***coumarin***

warfarin is the most common. Coumarins inhibit the vitamin K-dependent factors II, VII, IX and X in the liver.. This is monitored by the INR .Warfarin anticoagulation typically takes 3–5 days to become established, even using initial loading doses. Patients who require rapid initiation of therapy may receive higher initiation doses of warfarin. A typical regime in this situation is to give 10 mg warfarin on the first and second days, with 5 mg on the third day; subsequent doses are titrated against the INR. Patients without an urgent need for anticoagulation (e.g. atrial fibrillation) can have warfarin introduced slowly using lower doses.

The major problems with warfarin are:

• a narrow therapeutic window

• metabolism that is affected by many factors

• numerous drug interactions.

***MV prosthesis require high INR than AV.   
Venous TE→target INR=2.5 While if reccurent=3.5***

Drug interactions are common through protein binding and metabolism by the cytochrome P450 system. Major bleeding is the most common serious side effect of warfarin and occurs in 1–2% of patients each year. Fatal haemorrhage, most commonly intracranial, occurs in about 0.25% per annum.

**Management of warfarin** includes strategies for over-anticoagulation and for bleeding:

• If the INR is above the therapeutic level, warfarin should be withheld or the dose reduced. •If the patient is not bleeding, it may be appropriate to give a small dose of vitamin K either orally or IV (1–2.5 mg), especially if the INR is greater than 8.

• In the event of bleeding, withhold further warfarin. Minor bleeding can be treated with 1–2.5 mg of vitamin K IV. Major haemorrhage should be treated as an emergency with vitamin K 5–10 mg slowly IV, combined with coagulation factor replacement. This should optimally be a prothrombin complex concentrate (30–50 U/kg) which contains factors II, VII, IX and X; if that is not available, fresh frozen plasma (15–30 mL/kg) should be given.

***Antiphospholipid syndrome***

Antiphospholipid syndrome (APS) is a clinicopathological entity in which a constellation of clinical conditions, alone or in combination, is found in association with a persistently positive test for an antiphospholipid antibody.

The antiphospholipid antibodies are heterogeneous and typically are directed against proteins which bind to. In clinical practice, two types of test are used, which detect:

• antibodies which bind to negatively charged phospholipid on an ELISA plate (called an anticardiolipin antibody test)

•those which interfere with phospholipid-dependent coagulation tests like the APTT or the dilute Russell viper venom time (DRVVT; called a lupus anticoagulant test).

***Clinical manifestations***

• Adverse pregnancy outcome

- Recurrent first trimester abortion (≥ 3)

- Unexplained death of morphologically normal fetus after 10 wks’ gestation

- Severe early pre-eclampsia

• Venous thromboembolism

• Arterial thromboembolism

• Livedo reticularis, transverse myelitis, skin necrosis, chorea

***Conditions associated with secondary APS***

• Systemic lupus erythematosus

• Rheumatoid arthritis

• Systemic sclerosis

• Behçet’s syndrome

• Temporal arteritis

• Sjِgren’s syndrome

Targets for antiphospholipid antibodies

• β2-glycoprotein 1

• Protein C

• Prothrombin (may result in Haemorrhagic T)

Clinical features and management

Arterial thrombosis, typically stroke, associated with APS should be treated with warfarin, as opposed to aspirin. APS-associated VTE is one of the situations inwhich the predicted recurrence rate is high enough to indicate long-term anticoagulation after a first event. In women with APS, it is likely that intervention with heparin and possibly aspirin increases the chance of a successful pregnancy outcome.

***Disseminated intravascular coagulation***

Disseminated intravascular coagulation (DIC) may complicate a range of illnesses. It is characterized by systemic activation of the pathways involved in coagulation and its regulation. This may result in the generation of intravascular fibrin clots causing multiorgan failure, with simultaneous coagulation factor and platelet consumption causing bleeding.. There is consumption of platelets, coagulation factors (notably factors V and VIII) and fibrinogen. The lysis of fibrin clot results in production of fibrin degradation products (FDPs), including D dimers.

Underlying conditions

• Infection/sepsis

• Trauma

• Obstetric, e.g. amniotic fluid embolism, placental abruption, pre-eclampsia

• Severe liver failure

• Malignancy, e.g. solid tumours and leukaemias

• Tissue destruction, e.g. pancreatitis, burns

• Vascular abnormalities, e.g. vascular aneurysms, liver haemangiomas

• Toxic/immunological, e.g. ABO incompatibility, snake bites, recreational drugs

Investigations

Measurement of coagulation times (APTT and PT), along with fibrinogen, platelet count and FDPs, helps in the assessment of prognosis and aids clinical decision-making with regard to both bleeding and thrombotic complications.

Management

-Therapy is primarily aimed at the underlying cause.

-These patients will often require intensive care to deal with concomitant issues, such as acidosis, dehydration, renal failure and hypoxia.

-Blood component therapy, such as fresh frozen plasma, cryoprecipitate and platelets, should be given if the patient is bleeding or to cover interventions with high bleeding risk, but should not be prescribed routinely based on coagulation tests and

platelet counts alone.

-Prophylactic doses of heparin should be given, unless there is a clear contraindication. Established thrombosis should be treated cautiously with therapeutic doses of unfractionated heparin, unless clearly contraindicated.

- Patients with DIC should not be treated with antifibrinolytic therapy, e.g. tranexamic acid

***Thrombotic thrombocytopenic purpura***

Like DIC and also heparin-induced thrombocytopenia , thrombotic thrombocytopenic purpura (TTP) is a disorder in which thrombosis is accompanied by paradoxical thrombocytopenia. TTP is characterised by a pentad of findings, although few patients have all five components:

• thrombocytopenia

• microangiopathic haemolytic anaemia

• neurological sequelae

• fever

• renal impairment

It is an acute autoimmune disorder mediated by antibodies against ADAMTS-13. This enzyme normally cleaves vWF multimers to produce normal functional units, and its deficiency results in large vWF multimers which cross-link platelets. The features are of microvascular occlusion by platelet thrombi affecting key organs, principally brain and kidneys. It is a rare disorder ,which may occur alone or in association with

1- drugs (ticlopidine, ciclosporin, aciclovir ,OCP)   
2- SLE

3-HIV  
4- Post infection..urinary & GIT (shiga toxins)

5-malignancy

6-pregnancy.

It should be treated by emergency plasma exchange. ***Corticosteroids, aspirin and rituximab*** also have a role in management. Untreated mortality rates are **90%**

|  |
| --- |
| ***Idiopathic thrombocytopenic purpura (ITP)*** |

|  |
| --- |
| ITP is mediated by autoantibodies, most often directed against the platelet membrane glycoprotein IIb/IIIa, which sensitise the platelet, resulting in premature removal from the circulation by cells of the reticulo-endothelial system. It is not a single disorder; some cases occur in isolation while others are associated with underlying immune dysregulation in conditions such as  --connective tissue diseases,  --HIV infection,  --B cell malignancies,  --pregnancy  --certain drug therapies. However, the clinical presentation and pathogenesis are similar, whatever the cause of ITP. |

|  |
| --- |
| Clinical features and investigations |

|  |
| --- |
| The presentation depends on the degree of thrombocytopenia. Spontaneous bleeding typically occurs only when the platelet count is <20 × 109/L. At higher counts the patient may complain of easy bruising or sometimes epistaxis or menorrhagia. Many cases with counts of > 50 × 109/L are discovered by chance. |

|  |
| --- |
| In adults ITP more commonly affects females and has an insidious onset. Unlike ITP in children, it is unusual for there to be a history of a preceding viral infection. Symptoms or signs of a connective tissue disease may be apparent at presentation or emerge several years later. Patients aged over 65 years should have a bone marrow examination to look for an accompanying B cell malignancy and appropriate autoantibody testing performed if a diagnosis of connective tissue disease is likely. HIV testing should be considered. The peripheral blood film is normal, apart from a greatly reduced platelet number, whilst the bone marrow reveals an obvious increase in megakaryocytes. |

|  |
| --- |
| Management |

|  |
| --- |
| Many patients with stable compensated ITP and a platelet count > 30 × 109/L do not require treatment to raise the platelet count, except at times of increased bleeding risk such as surgery and biopsy.  1-First-line therapy for patients with spontaneous bleeding is with prednisolone 1 mg/kg daily to suppress antibody production and inhibit phagocytosis of platelets by reticuloendothelial cells.  2- Administration of intravenous immunoglobulin (IVIg) can raise the platelet count by blocking antibody receptors on reticuloendothelial cells, and is combined with corticosteroid therapy if there is severe haemostatic failure or a slow response to steroids alone.  3-A similar effect can be obtained by administering intravenous anti-D which will bind red cells and saturate antibody receptors in RhD-positive individuals who have a spleen.  Persistent or potentially life-threatening bleeding should be treated with platelet transfusion in addition to the other therapies. |

|  |
| --- |
| 4-The condition may become chronic, with remissions and relapses. Relapses should be treated by re-introducing corticosteroids. ***If a patient has two relapses, or primary refractory disease, Splenectomy produces complete remission in about 70% of patients and improvement in a further 20-25%***, so that following splenectomy only 5-10% of patients require further medical therapy.  5-If significant bleeding persists despite splenectomy, low-dose corticosteroid therapy, immunosuppressive therapy such as ***rituximab, ciclosporin and tacrolimus should be considered.*** |