

Unit 4: Gastrointestinal System, Second Part, and Hematological Diseases

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4.1 Cirrhosis

Cirrhosis is the end stage of chronic liver injury from any cause, in which long standing inflammation and hepatocyte death drive fibrosis that distorts liver architecture into regenerative nodules surrounded by fibrous bands, destroying normal blood flow and liver function together. Its causes are those of chronic hepatitis continued: viral hepatitis B and C, alcohol related disease, metabolic fatty liver disease, autoimmune and cholestatic diseases and inherited storage disorders. Two consequences produce nearly all of its clinical picture. Portal hypertension follows increased resistance to portal flow through the fibrotic liver, compounded by increased splanchnic inflow: it produces splenomegaly, portosystemic collaterals including oesophageal varices that may rupture and bleed catastrophically, and ascites, driven by portal pressure, sodium retention and low albumin. Hepatocellular failure follows lost functioning mass: impaired synthesis of albumin and clotting factors, impaired detoxification producing hepatic encephalopathy, jaundice, and endocrine and nutritional disturbance. Diagnosis combines the cause history, examination for the stigmata of chronic liver disease, blood tests of function, platelets and clotting, imaging and elastography measuring liver stiffness, and endoscopy to find varices.

Pharmacotherapy treats the cause, the portal hypertension and each complication; no drug reverses established fibrosis. Cause directed therapy, antivirals, abstinence support, immunosuppression in autoimmune disease, is the only intervention that can slow progression and is never too late to address. For variceal bleeding prevention, non selective beta blockers reduce portal pressure and are used to prevent first and further bleeding, with endoscopic band ligation as the mechanical partner; acute variceal bleeding is an emergency of resuscitation, vasoactive drug therapy constricting the splanchnic circulation, prophylactic antibiotics and urgent endoscopy. Ascites is managed by sodium restriction and diuretics pairing an aldosterone antagonist, the physiological first agent because secondary hyperaldosteronism drives the retention, with a loop diuretic, monitored by weight, renal function and electrolytes, with paracentesis and albumin cover for tense or diuretic resistant ascites. Hepatic encephalopathy is treated by reducing gut nitrogen production and absorption: lactulose, a non absorbable disaccharide that acidifies the colon, traps ammonium and acts as a laxative, is first therapy, the non absorbable antibiotic rifaximin added for recurrence, and precipitants, infection, bleeding, constipation, dehydration and sedatives, are found and treated.

4.2 Diarrhea and constipation

Diarrhea is an increase in stool frequency, liquidity or volume, acute over days to a few weeks, usually infective, and chronic when it persists, demanding a search for disease. Its mechanisms classify it: secretory, driven by toxins, hormones or bile acids; osmotic, from unabsorbed solute; inflammatory, from mucosal invasion, with blood and pus; and motility disorders speeding transit. Drug induced diarrhoea is common and examinable: antibacterials, including the dangerous overgrowth of *Clostridioides difficile* after broad spectrum therapy, metformin, magnesium products and many others. The danger is dehydration and electrolyte depletion, most lethal in children and the elderly, so assessment of fluid state governs urgency. Acute diarrhoea is usually diagnosed clinically, stool studies reserved for bloody, severe, prolonged or outbreak cases; chronic diarrhoea is investigated by the route of Section 3.3. Pharmacotherapy is

rehydration first and drugs second: oral rehydration solution, whose glucose coupled sodium absorption survives most secretory states, is the life saving therapy, intravenous fluids replacing it where oral replacement fails. Antibacterials are withheld in most acute watery diarrhoea and reserved for dysentery patterns, identified pathogens, severe disease and C. difficile infection, where the offending antibiotic is stopped and targeted therapy given. Chronic diarrhoea is treated by treating its cause, with bile acid sequestrants, pancreatic enzymes and the disease specific therapies of earlier sections as the mechanism dictates.

Constipation is infrequent, hard or difficult evacuation, defined by stool form and symptoms of straining and incomplete emptying rather than frequency alone. Causes divide into functional, slow transit and pelvic floor dysfunction among them, and secondary: low fibre and fluid intake, immobility, medicines, opioids above all, with anticholinergics, iron and calcium channel blockers, metabolic causes including hypothyroidism, neurological disease, and structural disease, new constipation in older patients with weight loss, anaemia or bleeding requiring exclusion of colorectal cancer. Management begins with fibre increased gradually, adequate fluid, exercise and responding to the urge to defecate. Laxative classes then follow a stepped order. Bulk forming agents such as ispaghula swell with water and restore the stool bulk that triggers peristalsis, the gentlest first choice for maintenance. Osmotic laxatives hold water in the lumen: lactulose and the macrogol preparations, the latter now preferred, are standard for continuing treatment and for softening impaction. Stimulant laxatives, senna and bisacodyl, provoke peristalsis and are used for short courses and rescue, and alongside osmotics in opioid induced constipation; peripherally acting opioid antagonists serve resistant opioid induced cases under appropriate care.

4.3 Drug induced liver disease

Drug induced liver disease, or drug induced liver injury, is liver damage caused by a medicine, herbal product or supplement, and it mirrors Section 2.3 as the hepatic counterpart of drug induced lung disease. It is classified by pattern from the liver enzyme picture: hepatocellular injury, with predominant transaminase elevation, cholestatic injury, with predominant alkaline phosphatase and bilirubin elevation and itch, and mixed patterns. Mechanistically it divides into predictable, dose related injury, of which paracetamol overdose is the archetype, its metabolite NAPQI exhausting glutathione and binding hepatocyte proteins to produce centrilobular necrosis, and idiosyncratic injury, unpredictable, dose independent in the usual range and immune or metabolic in origin, for which antitubercular agents such as isoniazid and pyrazinamide, amoxicillin clavulanate, antiepileptics, sulfonamides and many others are repeatedly reported; herbal and dietary supplements are an increasingly recognised source that the drug history must ask for, a link back to the medication history discipline. Presentation ranges from asymptomatic enzyme elevation found on monitoring, through a hepatitis picture indistinguishable from viral hepatitis, to cholestatic jaundice and, rarely, acute liver failure; certain drugs produce characteristic signatures, fatty liver, fibrosis, vascular injury or vanishing bile ducts with chronic use. Diagnosis is by exclusion and timeline: a complete drug and supplement history with start dates, exclusion of viral, autoimmune, metabolic and obstructive causes by the approach of Section 3.4, and improvement after withdrawal, the dechallenge, with causality assessment structured as in pharmacovigilance; rechallenge is diagnostic but generally unethical where injury was significant. Management is withdrawal of the suspect drug as the decisive step, supportive care, and specific antidotes where they exist, N acetylcysteine replenishing glutathione in paracetamol poisoning, where its early use is life saving, and in some other acute liver failure settings; corticosteroids are reserved for hypersensitivity and autoimmune like patterns. Prevention is baseline and interval liver monitoring for the high risk agents, dose adjustment in existing liver disease, avoidance of alcohol and interacting combinations, and patient education on the jaundice and dark urine warning signs, with the reaction documented and reported so that re exposure never occurs.

4.4 Anemia

Anemia is a reduction in haemoglobin and red cell mass below the level needed for oxygen delivery, approached by mechanism in three families. The first is blood loss, acute from haemorrhage and chronic and occult most importantly from the gastrointestinal tract, where finding the source is the treatment priority, and in women from menstrual loss. The second is decreased production: deficiency of iron for haem or of vitamin B12 and folate for DNA synthesis in dividing marrow cells, marrow failure and infiltration, the anaemia of chronic disease, in which inflammation sequesters iron and blunts erythropoietin response, and the erythropoietin deficiency of chronic kidney disease. The third is increased destruction, haemolysis: immune, mechanical, infective and inherited, the haemoglobinopathies and red cell enzyme and membrane defects. The size indices organise the diagnosis: microcytic anaemia points first to iron deficiency, macrocytic to B12 and folate deficiency, their drug causes, alcohol and hypothyroidism, and normocytic to chronic disease, kidney failure, marrow problems and haemolysis; history, blood film, iron studies, B12 and folate levels and reticulocyte response complete the usual work up.

Pharmacotherapy treats the cause and replaces what is missing, in that order. Iron deficiency is treated with oral iron salts over months while the bleeding source is found and treated, absorption improved on an empty stomach and reduced by food, tea and interacting medicines, a standard counselling set; parenteral iron serves intolerance, malabsorption, losses that outrun intake, and kidney disease programmes. B12 deficiency is treated with hydroxocobalamin by injection where absorption is the defect, as in pernicious anaemia, the autoimmune failure of intrinsic factor, and orally where intake is the only problem. Folate deficiency is treated with folic acid, with the cardinal rule that folate is never given alone in undifferentiated megaloblastic anaemia, because it may correct the blood picture while B12 neuropathy progresses, so B12 is secured first or together. Erythropoiesis stimulating agents replace the missing erythropoietin signal in kidney disease and selected settings, always with iron sufficiency ensured. Transfusion is reserved for haemodynamic compromise, severe symptoms and acute blood loss, a restrictive approach being standard.

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Anemia: mechanism first, replacement second
  Reduced haemoglobin: find which family
    |
    +-- Blood loss: find and treat the source,
    |   replace iron, transfuse only for compromise
    |
    +-- Underproduction: iron, B12 or folate deficiency,
    |   chronic disease, kidney failure, marrow failure
    |   replace what is missing, secure B12 before folate
    |
    +-- Destruction: haemolysis, immune, drug induced,
    |   inherited; treat the mechanism, stop oxidant drugs
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4.5 Deep vein thrombosis

Deep vein thrombosis is a thrombus in a deep vein, most often of the legs and pelvis, taught as one half of venous thromboembolism, the other half being pulmonary embolism, in which clot breaks away, travels through the right heart and lodges in the pulmonary arteries, causing breathlessness, chest pain, circulatory collapse and death in its major form. Its causes are organised by the Virchow triad, the classification examinations require: stasis of venous flow, from immobility, long travel, paralysis, hospitalisation and surgery; endothelial injury, from trauma, surgery, previous thrombosis and catheters; and hypercoagulability, from inherited thrombophilias such as factor V Leiden, antiphospholipid syndrome, malignancy, pregnancy and the puerperium, oestrogen containing contraceptives and hormone therapy, obesity and acute illness. Presentation is unilateral leg pain, swelling, warmth and tenderness, though many thromboses are silent and found only through their embolism; chronically, damaged valves produce the

post thrombotic syndrome of pain, swelling, skin change and ulceration. Diagnosis uses clinical probability assessment with D dimer testing, whose negative result helps exclude thrombosis in low probability patients, and compression ultrasound as the definitive imaging, the pathway designed to avoid both missed thrombosis and unnecessary anticoagulation.

Pharmacotherapy is anticoagulation. Anticoagulants do not dissolve existing clot directly; they prevent extension and embolisation while the body fibrinolytic system removes it, and they prevent recurrence. The classes divide by mechanism and route. Heparins, unfractionated and low molecular weight, potentiate antithrombin and inactivate thrombin and factor Xa, are parenteral and rapid, and are standard for initial treatment, pregnancy, severe renal impairment and hospital care. Warfarin blocks hepatic synthesis of the vitamin K dependent clotting factors, is oral and slow, needs a parenteral overlap at initiation because of its early prothrombotic protein C effect, and demands INR monitoring and interaction vigilance for as long as it is used. Direct oral anticoagulants inhibit factor Xa or thrombin directly, are predictable and monitoring free in routine use, and are now the usual choice for most patients, renal function, interactions and bleeding risk deciding suitability. Duration is individualised by whether the event was provoked by a transient or a persistent factor or was unprovoked, and by bleeding risk; cancer associated thrombosis is managed by its own evidence. Thrombolysis, which actively dissolves clot, is reserved for massive pulmonary embolism with circulatory compromise and a few limb threatening thromboses. Prevention is the other half of the subject: risk assessment of every inpatient, early mobilisation, mechanical methods and pharmacological prophylaxis with low molecular weight heparin where risk justifies it, balanced daily against bleeding.

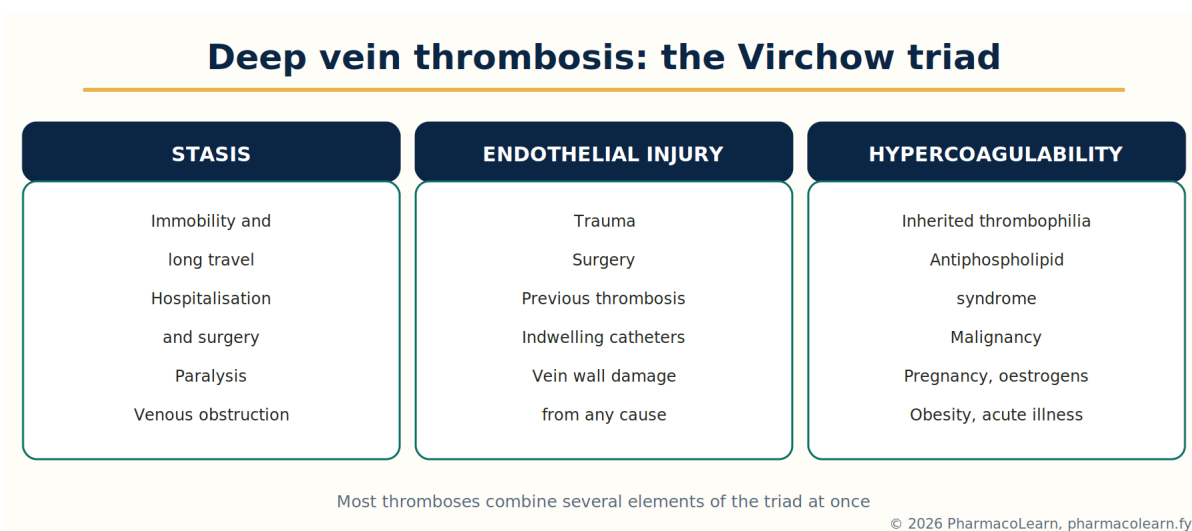


Figure: The Virchow triad. Naming which elements are present in a patient is the first step of both treatment and prevention.

4.6 Drug induced hematological disorders

Medicines injure every line of the blood, and the disorders classify by the element affected. Red cells are injured by immune and oxidant haemolysis, as in Section 4.4, and production is injured by aplastic anaemia, the rare, grave failure of the marrow stem cell compartment classically associated with chloramphenicol and reported with many other agents, presenting with pancytopenia and treated by withdrawal, support and specialist immunosuppression or transplantation. White cells are injured as neutropenia and its extreme, agranulocytosis, the abrupt loss of neutrophils presenting with fever and infection, for which the thionamides of Section 2.5, clozapine with its mandatory blood monitoring programme, cytotoxic agents predictably, sulfonamides and antiepileptics are responsible; management is immediate withdrawal, infection treatment and growth factor support in appropriate cases, and the fever warning given to every patient on an at risk drug is the preventive lesson. Platelets are injured by immune thrombocytopenia, in which drug dependent antibodies destroy platelets, reported with quinine,

sulfonamides and anticonvulsants, and by heparin induced thrombocytopenia, the paradoxical prothrombotic reaction in which heparin dependent antibodies activate platelets, so falling platelets during heparin therapy signal new clotting, not bleeding, and demand immediate heparin cessation and a non heparin anticoagulant. Clotting is injured in the opposite direction by the bleeding caused by anticoagulant and antiplatelet therapy itself, the commonest serious haematological drug event in practice. Medicines also disturb formation qualitatively: methotrexate and other folate antagonists produce megaloblastic change, and several agents produce sideroblastic pictures. The pharmacist pattern across all of them is constant: know the at risk drugs, ensure the baseline and monitoring counts the drug demands, connect a new cytopenia or bleeding picture with the drug timeline, stop the suspect drug and escalate urgently, document and report, and counsel the patient on the symptoms, fever, sore throat, bruising, bleeding and unusual pallor, that must be reported at once.

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