Myeloproliferative Neoplasia associated Splanchnic Vein Thrombosis (MPN-SVT)

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## Risks associated with SVT

### Risk factors

<table>
<thead>
<tr>
<th>Abdominal disorders and interventions</th>
<th>Inherited thrombophilic state</th>
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<tbody>
<tr>
<td>Acute</td>
<td>Antithrombin deficiency</td>
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<tr>
<td>Pancreatitis</td>
<td>Protein C deficiency</td>
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<td>Peritonitis and intraabdominal sepsis</td>
<td>Protein S deficiency</td>
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<td>Inflammatory bowel disease</td>
<td>Factor V Leiden</td>
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<td>Diverticulitis</td>
<td>G20210A mutation in prothrombin gene</td>
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<td>Hydatidosis</td>
<td>Antiphospholipid syndrome</td>
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<td>Splenectomy</td>
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<td>General abdominal surgery</td>
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<td>Sclerotherapy for esophageal varices</td>
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<td>Abdominal trauma</td>
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<td>Chronic</td>
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<td>Cirrhosis</td>
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<td>Abdominal cancer</td>
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<td>Portal hypertension</td>
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<td>Hematological disorders</td>
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<td>Philadelphia chromosome negative chronic MPNs</td>
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<td>Polycythemia vera</td>
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<td>Essential thrombocythemia</td>
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<td>Idiopathic myelofibrosis</td>
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<td>PNH</td>
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Ageno et al., *Blood* 2014, 124; No 25: p3685-3691
Meta-analysis of 32 studies of MPN in BCS and PVT (Smalberg et al Blood 2012)

**Budd Chiari Syndrome (n= 1062)**

- **40.9% MPN** (80.3% JAK2V617F pos)
- 41.1% JAK2pos
- 17.1% no MPN features, JAK2mut pos

**Portal Vein Thrombosis (n= 855)**

- **31.5 % MPN** (86.6% JAK2V617F pos)
- 27.7% JAK 2 pos
- 15.4% no MPN features, JAK2 pos

But in more recent studies including our own, the majority were de novo presentation of SVT with no prior MPN diagnosis.
Clinical diagnosis of MPN defined by blood counts and molecular mutations (JAK2, Calreticulin, mpl)

- **Polycythemia Vera (PV)**
  - Hb >16; Hct >52(M); >48%(F); RCM>25%;
  - Masked PV: normal Hb - not well defined

- **Essential Thrombocythaemia (ET)**
  - Plts >450

- **Myelofibrosis (MF)**
  - Cytopenia, BM fibrosis

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T. Klampfl, NEJM 2013
G.P. 56 yrs/M

Previously well
Investigated for abdominal symptoms
Portal vein thrombosis

Hb 136
WBC 7.2
Plts 241
Hct 0.42
RCC 5.52 (N<5.7)
MCV 77 (>80)
Ferritin 18 (>30)
Epo 6.2 (low)

JAK2 V617F positive

RCM: predicted=2426 mls
     measured= 3280 mls
     ratio: 1.35 (0.75-1.25)
UHB: Blood Counts in MPN SVT

- FBC for 64 patients (No cytoreductive therapy)
- Large no. of patients have normal FBC (37%)
- 26.6% have ↑ platelet (Plts)
- 28.1% ↑ WBC
- 14% have ↑ haemoglobin (Hb)
- 18.7% ↑ hematocrit (Hct)

But:

- 53% ↑ RCC
- 51% ↓ MCV

Masked PV
Most Studies show SVT-MPN associated with JAK2 mutation—only up to 2% is associated with CalR mutation.

**UHB data: Analysing the JAK2 617F allele burden in MPN SVT: A distinct group?**

**JAK2 V617F %**

*JAK2 V617F allele burden: de-novo SVT 17% (0.6%-81%), SVT diagnosed during MPN follow-up: 17% (4.5%-63%), ET: 24% (0.30%-64%), PV 45% (20%-89%), MF 69% (47%-89%).*
BCS vs. EH-SVT; Different JAK2 allele burden

EH-SVT has higher JAK2 V617F allele burden than BCS

Homozygous JAK2 mutation higher in EH-SVT
MPN-SVT present with distinctive features

- SVT present at younger age than ET, PV or MF (mean 44 years)
- F>M (F 64%:M 34%)
- Large proportion have normal counts (~40%)
- They have low JAK2 V617F allele burden

- BCS and extra-hepatic vein thrombosis are different at the molecular level

- High frequency of additional myeloid mutations
Recurrently mutated genes

Nangalia et al 2013
**Additional mutations by Next Generation Sequencing**

**A.** (Number of patients with each mutation in NGS-MPN panel for 25 genes

**B.**

<table>
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<tr>
<th>No. Additional mutations plus JAK2 V617F</th>
<th>% of MPN SVT patients</th>
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<tbody>
<tr>
<td>1</td>
<td>34.1%</td>
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<tr>
<td>2</td>
<td>11.4%</td>
</tr>
<tr>
<td>3</td>
<td>1.0%</td>
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<tr>
<td>Patients with additional mut. 24/44</td>
<td>54.5%</td>
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Diagnostic Algorithm

- JAK2/CaIR mut+
  - BM biopsy
  - MPN-SVT
    - (with subdiagnosis and risk stratification)

- Mutation negative
  - BM biopsy?
    - MPN-SVT in 5%-10%?
      - Other diagnosis
        - Genetic screening (NGS panels)?
    - MPN-SVT

Investigations

- FBC
- Blood Film
- EPO
- JAK2/CALR/Mpl
- Iron studies
- PNH
- LAC/ACA
- (Thrombophilia screen)
- BM biopsy
- Red cell mass
Therapy of thrombosis and MPN: basic principles

1. Indefinite anticoagulation is recommended in the presence of continuing risk/unprovoked (NICE 2012; Kearon et al. 2016; Watson et al. 2015)

1. Thrombosis in MPN is high risk and should be cytoreduced. (BCSH, McMullin 2018, ESMO, Vannucchi 2018)

**MPN-SVT**

- Increased counts
  - Cytoreductive therapy
    - (Hydroxycarbamide, IFN, Jak inhibitor depend. on subtype)

- Normal counts
  - No data Targets?
    - One approach is to target Hct <42 and PLts < 20 based on an IFN trial
A Multidisciplinary Approach is required

- Interventional radiology
  - TIPSS
- Hepatology/GI
  - Beta Blockers
  - HCC & varices
    surveillance (endoscopy)
  - Liver transplantation
  - Nutritional support
    for bowel resection
- Anticoagulation
  - LMWH /Warfarin
  - Anti-platelet agents?
- Cytoreductive therapy for MPN and FU
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