: increased mortality from cerebrovascular events and mesenteric thrombosis

- $PHD2$ and $HIF2A$ mutations associated with thromboembolic events
Kaplan-Meier survival curves for Chuvash polycythemia patients and spouses or community members matched for age, sex and place of birth.
Baseline characteristics of adult Chuvash polycythemia (CP) patients and controls at time of enrollment in the case-control study.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>CP Result</th>
<th></th>
<th>N</th>
<th>Controls Result</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>128</td>
<td>38 (26-50)</td>
<td></td>
<td>128</td>
<td>40 (26-50)</td>
<td>0.4</td>
</tr>
<tr>
<td>Female sex</td>
<td>128</td>
<td>70 (54.7%)</td>
<td></td>
<td>128</td>
<td>68 (53.1%)</td>
<td>0.8</td>
</tr>
<tr>
<td>History of phlebotomy therapy</td>
<td>128</td>
<td>100 (78.1%)</td>
<td></td>
<td>128</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of smoking</td>
<td>128</td>
<td>41 (32.0%)</td>
<td></td>
<td>128</td>
<td>23 (18.0%)</td>
<td>0.009</td>
</tr>
<tr>
<td>History of thrombosis*</td>
<td>128</td>
<td>27 (21.9%)</td>
<td></td>
<td>128</td>
<td>3 (2.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>128</td>
<td>14 (10.9%)</td>
<td></td>
<td>128</td>
<td>2 (1.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>128</td>
<td>8 (6.3%)</td>
<td></td>
<td>128</td>
<td>27 (21.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>128</td>
<td>3 (2.3%)</td>
<td></td>
<td>128</td>
<td>1 (0.8%)</td>
<td>0.3</td>
</tr>
<tr>
<td>History of malignancy**</td>
<td>128</td>
<td>2 (1.6%)</td>
<td></td>
<td>128</td>
<td>1 (0.8%)</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>128</td>
<td>21.5 (19.8-23.7)</td>
<td></td>
<td>128</td>
<td>23.3 (21.1-26.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>128</td>
<td>91 (85-97)</td>
<td></td>
<td>128</td>
<td>94 (88-102)</td>
<td>0.009</td>
</tr>
<tr>
<td>Erythrocytes (x10⁶/ul)</td>
<td>127</td>
<td>6.45 (6.00-7.19)</td>
<td></td>
<td>127</td>
<td>4.69 (4.22-4.99)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>127</td>
<td>17.9 (15.9-19.8)</td>
<td></td>
<td>128</td>
<td>13.8 (12.6-15.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Hematocrit (%)</td>
<td>115</td>
<td>53.4 (47.7-58.5)</td>
<td></td>
<td>127</td>
<td>40.3 (37.2-43.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>110</td>
<td>80.7 (74.0-87.0)</td>
<td></td>
<td>127</td>
<td>87.7 (84.3-90.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCH (g/dL)</td>
<td>119</td>
<td>27.3 (23.7-30.9)</td>
<td></td>
<td>128</td>
<td>29.9 (28.4-31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCHC (g/dL)</td>
<td>111</td>
<td>33.2 (31.3-35.0)</td>
<td></td>
<td>127</td>
<td>34.2 (33.0-35.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>White blood cells (per ul)</td>
<td>127</td>
<td>5.70 (4.60-7.12)</td>
<td></td>
<td>128</td>
<td>6.40 (5.34-7.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutrophils (per ul)</td>
<td>92</td>
<td>3.08 (2.07-3.79)</td>
<td></td>
<td>128</td>
<td>3.52 (2.95-4.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocytes (per ul)</td>
<td>98</td>
<td>1.90 (1.55-2.32)</td>
<td></td>
<td>126</td>
<td>2.19 (1.83-2.54)</td>
<td>0.003</td>
</tr>
<tr>
<td>Platelets (per ul)</td>
<td>127</td>
<td>219 (165-268)</td>
<td></td>
<td>128</td>
<td>247 (209-300)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Erythropoietin (U/L)</td>
<td>89</td>
<td>48.6 (24.4-88.3)</td>
<td></td>
<td>44</td>
<td>8.9 (7.3-13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum ferritin (ug/L)</td>
<td>86</td>
<td>11 (6-23)</td>
<td></td>
<td>43</td>
<td>53 (23-105)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Twenty-seven CP patients had a history of 40 thromboses: 18 with 1 thrombosis, 5 with 2 thromboses, 4 with 3 thromboses, 2 with 4 thromboses, 1 with 5 thromboses, 1 with 6 thromboses, 1 with 8 thromboses, 1 with 9 thromboses, 1 with 10 thromboses, 1 with 11 thromboses, 1 with 12 thromboses, 1 with 13 thromboses, 1 with 14 thromboses, 1 with 15 thromboses, 1 with 16 thromboses, 1 with 17 thromboses, 1 with 18 thromboses, 1 with 19 thromboses, 1 with 20 thromboses, 1 with 21 thromboses, 1 with 22 thromboses, 1 with 23 thromboses, 1 with 24 thromboses, 1 with 25 thromboses, 1 with 26 thromboses, 1 with 27 thromboses, 1 with 28 thromboses, 1 with 29 thromboses, 1 with 30 thromboses, 1 with 31 thromboses, 1 with 32 thromboses, 1 with 33 thromboses, 1 with 34 thromboses, 1 with 35 thromboses, 1 with 36 thromboses, 1 with 37 thromboses, 1 with 38 thromboses, 1 with 39 thromboses, 1 with 40 thromboses. **History of breast carcinoma and Hodgkin lymphoma in CP patients, history of breast carcinoma in a control. BMI: body mass index; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration.
Multivariate Cox Proportional Hazards Model of predictors of new thrombosis during follow up in 128 CP patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazards Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of past thromboses (range from 0 to 3)</td>
<td>1.9</td>
<td>1.3-2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Treatment with pentoxifylline</td>
<td>3.3</td>
<td>1.5-7.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Average number of cigarettes smoked per day in the past year (increments of 10)</td>
<td>1.9</td>
<td>1.1-3.3</td>
<td>0.018</td>
</tr>
<tr>
<td>Remote and recent phlebotomy categories</td>
<td>2.0</td>
<td>1.01-3.8</td>
<td>0.045</td>
</tr>
<tr>
<td>Age (increments of 10 years)</td>
<td>1.3</td>
<td>0.99-1.9</td>
<td>0.060</td>
</tr>
</tbody>
</table>

- Prospective evaluation of 128 CP subjects & controls (matched by age, sex, residence) over median of 8.8 years.

- The rate of new thrombosis was higher in CP subjects (HR 12.7).

Adelina Sergueeva et al. Haematologica 2017;102:e166-e169
Thrombosis and THBS1 expression in Chuvash polycythemia

Adelina Sergueeva et al. Haematologica 2017;102:e166-e169
Chuvash polycythemia patients have different cardiovascular responses to hypoxia........
Chuvash polycythemia patients have different cardiovascular responses to hypoxia………

This was also seen in PHD2 mutation proband and mimics by iron deficiency and chronic hypoxia

*Smyth, PLOS, 2005, 3, e290*
Chuvash polycythemia patients have different cardiovascular responses to hypoxia

Implications for therapy and monitoring for complications
Paraganglioma have been reported in patients with HIF 2α mutations.
Management options: Congenital erythrocytosis

- Rare individuals may have a congenital erythrocytosis which often present at a young age and have a family history
- An investigation for known molecular defects should be carried out
- Venesection and low dose aspirin are possible management options
- Ruxolitinib may have efficacy in managing Chuvash polycythaemia
- Screening for complications such as pulmonary hypertension
Lifestyle modification:
Just as important for congenital erythrocytosis
Erythrocytosis & symptoms response: Ruxolitinib in Chuvash Polycythaemia

Zhou et al NEJM 2016
Management of a congenital erythrocytosis

- Assess individual patient
- Consider reduction of HCT to achievable target level < 0.5
- Consider aspirin if no specific contraindication
- Need for long-term follow-up of treatments and outcomes

? Need for global registry
Summary:

- Erythrocytosis is classified by cause measurement of EPO levels are useful way to subclassify
- Red cell mass is a useful test and HCT is more predictive than Hb
- Most cases of secondary acquired erythrocytosis are best managed by addressing the underlying cause and venesection is NOT a mainstay of therapy
- Congenital erythrocytosis is rare but important venesection needs to be carefully considered and long term monitoring for other late complications is important
- A registry for these conditions would inform future management