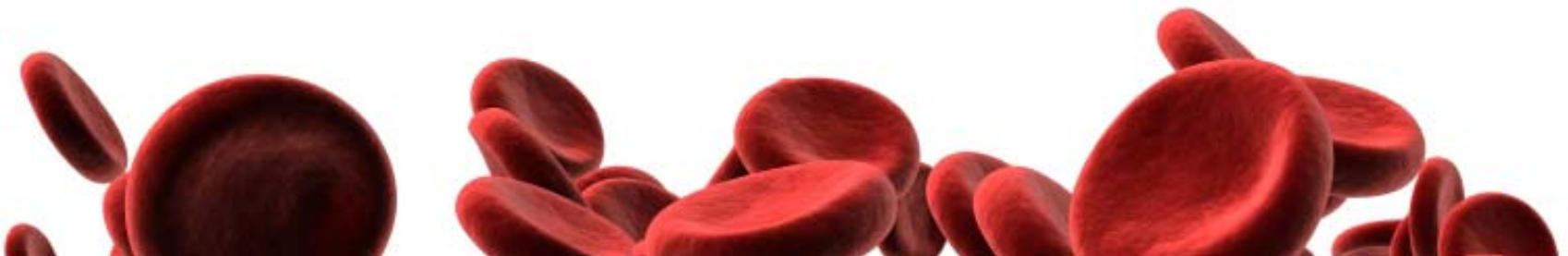
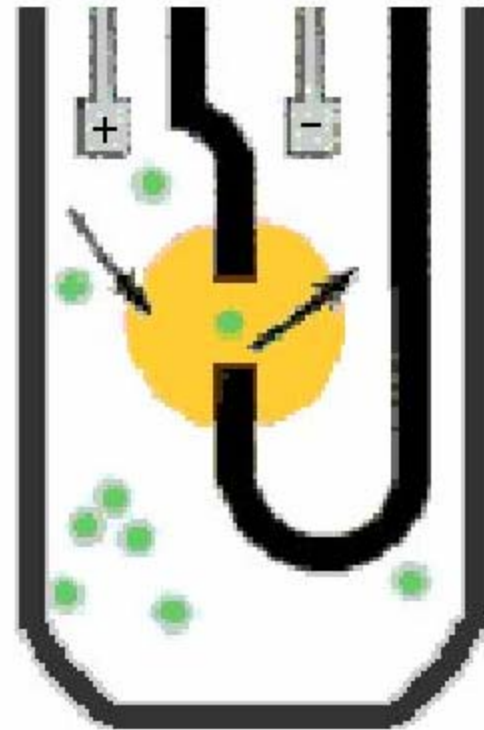


- Unexplained macrocytosis is a frequent finding in routine full blood count analysis
- The differential diagnosis is broad including important “not to be missed diagnoses”
- Recent laboratory developments include better ability to define “true” vitamin B12 deficiency



# Macrocytosis

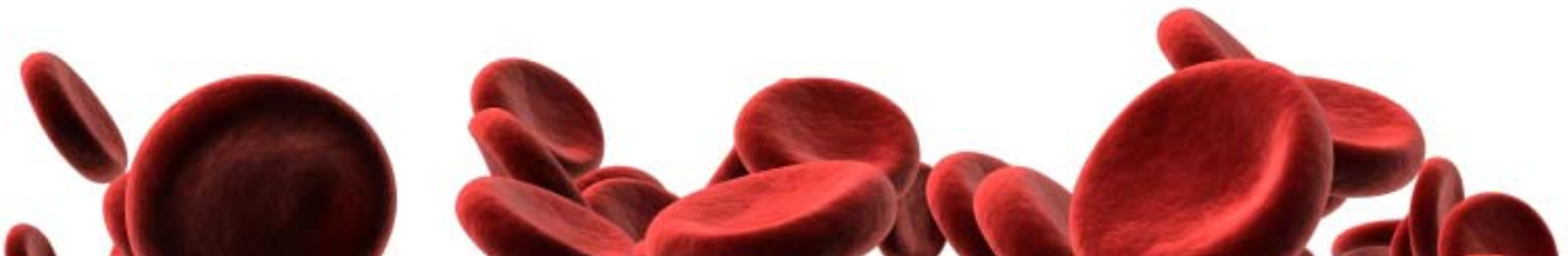
- Full blood COUNT
  - Relies on Coulter principle
  - Simply counts and sizes red cells by impedance method



# Macrocytosis

---

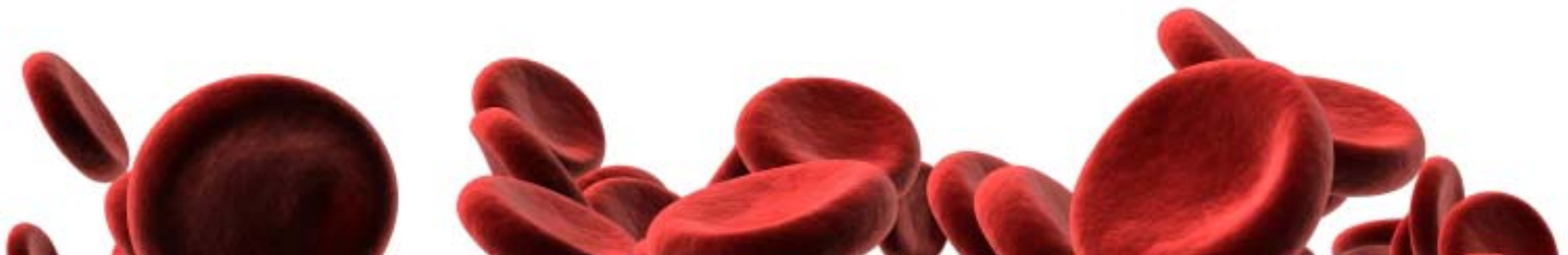
- Common causes of macrocytosis
  - Medications 37%
  - Alcohol +/- liver disease 26%
  - Haemolysis 8%
  - Vitamin B12 and folate deficiency 6%
  - Primary marrow disorders 6%
  - Non alcohol liver disease 6%
  - Other (Pregnancy, Hypothyroidism) 3%
  - Not established 7%



# Macrocytosis

---

- Common causes of macrocytosis
  - Medications 37%
  - Alcohol +/- liver disease 26%
  - Haemolysis 8%
  - **Vitamin B12** and folate deficiency 6%
  - Primary marrow disorders 6%
  - Non alcohol liver disease 6%
  - Other (Pregnancy, Hypothyroidism) 3%
  - Not established 7%



## Diagnostic Approach (1)

---

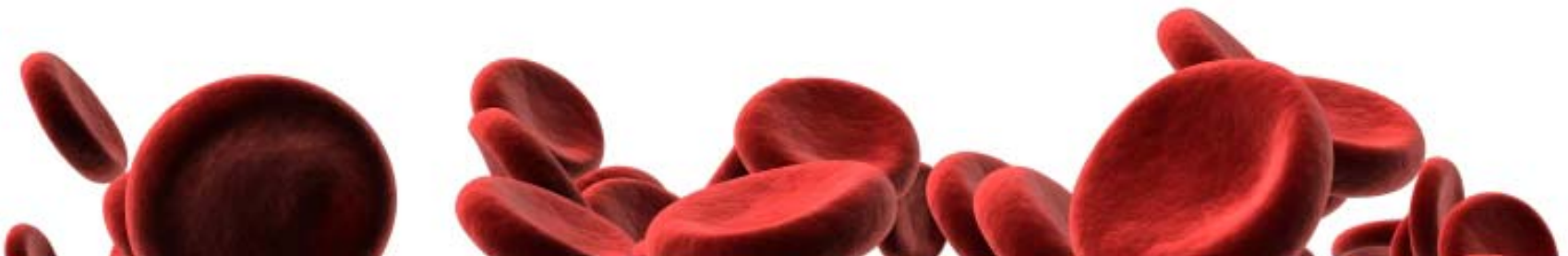
- Liver function tests, a serum VB12 measurement, reticulocyte count, and review of the blood film are recommended in all patients.
- Diagnostic clues
  - Alcoholism, hemolytic anemia or bleeding, drugs and abnormalities on physical examination, such as jaundice, glossitis, or neuropathy.
  - Findings of cytopenias may reflect an underlying marrow disorder and lead to immediate examination of the bone marrow.



## Diagnostic Approach (2)

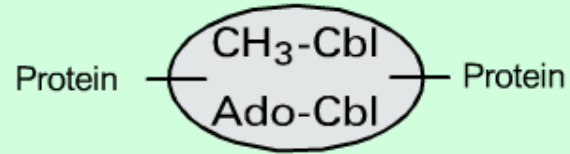
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- In the remaining patients, the primary question is whether the macrocytosis is caused by VB12 deficiency.

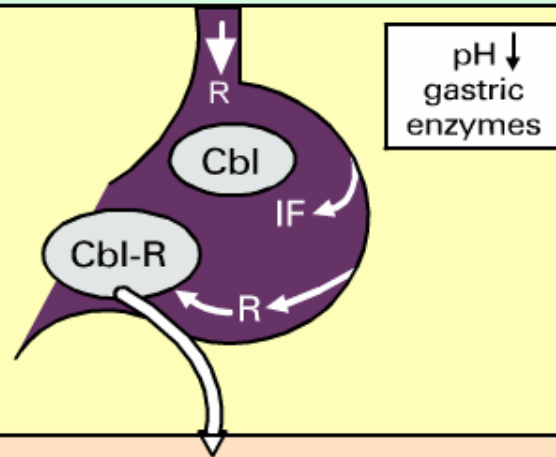


# Cobalamins

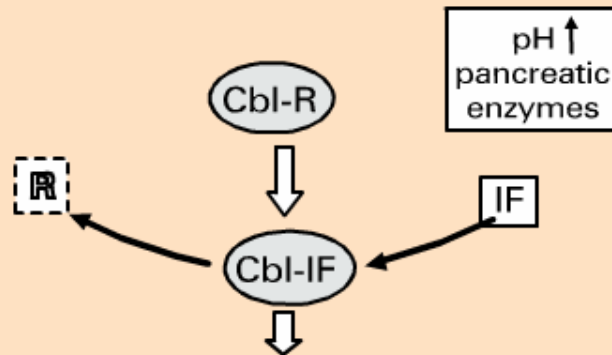
Food



Stomach



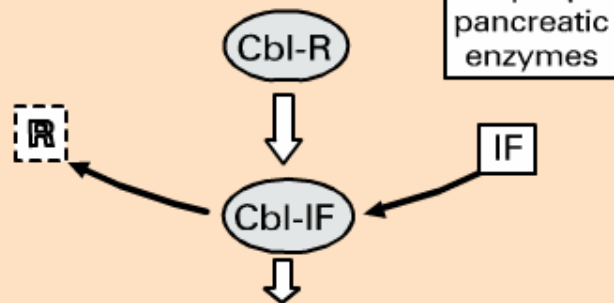
Duodenum



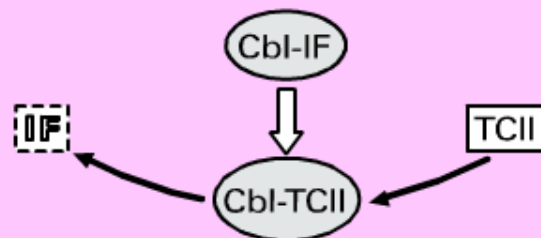
Hide Full Screen

# Cobalamins

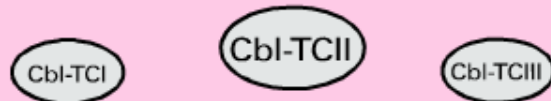
Duodenum



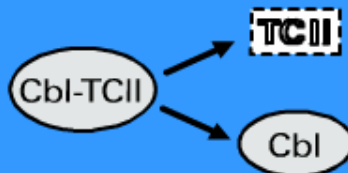
Terminal Ileum Mucosal Cells



Blood



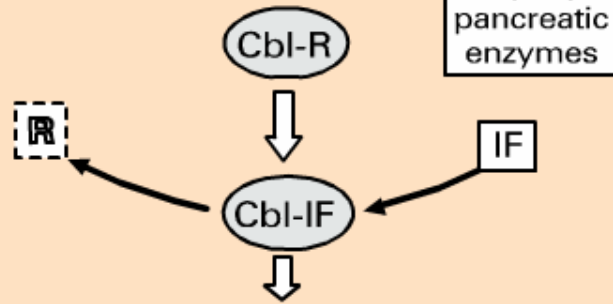
Tissue Cells



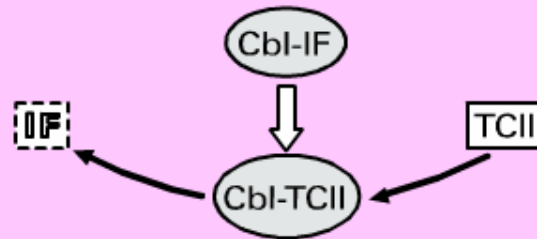
Hide Full Screen

# Cobalamins

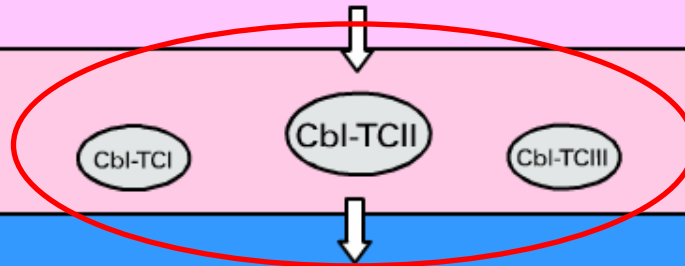
Duodenum



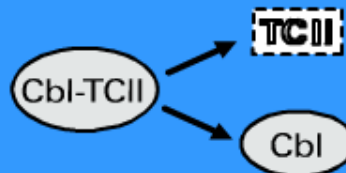
Terminal Ileum Mucosal Cells



Blood



Tissue Cells



Hide Full Screen

## Diagnostic Approach (3)

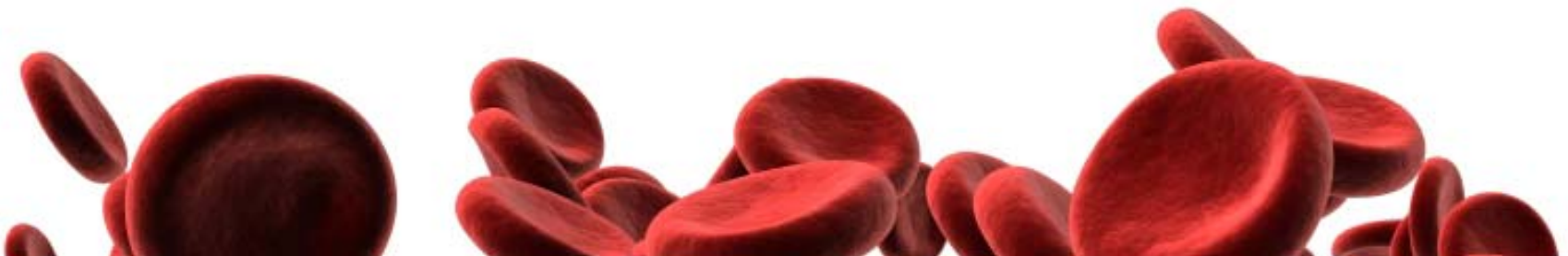
- Assessment of Vitamin B12 status difficult
  - “Serum B12” measures B12 bound to TC I TC II and TC III but only TC II is “Active B12” (also called HOLO TC II).
- **Melbourne Pathology now offer Active B12 routinely (no additional cost) and may provide more accurate measure of tissue vitamin B12 deficiency**



## Diagnostic Approach (4)

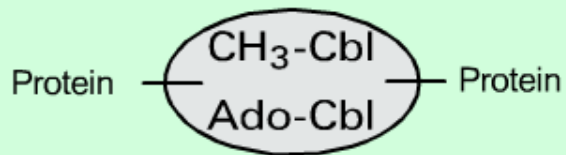
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- Once Vitamin B12 deficiency has been identified then cause of deficiency needs elaborating

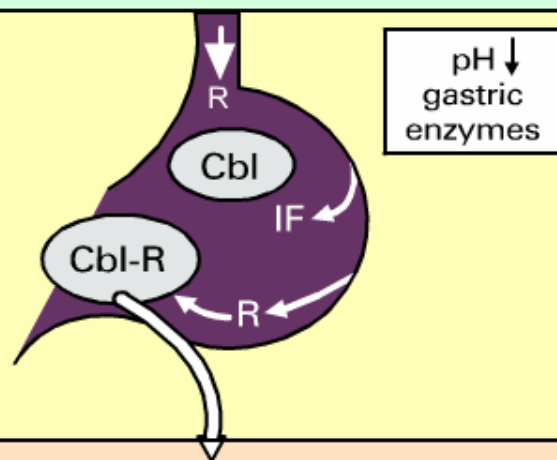


# Cobalamins

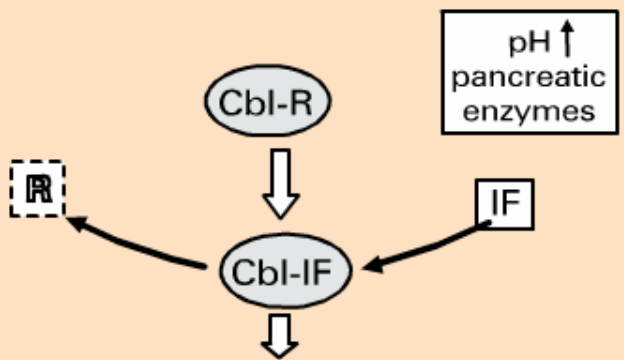
Food



Stomach



Duodenum



Dietary Deficiency in strict vegans (rare)

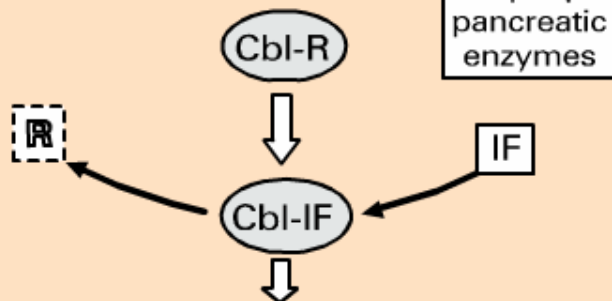
↓  
Pernicious Anaemia, post gastrectomy, atrogenic achlohydria

↓  
Pancreatic disease

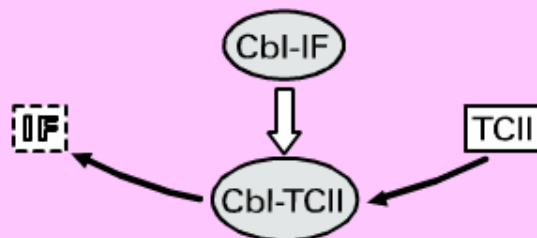
Hide Full Screen

# Cobalamins

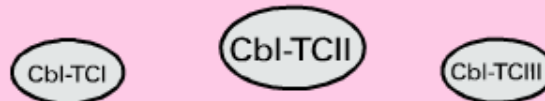
Duodenum



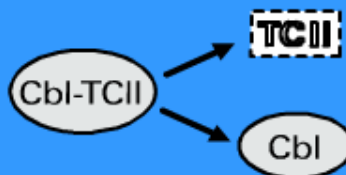
Terminal Ileum Mucosal Cells



Blood



Tissue Cells

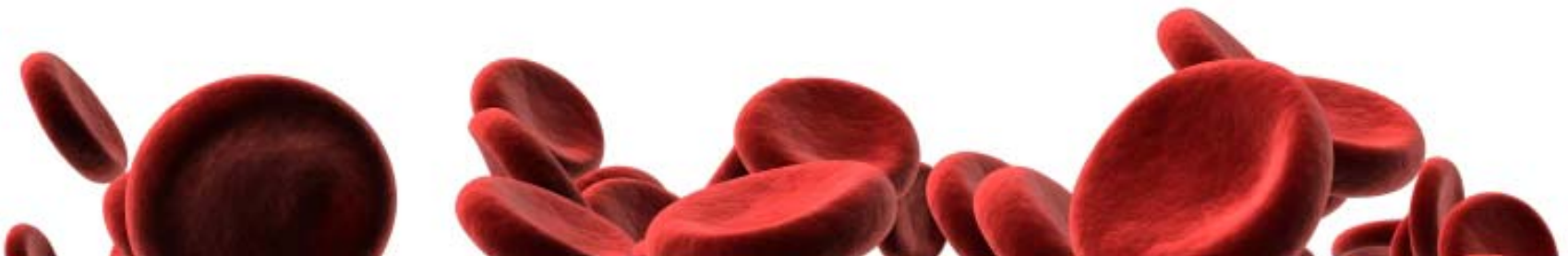


↓  
Gastrointestinal causes  
IBD  
Bacterial overgrowth  
↓  
↓  
↓  
Congenital TCII deficiency

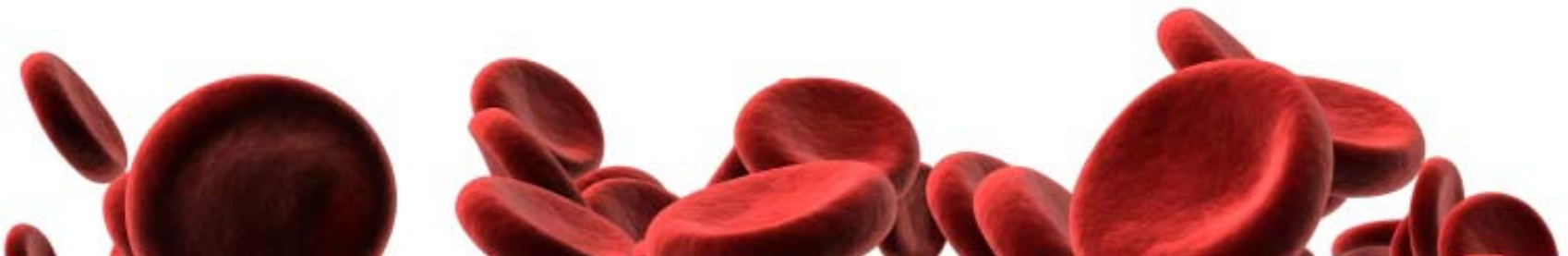
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## Diagnostic Approach (4)

- Antiparietal cell antibodies
  - 80% of patients with PA but 40 – 50% with other organ specific autoimmune disorders (more sensitive, less specific)
- Anti IF antibodies
  - 70% of patients with PA (more specific but less sensitive)



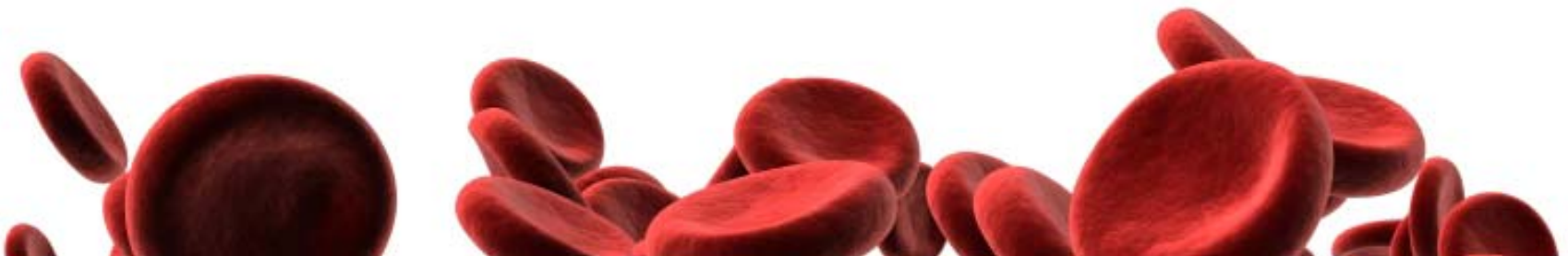
- The clinical scenario of a patient presenting with a DVT is not uncommon
- How to investigate and how long to treat these patients can be difficult
- There is a potential rational approach to the decision of duration of treatment in patients with DVT



# Introduction

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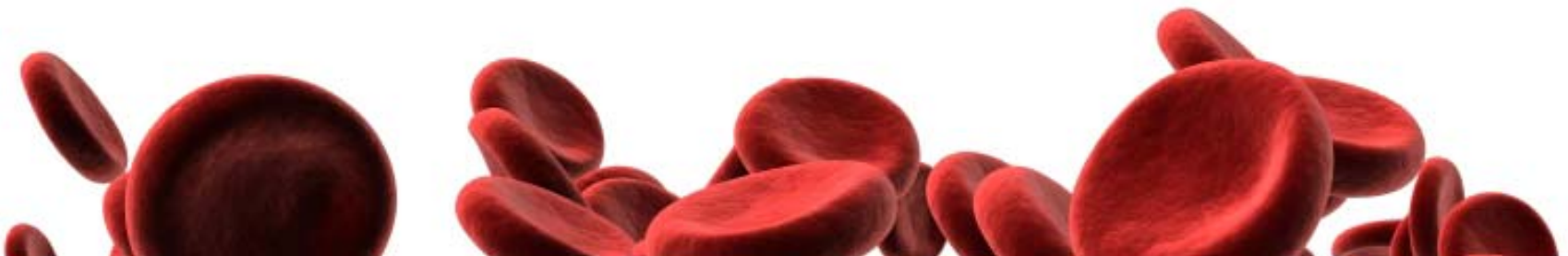
- Epidemiology
  - Common
  - General population: 0.1%
  - Elderly: 1%
  - Hospitalized patients: 15%



# Diagnosis of First Episode DVT

---

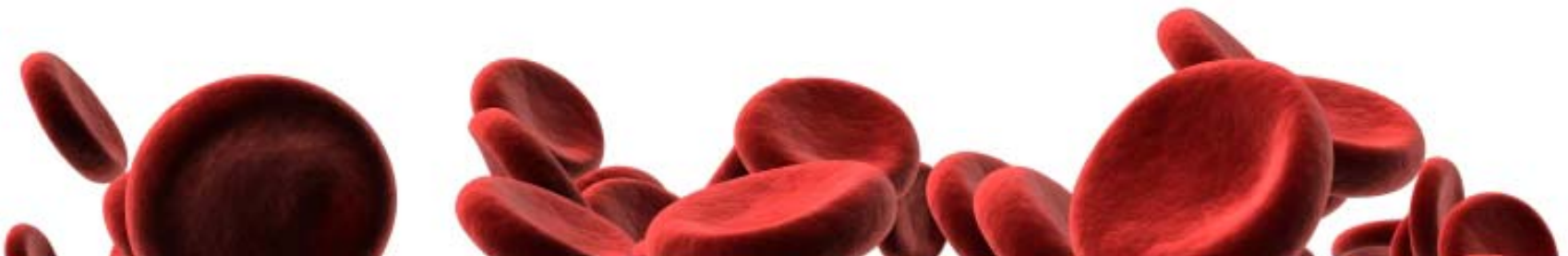
- Symptoms of DVT are sensitive but not specific for the presence of DVT
  - Only 25% of patients with symptoms suggestive of DVT will have DVT
  - Treatment is available but not appropriate to be given to all patients with suspected DVT



# Diagnosis of First Episode DVT

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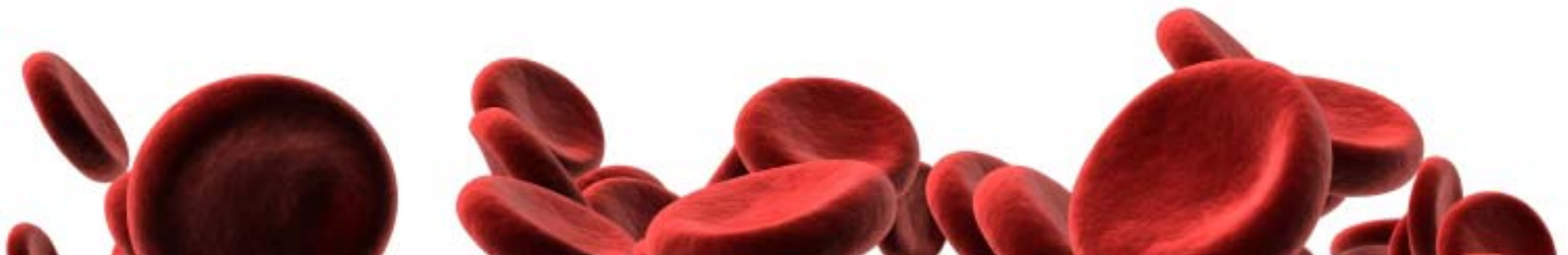
- Clinical Assessment
  - Typical symptoms
    - Exclude other causes (MS causes, cellulitis)
  - Look for risk factors
    - Malignancy
    - Recent major surgery or immobilization
    - Pregnancy, post partum and hormonal agents
    - Thrombophilia
    - Obesity smoking and long distance flights (weak risk factors)



# Initial Objective Testing

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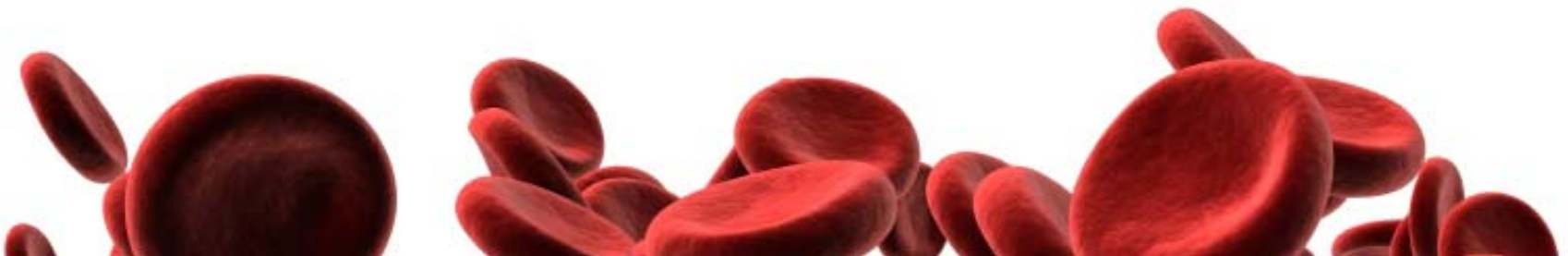
- Venous ultrasonography
- D-Dimers



# Pregnancy and Suspected DVT

---

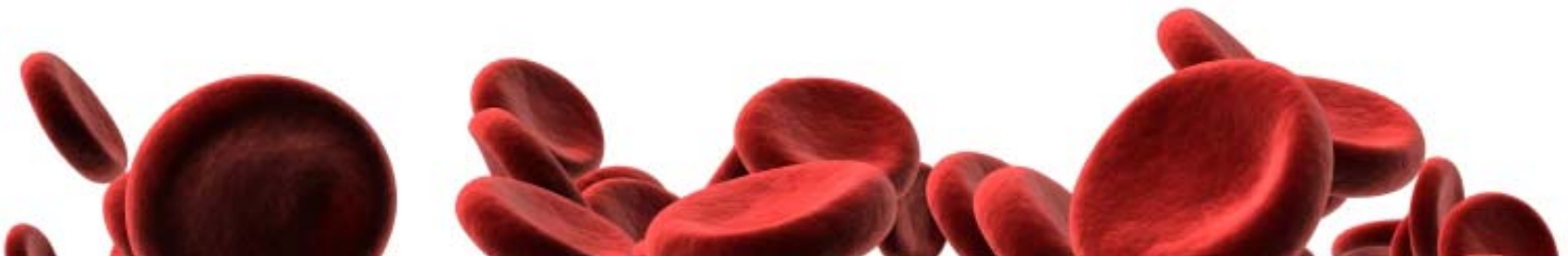
- Common cause of non obstetric maternal death
  - Majority left leg and may be isolated to the ileofemoral
  - Related to changes in haemostasis / venous stasis
- Diagnosis can be difficult
  - Ultrasound preferred investigation
  - Venography in cases where ultrasonography not helpful



# Initial Treatment DVT

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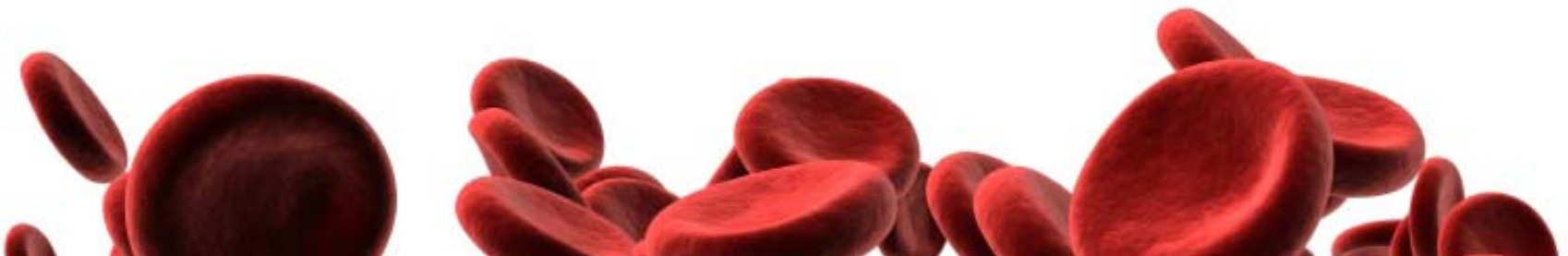
- LMWH as effective as UH
  - Supported by multiple large meta-analyses
  - Monitoring in patients with renal disease, pregnancy or morbidly obese
  - Home treatment available for 80% of patients
- UH for more complex patients



# Long-term Anticoagulation

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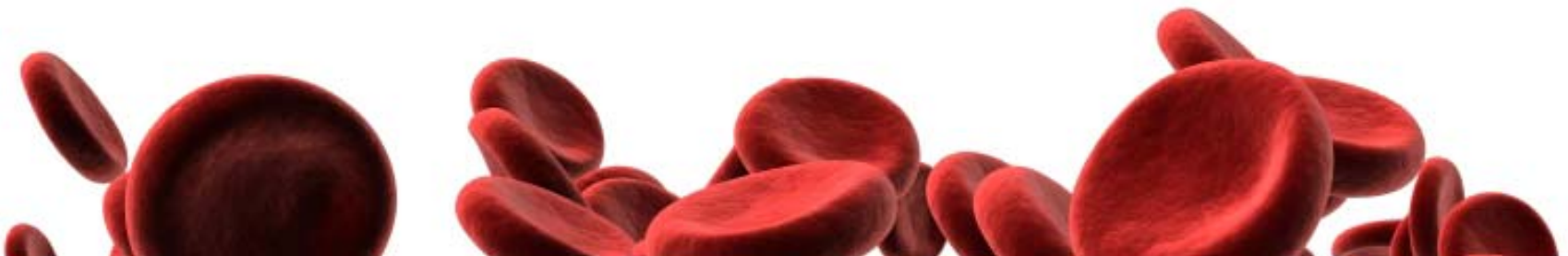
- Warfarin to start on first day of heparin
  - No loading dose
  - INR the day after the first dose of warfarin
- Long-term LMWH an option in patients with recurrent DVT despite adequate oral anticoagulation
- Cost and side effects of long-term LMWH



# Duration of Anticoagulant Therapy

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- Duration of therapy determined by competing risks of bleeding and thrombosis
- Bleeding risk of LMWH 2 – 5% and 1 – 3% with warfarin per year of treatment
  - 20% of bleeds are fatal
  - Greater risk in patients just started treatment
  - Estimated to need a 12% annual risk of recurrent thrombosis to justify prolonged anticoagulation

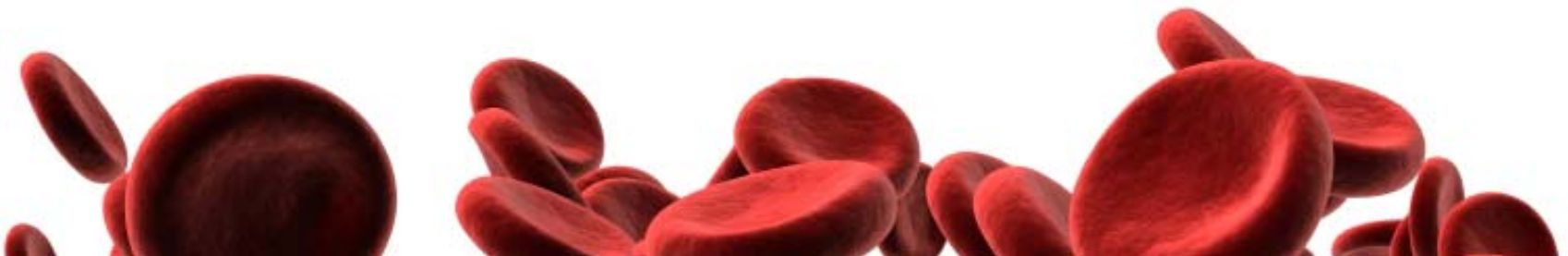


- **Low risk** 3 months
  - Reversible major risk factor (major surgery)
  - 4-5% risk of recurrence within the next 12 months
  
- **Moderate risk** 6 months
  - Weak risk factor (OCP, travel, minor trauma) and no thrombophilia
  - <10% recurrence within 12 months after ceasing anticoagulation
  
- **High** 6-12 months
  - Unprovoked event with no thrombophilia (or with FVL / prothrombin gene mutation)
  - Approximately 10% risk of recurrence within 12 months
  
- **Very high** Extended
  - Recurrent unprovoked
  - Unprovoked with major thrombophilia (AT, PC, PS def. homozygous FVL, APA, Advanced malignancy)
  - > 12% risk annually

# Thrombophilia Screening

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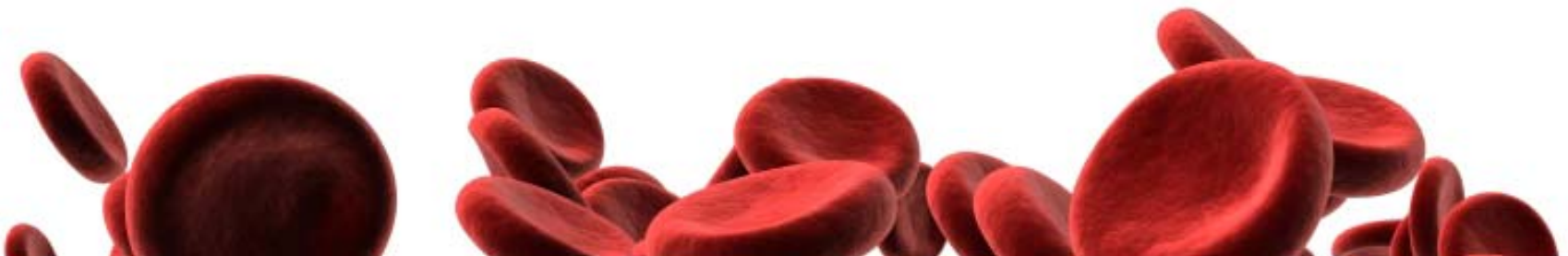
- Appropriate to provide screening if
  - Unprovoked event occurs in patients less than 50 years of age
  - History of two or more unprovoked event
  - Strong family history (first degree relative with documented unprovoked thrombosis)
  - Women with unexplained pregnancy loss



# Thrombophilia Screening

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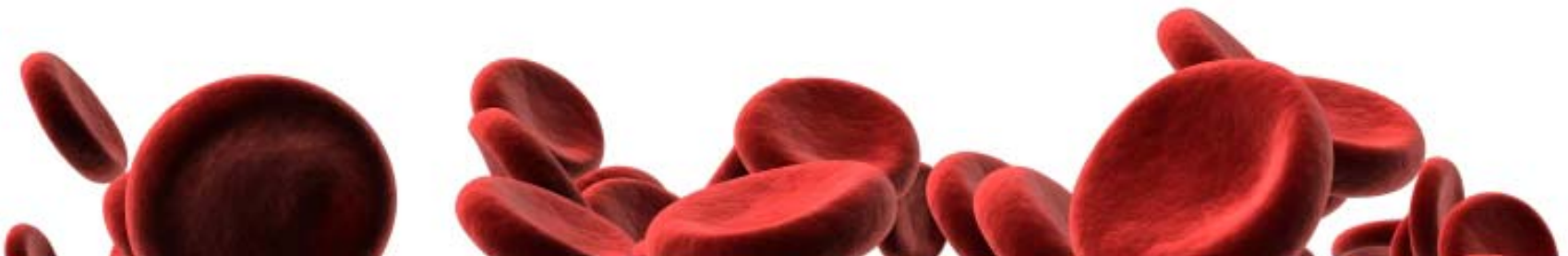
- Factor V Leiden
- Prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency



# Factor V Leiden

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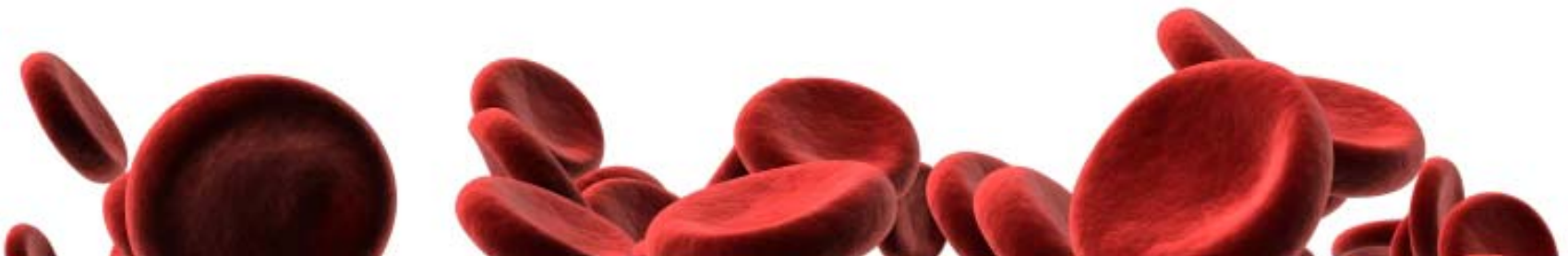
- Factor V Leiden
  - (Activated protein C resistance)
  - 4% of Caucasian population
  - Reduced blood loss with periods / child birth
  - Heterozygote 8 fold increase in thrombosis, homozygote 80 fold increase



# Prothrombin Gene Mutation

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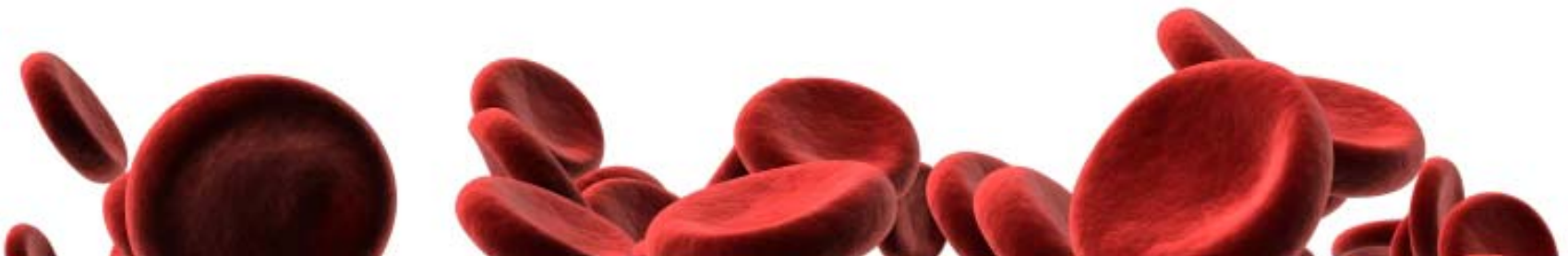
- Prothrombin gene mutation
  - Likely leads to increased levels of prothrombin and therefore reducing the threshold for pathological thromboisis
  - Present in 2% of population
  - Associated with 3 – 4 fold increase in the risk of thrombosis



# Protein C Deficiency

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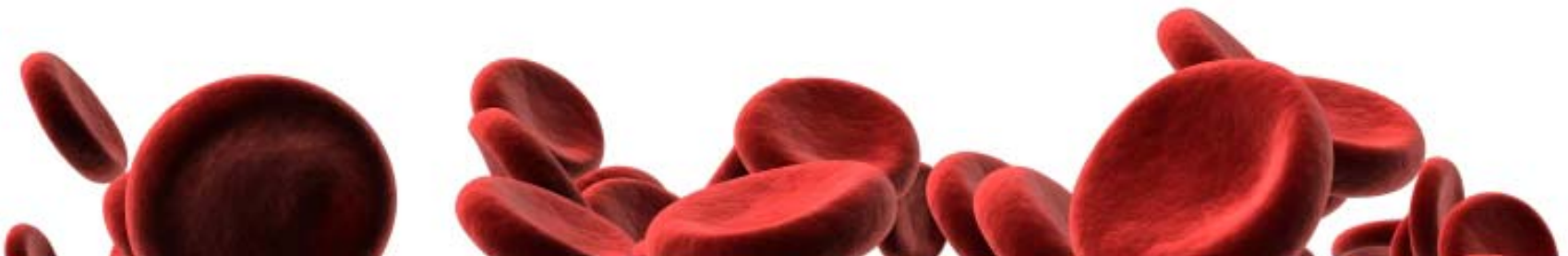
- Protein C deficiency
  - Protein C “natural anticoagulant”
  - Heterozygote deficiency up to 0.5% of population associated with an increased risk of thrombosis
  - Deficiency associated with an up to 10 fold increased risk in thrombosis



# Protein S Deficiency

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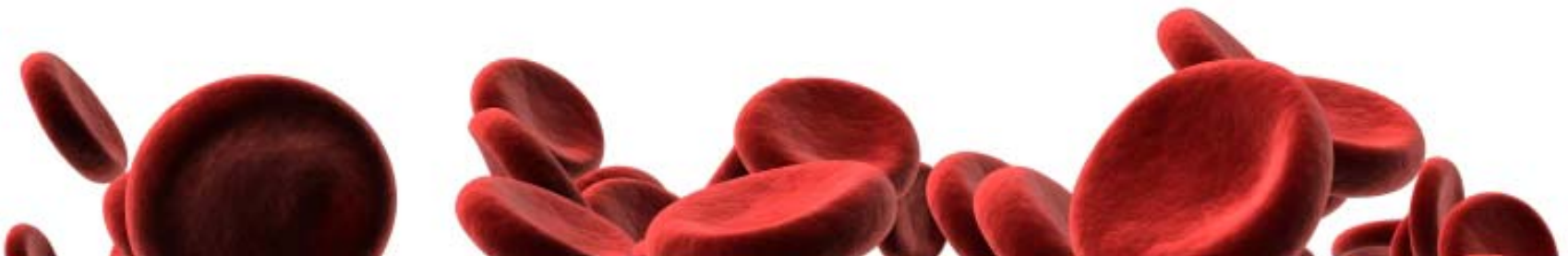
- Protein S Deficiency
  - Protein S is a “natural anticoagulant”
  - Incidence of heterozygote deficiency around 1.3% of population
  - Associated with a 3 fold increased risk in thrombosis



# Antithrombin Deficiency

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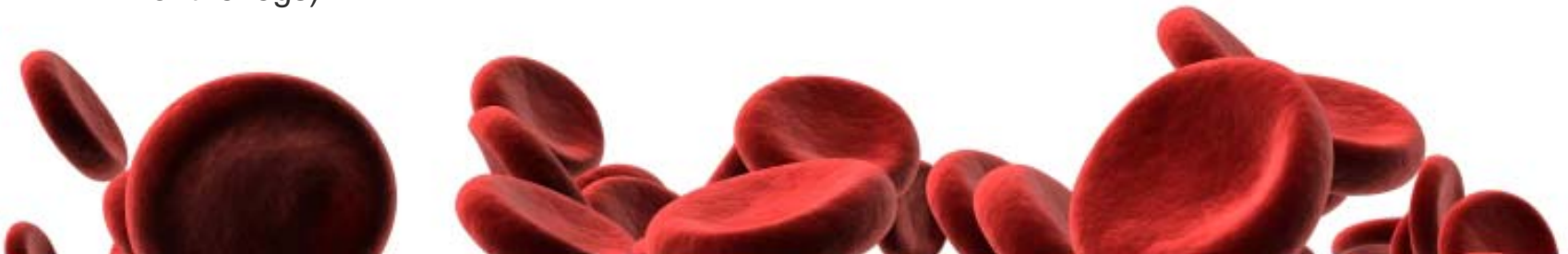
- Antithrombin deficiency
  - “Natural anticoagulant”
  - Incidence of 0.02% population
  - Increased risk of thrombosis up to 50 fold



# Graduated Compression Stockings

---

- Anti-embolism stockings (Pressure at ankle approximately 15 mmHg)
  - Used for light support and prevention of clots developing (e.g. in the setting of long flights or following operations)
- Class 1 Graduated Compression Stockings (Pressure at ankle 20 – 30 mmHg)
  - Used for greater support (e.g. following a patient who has a past history of a clot and may have some minor swelling or ongoing discomfort) Class 1 stockings may also be used to prevent clots in flights.
- Class 2 Graduate Compression Stockings (Pressure at ankle 30 – 40 mmHg)
  - Used when more support is required. Often patients with a recent clot who have significant swelling of the leg would benefit from having greater, Class 2, support
- Class 3 Graduated Compression Stockings (Pressure at ankle 40+ mmHg)
  - Used for maximal support (e.g. when the veins are damaged and there is long term swelling of the legs)



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- ELEVATED SERUM FERRITIN
- FACTOR V LEIDEN
- NEUTROPEMIA
- CLOTS AND FLYING
- PROTHROMBIN GENE
- POST THROMBOTIC SYNDROME
- THROMBOPHLEBITIS
- WARFARIN MANAGEMENT

## DR CHRIS BARNES

MBBS FRACP FRCPA

Paediatric and adult  
non malignant haematology



### Home

## Paediatric and adult non malignant haematology.

Chris Barnes is a consultant clinical and laboratory haematologist at the Royal Childrens and Royal Women's Hospital and is Director of the Henry Ekert Haemophilia Treatment Centre at the Royal Children's Hospital.

Chris has a particular interest in the diagnosis and management of non – malignant adult and paediatric haematological conditions including thrombosis and bleeding disorders.

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