HEMATOLOGY

Acute Leukemia (AML or ALL)

- Chemotherapy
  ° Systemic chemotherapy
  ° Intrathecal chemotherapy (commonly used): Consider adding for patients with or at high risk of CNS infiltration (e.g., all patients with ALL). - administration of chemotherapeutic agents (e.g., triple therapy with methotrexate, cytarabine, and hydrocortisone) directly into the subarachnoid space via lumbar puncture or using an intraventricular catheter with a reservoir placed under the scalp
  ° Targeted chemotherapy: Consider adding for leukemias with specific immunophenotype and genetic profiles, e.g., Philadelphia translocation (e.g. Tyrosine kinase inhibitors (TKIs)
- Adjunctive treatment, e.g., radiation therapy, immunotherapy, or stem cell transplantation (SCT): Consider based on individual evaluation.
- Management of complications: initiate monitoring, prevention, and early aggressive treatment as needed for infection, bleeding, pancytopenia, and oncologic emergencies
  ° Tumor lysis syndrome (TLS) - typically includes fluid therapy (oral or IV) and rasburicase
  ° Leukostasis (e.g., due to hyperleukocytosis): Consider IV fluid resuscitation and/or cytoreductive therapy.

CHRONIC MYELOID LEUKEMIA (CML)

- Targeted therapy: tyrosine kinase inhibitors - first-line and second-line treatment
- Adjunctive medical treatment or hematopoietic stem cell transplantation (HSCT) may be considered if other treatments fail.
- Hydroxyurea or IFN-α may be used to reduce leukocyte counts and control symptoms associated with extreme leukocytosis or thrombocytosis

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

- Targeted therapy, e.g., ibrutinib, rituximab, alemtuzumab
- Chemoimmunotherapy, e.g., FCR: fludarabine, cyclophosphamide, rituximab
- Allogeneic HSCT: currently the only curative treatment option (not routinely performed)

HODGKIN LYMPHOMA

- Limited-stage favorable HL: short-courses of chemotherapy + radiation therapy
- Advanced-stage HL: longer courses of chemotherapy without radiation
- First-line treatment for all patients is typically ABVD: doxorubicin (Adriamycin®), bleomycin, vinblastine, dacarbazine.

MULTIPLE MYELOMA

- HSCT eligible: induction chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT)
- HSCT ineligible: chemotherapy alone (e.g., dexamethasone and lenalidomide)

- Prevention and management of complications (e.g., AKI, bone lesions) is an integral part of treatment.
- Treatment of pain (e.g., due to compressive myelopathy or pathological fractures) includes low-dose radiotherapy, high-dose corticosteroids, and invasive therapy (e.g., vertebroplasty, balloon kyphoplasty).

Management of complications [11]

Overview of the management of complications of multiple myeloma

Complication		Management options
Bone disease [18][22]		• Bisphosphonates • Denosumab • Calcium and vitamin D supplementation
Renal disease [23]		• High fluid intake
Peripheral neuropathy [17]		• Consider pain management with gabapentin or opioid medications.
Hematological complications [11][17][18]	**Anemia**	• Blood transfusion • Erythropoietin (EPO)
	Neutropenia	• Granulocyte-colony stimulating factor (G-CSF)

AL Amyloidosis

- Control of the underlying plasma cell dyscrasia with Chemotherapy: e.g., melphalan plus corticosteroids, thalidomide, bortezomib

AA Amyloidosis

- Treat the underlying condition to reduce AA production (mainstay of treatment)

ATTRmt amyloidosis

- Liver transplantation should be considered to decrease the source of amyloid protein

Gastric MALToma

- First-line: H. pylori eradication therapy

- If H. pylori eradication therapy fails: radiotherapy or chemotherapy
- Surgery: gastric resection only necessary if complications (e.g., perforation, bleeding, obstruction) occur.

Non gastric MALToma

- radiation, chemotherapy, surgery for local diseases

Mycosis fungoides

Treatment for early stage disease

- First line - topical corticosteroids
- Second line - topical nitrogen mustard

Treatment for moderate to late stage disease

- Total skin electron beam therapy (TSEBT)
- Systemic chemotherapy (e.g. bexarotene)
- Topical corticosteroids may also be used

THALASSEMIA

- Transfusion therapy (erythrocyte concentrates)
- Surveillance and treatment of complications (Iron overload diseases: chelating agents, e.g., deferasirox, indicated when iron accumulation reaches toxic levels) (Other complications: e.g., gallstones, asplenia, extramedullary hematopoietic pseudotumors)
- Splenectomy
- Potentially curative treatment
    - Stem cell transplantation: allogenic HSCT
    - Gene therapy

IRON DEFICIENCY ANEMIA

- Treatment of the underlying condition
- Dietary modifications for IDA - Iron-rich foods, Foods with vitamin C (to enhance oral iron absorption)
- Oral iron therapy is effective, inexpensive, and is typically the initial treatment for most patients with IDA. Parenteral iron therapy is beneficial in certain cases
- Blood transfusion - Consider pRBCs in Hemodynamically unstable patients with anemia

METHEMOGLOBINEMIA

- Methylene blue is the first-line treatment for acquired methemoglobinemia
- Alternative treatments - Reducing agents: ascorbic acid (vitamin C) or riboflavin

PYRUVATE KINASE DEFICIENCY

- Phototherapy and/or exchange transfusions
- In the case of severe anemia or excessively enlarged spleen: splenectomy

Hemoglobin C Disease

- Most patients do not require treatment.
- Consider folic acid supplements in hemoglobin C disease.
- Consider cholecystectomy in patients with symptomatic gallstones.
- Splenectomy is rarely indicated.

Microangiopathic hemolytic anemia (MAHA)

- If an evident secondary cause is identified (e.g., HELLP syndrome, hypertensive emergency, DIC), treat accordingly.
- If suspicion for TTP is high:
    - Refer for urgent plasma exchange
    - Consider corticosteroid therapy (e.g., prednisone).

Cold AIHA

- Acute therapy - In addition to blood transfusion, temporizing measures include plasmapheresis and trial of glucocorticoids (e.g., prednisolone).

Long term management

- Cold temperature avoidance
- Cold agglutinin disease (CAD): chronic systemic immunomodulators, e.g., rituximab
- Cold agglutinin syndrome (CAS): Treat underlying condition.
- Splenectomy is not recommended for cold AIHA. It is not effective as most extravascular hemolysis occurs in the liver.

Warm AIHA

- Acute therapy - In addition to blood transfusion, temporizing measures include high-dose glucocorticoids (e.g., methylprednisolone), IVIG, and plasmapheresis.

Long term management

- high-dose glucocorticoids
- other systemic immunomodulators (e.g., rituximab)
- Splenectomy

Paroxysmal Nocturnal Hemoglobinuria

- Patients with mild or no clinical manifestations: watchful waiting with close surveillance
- Indications for targeted therapy include severe anemia, thrombosis, severe fatigue, pain crises, and end-organ damage
- Targeted therapy for patients with significant clinical manifestations - First-line treatment: complement inhibition with an anti-C5 antibody (e.g., eculizumab, ravulizumab)

Provide supportive care for all patients.

- Consider RBC transfusion in symptomatic or severe anemia (e.g., Hb < 7.0 mg/dL).
- Avoid medications that increase the risk of thrombosis (e.g., oral contraceptives).
- Start therapeutic anticoagulation without delay for any venous thromboembolic event (e.g., deep vein thrombosis, pulmonary embolism).

- Consider vaccination and antibiotic prophylaxis for Neisseria meningitidis infection as there is high risk of infection in patients receiving eculizumab

Hereditary Spherocytosis

- Phototherapy and/or exchange transfusions may be necessary in neonates (e.g., to avoid kernicterus).
- Blood transfusions may be required in cases of aplastic or hemolytic crisis
- Folic acid supplementation to maintain erythropoiesis
- Splenectomy - Sole definitive treatment
- Prior to splenectomy, vaccinate against Streptococcus pneumoniae, Haemophilus influenzae type B, and Neisseria meningitidis

Sickle cell disease

Infection prevention

- Immunizations - Pneumococcal vaccines and meningococcal vaccines are particularly important
- Antibiotic prophylaxis against invasive pneumococcal disease - Daily prophylactic penicillin Recommended from early infancy (1–2 months of age) until 5 years of age for children with HbSS, Continue penicillin prophylaxis in children who have had a splenectomy or history of invasive pneumococcal infection (Erythromycin prophylaxis is suitable for children with penicillin allergy.)

Prevention of vasoocclusive crises and anemia

- First-line agent: hydroxyurea - reduces the incidence of acute painful episodes and improves survival.
- Hydroxyurea and chronic blood transfusions are the most established disease-modifying therapies for sickle cell disease.
- Allogeneic bone marrow transplantation (allogeneic HSCT) - Currently the only potentially curative option
- Splenectomy or partial splenectomy may be indicated

Transfusion therapy

- Achieved by diluting (simple transfusion) or replacing (exchange transfusion) patient's HbS erythrocytes with donor HbA erythrocytes
- Simple transfusions - Transfusion of donor erythrocytes without prior removal of recipient blood
- Exchange transfusions - Removal of the recipient's blood (erythrocytapheresis) and replacing it with allogeneic (donor) erythrocyte infusion

Vasoocclusive crisis (sickle cell pain crisis)

- Provide prompt and proactive pain management.
- Ensure adequate hydration (if due to dehydration)
- Administer supplemental oxygen (if due to hypoxia)

Polycythemia Vera

- Regular therapeutic phlebotomy (removal of blood (e.g., 250–500 mL) via venipuncture at scheduled intervals) PLUS low-dose aspirin
- Treat associated symptoms, e.g., allopurinol for gout, antihistamines for pruritus
- For High-risk patients or low-risk patients with persistent symptoms - Start cytoreductive therapy with hydroxyurea
- Assess need for anticoagulation (The management of polycythemia vera focuses on decreasing the risk of thromboembolic events, which are the most common cause of mortality in patients with polycythemia vera.)
- JAK2 inhibitors e.g., ruxolitinib are highly effective at treating symptomatic splenomegaly; splenectomy is now rarely required in patients with polycythemia vera.

Symptomatic management

- Symptomatic hyperuricemia (e.g., gouty arthritis): Initiate allopurinol.
- Pruritus: Treatments include antihistamines, SSRIs, and interferon-alpha.
- Peptic ulcer prophylaxis: PPIs or H2 receptor blockers

PORTAL VEIN THROMBOSIS

- Traditional anticoagulants (heparin, warfarin)
- Direct oral anticoagulants: e.g., apixaban
- Pharmacological thrombolysis (local or systemic): Consider in selected patients with persistent ischemia despite anticoagulation.
- TIPS placement: can be considered in selected cases

Inherited von Willebrand disease

- Desmopressin (DDAVP): stimulates vWF release from endothelial cells - Best initial treatment for mild or moderate symptoms
- Concentrates containing vWF and factor VIII: indicated for severe bleeding, as prophylaxis for surgical procedures and if DDAVP treatment is ineffective
- Other treatment options: antifibrinolytic drugs (i.e., aminocaproic acid, tranexamic acid), oral contraceptives for menorrhagia

Acquired von Willebrand syndrome

- Desmopressin and vWF/VIII concentrates are often less effective than in inherited vWD.
- Patients may benefit from intravenous immune globulin (IVIG) treatment.
- Treatment of the underlying cause.

THROMBOCYTOPENIA

- Treat any significant bleeding
- Treat underlying cause - Immediately treat serious or life-threatening underlying illnesses e.g. TTP, HIT, HUS, DIC
- Consider empiric treatment for ITP (e.g., corticosteroids, IVIG) if platelet count < 30,000/mm3 without another apparent cause
- Consider stopping medications that impair platelet function and increase bleeding risk, e.g., NSAIDs
- Emergency management of thrombocytopenia

• Immediate platelet transfusion
• If an immune cause is suspected: Administer IVIG (prior to transfusion).

IMMUNE THROMBOCYTOPENIA

- First-line medical therapy consists of corticosteroids, IVIG, or anti-D immunoglobulin
- Second-line treatments (i.e., thrombopoietin receptor agonists, rituximab, splenectomy) may be required for refractory, persistent or chronic cases.

Thrombotic thrombocytopenic purpura

Supportive care

- Provide intravenous fluid therapy as indicated
- Consider therapeutic platelet transfusions for patients who are bleeding or require an invasive procedure.
- RBC transfusions: Follow a restrictive transfusion strategy (consider pRBC transfusion if Hb is ≤ 7 g/dL).

Empiric therapy

- Prompt initiation of plasma exchange therapy (PEX)
- High-dose glucocorticoids - Prednisone or methylprednisolone
- Patients with a high pretest probability of TTP (based on clinical judgment) - Consider early caplacizumab, rituximab

Hemolytic uremic syndrome (HUS)

- Dialysis (as indicated for AKI): Up to 50% of HUS patients require dialysis.
- Plasma exchange therapy: only in refractory cases
- Eculizumab - Effective for the treatment of atypical HUS

Supportive care

- Avoid antibiotics and antimotility agents (may increase the likelihood of HUS in suspected infection with Enterohemorrhagic E.coli (EHEC)
- Monitor and correct fluid status abnormalities, electrolyte disturbances, Acid-base disorders, blood pressure, RBC transfusions

Heparin-induced thrombocytopenia (HIT)

- Stop all heparin exposure
- Patients on vitamin K antagonists (e.g., warfarin): Stop the medication and consider reversal with vitamin K.
- Initiate nonheparin anticoagulation - Initiate fondaparinux or oral anticoagulation in clinically stable patients. In critically ill patients, Initiate parenteral anticoagulation before transitioning to oral therapy.
- Consider platelet transfusion only for significant bleeding or patients at high risk of bleeding (e.g., during invasive procedures).
- Intravenous direct thrombin inhibitors (argatroban or bivalirudin) - Preferred in critical illness and in patients with increased risk of bleeding or potential need for urgent procedure

HEMOPHILIA

- Substitution of clotting factors - Factor VIII concentrate for hemophilia A, Factor IX concentrate for hemophilia B, Factor XI concentrate for hemophilia C
- Desmopressin - Triggers the release of vWF from endothelial cells, which leads to an increase in factor VIII plasma concentration
- Antifibrinolytic therapy (e.g., ε-Aminocaproic acid, tranexamic acid)
- Emicizumab - a humanized monoclonal bispecific antibody that reduces the risk of bleeding events in hemophilia A

Anti phospholipid syndrome

- Treat acute thrombotic events (e.g., DVT, MI).
- Initiate long-term thromboprophylaxis.
- Primary thromboprophylaxis: low-dose aspirin therapy
- Secondary thromboprophylaxis: warfarin (first line), LMWH or UFH (second line)
- Thromboprophylaxis in pregnant individuals: low-dose aspirin therapy PLUS heparin (LMWH or UFH)

Disseminated intravascular coagulation (DIC)

- First-line: treatment of the underlying disease

Blood products

- pRBCs: indicated for patients with active bleeding or Hb ≤ 7 gr/dL
- Platelets - Active bleeding or high risk of bleeding (e.g, planned invasive procedure): platelet count < 50,000/mm3
- Fresh frozen plasma (FFP) - PT or aPTT > 1.5 times the normal value if patient is bleeding or will undergo an invasive procedure
- Cryoprecipitate - bleeding and fibrinogen levels < 150 mg/dL despite FFP or when FFP transfusion is not possible

Anticoagulation

- Prophylactic heparin: indicated as DVT prophylaxis in critically ill patients in the absence of bleeding
- Therapeutic heparin: indicated for clinically overt thromboembolic events
- Other coagulation inhibitors: Plasma-derived activated protein C (APC), Recombinant human thrombomodulin (rhTM), Synthetic inhibitors of serine proteases

Contraindications

- Warfarin is ineffective and possibly harmful in DIC, as it inhibits production of protein C and protein S, which can worsen coagulopathy.
- Fibrinolytic therapy (e.g., tPA) should be avoided in all types of DIC

Budd Chiari Syndrome

- Treat the underlying disease
- Anticoagulation (to prevent propagation of the thrombus)
- Restore blood flow - Localized thrombolysis, Balloon angioplasty and stenting

- TIPS (transjugular intrahepatic portosystemic shunt) if complications of portal hypertension occur
- Liver transplantation in the event of liver failure