PNH and Thrombosis

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Thrombosis and PNH

- How blood clots form normally
- How unwanted blood clots form
- Consequences of abnormal blood clots
- Sites of abnormal blood clots in PNH
- Symptoms of blood clots
- Why blood clots form in PNH
- Treatment and prevention
Tendency to clot inappropriately

- Hypercoagulability
- Hypercoagulable state
- Thrombophilia
- Thrombotic tendency
- Pro-thrombotic state
- Clotting tendency

All mean the same thing
Blood clot at the site of a broken vessel

- Clotting factor
- Platelet
- Fibrin

Red blood cell
Red cells moving in a blood vessel
Red cells caught in a web of fibrin
Normal blood clotting stops bleeding
Abnormal blood clotting

- Starts when there is no trauma to the vessel
- or an exaggerated response to trauma
- Can partially or completely block the vessel
Blockage of blood vessels slows down the flow

- Slow flow leads to more clotting
- Clot begets clot
Tissue factor

Coagulation cascade
Many different proteins are involved

Tissue factor
We do not know which of these proteins is Affected by PNH to produce a tendency to clot
Abnormalities in any one of these proteins can produce a tendency to bleed (hemophilia).

Tissue factor
Anticoagulants* work to prevent the action of some of these Proteins, to mimic hemophilia in a way

*Often called blood thinners, actually not a good name for them

Tissue factor

Site of action of coumadin

Site of action of low molecular weight heparin
Or Arixtra (Fondaparinux)

Site of action of clot busting drugs
(TPA)
There is a Naturally occurring Anticoagulant system

Tissue factor

Sites where the anticoagulant Proteins work
clot

artery

capillary

vein
Clot in artery:
Tissue does not get any blood flow: heart attack or stroke
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Clot in a vein. Blood can not get out of the capillaries, the tissue behind it swells up.
Clot in a vein. Blood cannot get out of the capillaries, the tissue behind it swells up.
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Causes of abnormal blood clots

- Infection
- Trauma
- Cancer
- Pregnancy, Oral Contraception, Estrogen replacement
- Genetics
- Blood diseases
- Immobilization (airline flights)
  -- red cell diseases: PNH, polycythemia vera, sickle cell disease
  -- lupus anticoagulant
## Blood Clots in PNH Patients

**(Hillmen NEJM 1996)**

*(Largest single cause of death of PNH patients)*

<table>
<thead>
<tr>
<th>Intraabdominal</th>
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<tbody>
<tr>
<td>Hepatic Vein</td>
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<tr>
<td>Inferior Vena Cava (IVC)</td>
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<tr>
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<tr>
<td>Renal Vein</td>
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<tr>
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<table>
<thead>
<tr>
<th>Other veins</th>
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<tr>
<td>Cerebral Veins</td>
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<tr>
<td>Pulmonary Veins</td>
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<tr>
<td>Deep Veins of Legs</td>
<td>7</td>
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<tr>
<td>Superficial Veins</td>
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<table>
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<tr>
<th>Arterial</th>
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<tr>
<td>Heart Attacks (MI)</td>
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<tr>
<td>Stroke (CVA)</td>
<td>2</td>
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</tbody>
</table>

_Hillmen et al 1996_
BUDD CHIARI SYNDROME
Sonogram of the Abdomen

clot

LIVER
Watt BJ Haematol 2007 Dermal thrombosis in a PNH patient
Normal Magnetic Resonance Venogram

- Superior Sagittal Sinus
- Inferior Sagittal Sinus
Superior & Inferior Sinus Thrombosis
Retinal Vein Thrombosis

Fig. 1 Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare haemolytic anaemia leading to a variety of symptoms including the triad of anaemia, thrombocytopenia and cytopenia: a, c, d show OD and b, d, f OS; c-f show the records of fluorescein angiography, after 1 min (c, d) and after 12 min (e, f). PNH may lead to macular oedema, scar formation due to toxoplasmosis (b). Retinal occlusions can be found on both eyes (c, d, arrows). OD and OS demonstrate mild pallor of the optic discs (a, b) and macular oedema (a, c, d). The macular scar on OS is related to an Toxoplasmosis infection in childhood and not caused by PNH.
Deep Vein thrombosis (DVT)
Deep Vein thrombosis (DVT) moving to the lung (pulmonary embolus, PE)
Symptoms of Blood Clots

DVT:
- leg swelling, difficulty walking

Pulmonary embolus
- difficulty breathing
- pain on taking a deep breath

Sudden onset
Fainting
Cough
Coughing up blood
Symptoms of Blood Clots

Abdominal Veins
-- Abdominal swelling
-- rapid water weight gain
-- yellow eyes (jaundice)
-- abdominal pains

Splenic Vein
-- sudden drop in platelet count
Symptoms of Blood Clots

Veins of Brain
-- Visual changes
-- difficulty speaking
-- loss of strength in an arm or leg
-- headache
• Most of these symptoms can occur in PNH due from time to time anyway

• Some of these symptoms can occur in normal people

• How can the patient know if this is a symptom of a clot or a false alarm?
Low threshold for radiologic tests

- It is better to get 10 X-rays that have normal findings than to miss a serious blood clot.

- Over time, most patients with PNH will recognize their usual symptoms and be able to distinguish them from something more serious.
Why clotting in PNH

- Hemolysis
- Platelets are affected by complement
- Two parts of the anti-clotting system are affected on white cells of patients with PNH
marked worldwide differences

• high rates reported to occur in the United States, Europe and India

• much lower rates in Mexico, Japan, China, and Thailand
Ethnicity as a risk factor for thrombosis and death

Araten et al 2005
Risk of Thrombosis: Small PNH versus Large PNH clones

Araten et al 2005
Second Thrombosis in Anticoagulated Patients
Management of Blood Clots

An ounce of prevention is worth a pound of cure

--Coumadin
--Low Molecular Weight Heparin (Lovenox)
--Fondaparinux (Arixtra)
--Eculizumab
Coumadin

- Some clotting factors depend upon vitamin K
- Coumadin acts against Vitamin K
- Dose is balanced against the intake of Vitamin K in the diet
- Bacteria make vitamin K in the intestines
- Different people eat different foods
- Different people metabolize the drug differently
Coumadin

- No one dose of Coumadin is right for everyone
- No one dose of Coumadin will always be right for the same person
- Effect monitored by the clotting time (PT, INR, ProTime)
Clotting Times

Pro-Time:
Blood is sent to the lab
How many seconds does it take to make a clot
(normal might be 10 seconds)

INR (International normalized ratio)
Patient’s Pro-Time (e.g. 20 secs) divided by the
normal Pro-Time (10 secs). So the INR might be 2

INR <1.2 no effect
INR 1.3 to 1.5 not enough effect
INR 1.5 to 1.8 Almost enough effect
INR 1.8 to 3 Desired effect [more or less]
INR > 3 too much of an effect
INR >4 May be dangerous,
INR >5 may need to go to the ER
Coumadin Doses

Typically require adjustment when:
-- starting new drugs
-- especially antibiotics
-- change in diet
-- feeling unwell
-- most patients will need blood work 3x per week when first starting coumadin
-- eventually down to once every 3 weeks

Coumadin takes days to work, changes in doses on a Monday may not affect the INR until Wednesday. Takes days for the effect to wear off.
Frequent blood drawing to monitor effect of Coumadin on The Pro-Time
Initial hypercoagulability when coumadin is first started (!)

- Opposite of desired effect
- Can occur within a few hours
- Usually this occurs before the INR reaches 1.8 to 2
- Can be prevented by giving injectable anticoagulant until the anti-coagulant effect starts to work (bridging)
Coumadin

- Shouldn’t be taken during pregnancy
- Bleeding risk
- Effect can be reversed instantly by giving plasma transfusion
- Effect can be reversed within a few hours by giving vitamin K
- Reversal should be done if patient is bleeding or if the INR drifts up very high
Why take Coumadin at all?

- Tried and true
- Millions of Americans on Coumadin
- 1% bleeding risk per year
- Shown in a British trial to prevent blood clots in PNH patients
- Better oral drugs are on the horizon
Injectable anticoagulants

- Old Fashioned Heparin: recent manufacturing disaster
  -- can lower the platelet count, sometimes in a dangerous way

- New (Low Molecular Weight) Heparin
  --lovenox, fragmin. Possible to monitor by a special coagulation test, not always necessary. Much more predictable. Probably should be given twice a day for best effect

--Fondaparinux (Arixtra) Like Lovenox. Longer half-life. Given once a day.

Bone loss
Bleeding risk
Not easily reversible
On the other hand, unlike coumadin, much less likely to have an unintended overdose. Dose based on weight, predictable effect
In 3 years, all of these drugs may be obsolete…
Who should be on anticoagulation to prevent blood clots?

Anyone who has already had a clot (even if it is picked up on a screening MRI Or CAT scan)

Pregnancy, anyone who is unable to avoid oral contraception

Anyone who has another reason in addition to PNH to have a clot
-- temporary (surgery, airline flight)
-- genetic risk factors

Anyone who has a PNH clone size large enough to confer risk of clotting
(Dark urine? Requiring transfusions? High LDH? >10% PNH red cells, >20-50% PNH granulocytes
Additional Risk Factors for Blood Clotting

• Protein C deficiency
• Protein S deficiency
• Antithrombin III deficiency
• Factor V Leyden
• Prothrombin gene mutation

• Pregnancy

Antiphospholipid antibody
(lupus anticoagulant, anti beta 2 glycoprotein 1 antibody, anti cardiolipin antibody test)

Family members who have had blood clots
Who should NOT be on anticoagulation to prevent blood clots?

High bleeding risk (e.g. blood in stool-- everyone should be tested first for this)

Patient at high risk for trauma (professional ice hockey players)

Low platelet count (for example, less than 50 for primary prevention, less than 20 for prevention of a second blood clot)

Small PNH clone size (Aplastic Anemia with small PNH clone, “AA/PNH”)

Patients on Eculizumab who have never had a blood clot (?)
Reversal of blood clots

Clot busting drugs
Fibrinolysis
Thrombolysis
Tissue plasminogen activator
TPA

Activates the patient’s own system for removing clots

Much more effective when given early after the start of a clot

These drugs are also given for heart attacks and strokes

Different dosing for venous thrombosis in PNH patients
Who should be considered for thrombolysis

- Anyone with a recent blood clot in the brain or abdomen
- Any serious pulmonary embolus
- Any life threatening clot
Sonogram: Portal Vein

Before TPA

After TPA
Tissue plasminogen activator for hepatic vein thrombosis in PNH

ABSTRACT:
Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal disorder thought to arise in a multipotent haemopoietic stem cell. A distinct clinical feature is a tendency to thrombosis, with a particular predilection for the hepatic veins (Budd-Chiari syndrome). We report here on two patients with PNH who developed hepatic vein thrombosis (HVT) and who were treated with tissue plasminogen activator (t-PA). Both patients had a marked clinical and radiological improvement following the t-PA treatment and remain well over 2 years and 6 years after the treatment. This method of thrombolysis for HVT occurring in PNH has only been reported in two previous patients with limited follow-up. We suggest that this therapy is a useful first-line treatment for PNH patients who develop HVT.
Prevention of thrombosis in PNH

- Warfarin as primary prophylaxis (Hall et al 2003)

- Eculizumab (anti C5 monoclonal antibody, Hillmen et al 2007)
  - 7 events per 100 patient years (untreated)
  - 1 event per 100 patient years (on treatment)
  - 1 infectious complication (meningococcemia) per 100 patient years of treatment
### Fewer Thrombotic Events With SOLIRIS

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<th>SOLIRIS Treatment</th>
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</tr>
<tr>
<td>Thrombotic Events</td>
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<td>3†</td>
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<tr>
<td>Cumulative Observation Period</td>
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<td></td>
</tr>
<tr>
<td>(patient-years)</td>
<td>272</td>
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- On an individual patient basis, pre-treatment and SOLIRIS-treatment periods were matched
  - Duration of SOLIRIS treatment was used to define the duration of the pre-treatment period
- Thrombotic events were defined by MAVE criteria based on an intent-to-treat analysis
- Majority of patients (63%) received concomitant anticoagulant therapy
- The effect of anticoagulant withdrawal was not studied

*N = 195 Soliris-treated patients: 11 Pilot; 43 TRIUMPH (SOLIRIS group); 44 TRIUMPH (placebo patients who crossed over to SOLIRIS treatment upon entering the extension); 97 SHEPHERD.†P < 0.001.

MAVE = Major adverse vascular event.
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Recommendations regarding Eculizumab (Soliris) and anticoagulation

Patients who have had blood clots and are at high risk of recurrence should really be on Eculizumab (e.g. patients who have had two blood Clots, genetic or other risk factors in addition to PNH)

Patients who have had blood clots even if no increased risk should probably be on Eculizumab, provided that they will be able to manage the risk of infection in a responsible manner

Patients who are on Eculizumab who have never had a blood clot (and have negative MRvenogram studies proving this) probably do not also need anticoagulation
When considering whether Eculizumab or Anticoagulation is more appropriate for preventing clots, consider that the risk of bleeding on anticoagulation (about 1% per year) is similar to the risk of meningococcal infection in patients on Soliris. However, for individual patients, one may be of greater concern than the other.
Questions regarding Eculizumab (Soliris) and anticoagulation

Is Eculizumab or Coumadin better at preventing clots in patients with PNH in patients who have never had a clot?

Is Eculizumab safe in pregnancy

Would eculizumab make pregnancy safer?
Recent Improvement in Survival of PNH patients

De Latour et al. *BLOOD* June 2008