Blood transfusion therapy

COMPONENT	DOSAGE EFFECT	CLINICAL USE
Packed RBCs	↑ Hb and O_2 binding (carrying) capacity	Acute blood loss, severe anemia
Platelets	↑ platelet count (↑ ~ 5000/mm^3/unit)	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)
Fresh frozen plasma/ prothrombin complex concentrate	↑ coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, as well as protein C and S	Cirrhosis, immediate anticoagulation reversal
Cryoprecipitate	Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin	Coagulation factor deficiencies involving fibrinogen and factor VIII
Albumin	↑ intravascular volume and oncotic pressure	Post-paracentesis, therapeutic plasmapheresis

Blood transfusion risks include infection transmission (low), transfusion reactions, iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a Ca^{2+} chelator), and hyperkalemia (RBCs may lyse in old blood units).

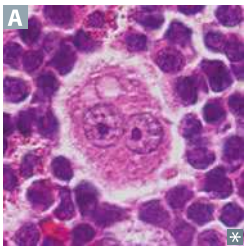
Leukemia vs lymphoma

Leukemia	Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.
Lymphoma	Discrete tumor mass arising from lymph nodes. Variable clinical presentation (eg, arising in atypical sites, leukemic presentation).

Hodgkin vs non-Hodgkin lymphoma

Hodgkin	Non-Hodgkin
Both may have constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss.	
Localized, single group of nodes with contiguous spread (stage is strongest predictor of prognosis). Better prognosis.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread. Worse prognosis.
Characterized by Reed-Sternberg cells.	Majority involve B cells; rarely of T-cell lineage.
Bimodal distribution: young adults, > 55 years.	Can occur in children and adults.
Associated with EBV.	May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV).

Hodgkin lymphoma

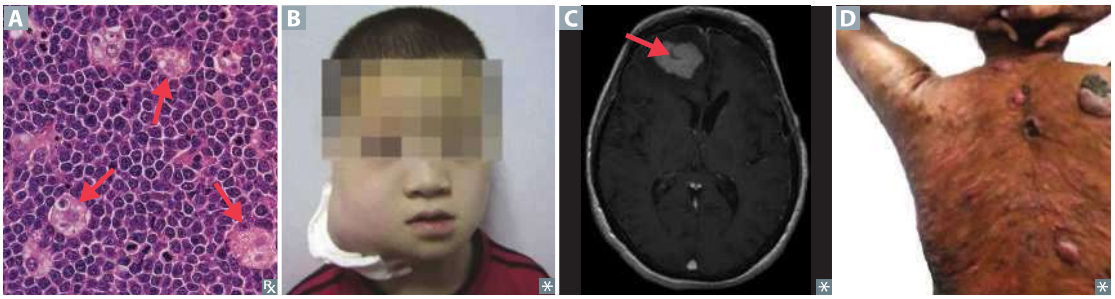


Contains Reed-Sternberg cells: distinctive tumor giant cells; bilobed nucleus with the 2 halves as mirror images ("owl eyes" A). RS cells are CD15+ and CD30+ B-cell origin. 2 owl eyes × 15 = 30.

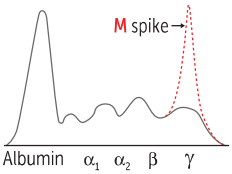
SUBTYPE	NOTES
Nodular sclerosis	Most common
Mixed cellularity	Eosinophilia; seen in immunocompromised patients
Lymphocyte rich	Best prognosis (the rich have better bank accounts)
Lymphocyte depleted	Worst prognosis (the poor have worse bank accounts); seen in immunocompromised patients

Non-Hodgkin lymphoma

TYPE	OCCURS IN	GENETICS	COMMENTS
Neoplasms of mature B cells			
Burkitt lymphoma	Adolescents or young adults	t(8;14)—translocation of c-*myc* (8) and heavy-chain Ig (14)	"Starry sky" appearance (StarBurst), sheets of lymphocytes with interspersed "tingible body" macrophages (arrows in A). Associated with EBV. Jaw lesion B in endemic form in Africa; pelvis or abdomen in sporadic form.
Diffuse large B-cell lymphoma	Usually older adults, but 20% in children	Mutations in *BCL-2*, *BCL-6*	Most common type of non-Hodgkin lymphoma in adults.
Follicular lymphoma	Adults	t(14;18)—translocation of heavy-chain Ig (14) and *BCL-2* (18)	Indolent course with painless "waxing and waning" lymphadenopathy. Bcl-2 normally inhibits apoptosis.
Mantle cell lymphoma	Adult males >> adult females	t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD5+	Very aggressive, patients typically present with late-stage disease.
Marginal zone lymphoma	Adults	t(11;18)	Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma; may regress with *H pylori* eradication]).
Primary central nervous system lymphoma	Adults	EBV related; associated with HIV/AIDS	Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients C, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.
Neoplasms of mature T cells			
Adult T-cell lymphoma	Adults	Caused by HTLV (associated with IV drug use)	Adults present with cutaneous lesions; common in Japan (T-cell in Tokyo), West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.
Mycosis fungoides/ Sézary syndrome	Adults		Mycosis fungoides: skin patches and plaques D (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with "cerebriform" nuclei and intraepidermal neoplastic cell aggregates (Pautrier microabscess). May progress to Sézary syndrome (T-cell leukemia).



Plasma cell disorders



Characterized by monoclonal immunoglobulin (paraprotein) overproduction due to plasma cell disorder.

Labs: serum protein electrophoresis (SPEP) or free light chain (FLC) assay for initial tests (M spike on SPEP represents overproduction of a monoclonal Ig fragment). For urinalysis, use 24-hr urine protein electrophoresis (UPEP) to detect light chain, as routine urine dipstick detects only albumin.

Confirm with bone marrow biopsy.

Multiple myeloma

Overproduction of IgG (55% of cases) > IgA.

Clinical features: CRAB
- HyperCalcemia (↑ secretion of cytokines [eg, IL-1, TNF-a, RANK-L] by malignant plasma cells → ↑ osteoclast activity)
- Renal involvement
- Anemia
- Bone lytic lesions ("punched out" on X-ray A) → back pain.

Peripheral blood smear shows rouleaux formation B (RBCs stacked like poker chips).

Urinalysis shows Ig light chains (Bence Jones proteinuria) with ⊖ urine dipstick.

Bone marrow analysis shows > 10% monoclonal plasma cells with clock-face chromatin C and intracytoplasmic inclusions containing IgG.

Complications: ↑ infection risk, 1° amyloidosis (AL).

Waldenstrom macroglobulinemia

Overproduction of IgM (macroglobulinemia because IgM is the largest Ig).

Clinical features:
- Peripheral neuropathy
- No CRAB findings
- Hyperviscosity syndrome:
  - Headache
  - Blurry vision
  - Raynaud phenomenon
  - Retinal hemorrhages

Bone marrow analysis shows > 10% small lymphocytes with intranuclear pseudoinclusions containing IgM (lymphoplasmacytic lymphoma).

Complication: thrombosis.

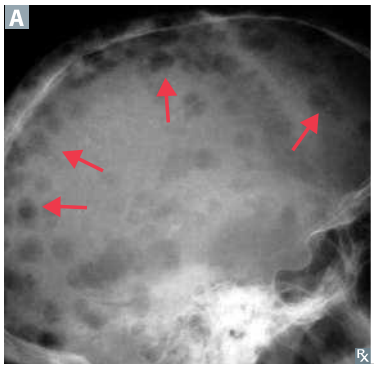
Monoclonal gammopathy of undetermined significance

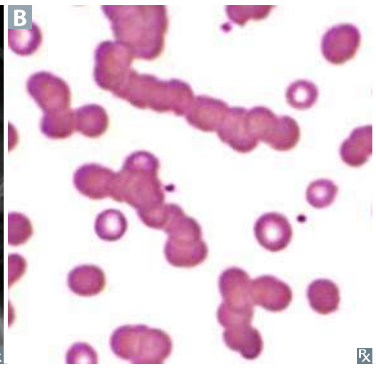
Overproduction of any Ig type.

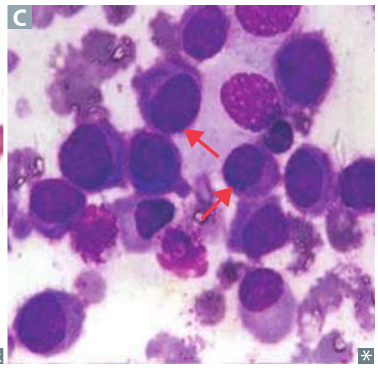
Usually asymptomatic. No CRAB findings.

Bone marrow analysis shows < 10% monoclonal plasma cells.

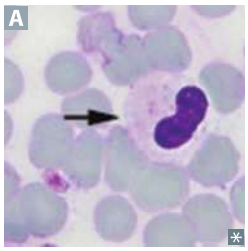
Complication: 1–2% risk per year of transitioning to multiple myeloma.







Myelodysplastic syndromes



Stem cell disorders involving ineffective hematopoiesis → defects in cell maturation of nonlymphoid lineages. Bone marrow blasts < 20% (vs > 20% in AML). Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML. More common in older adults.

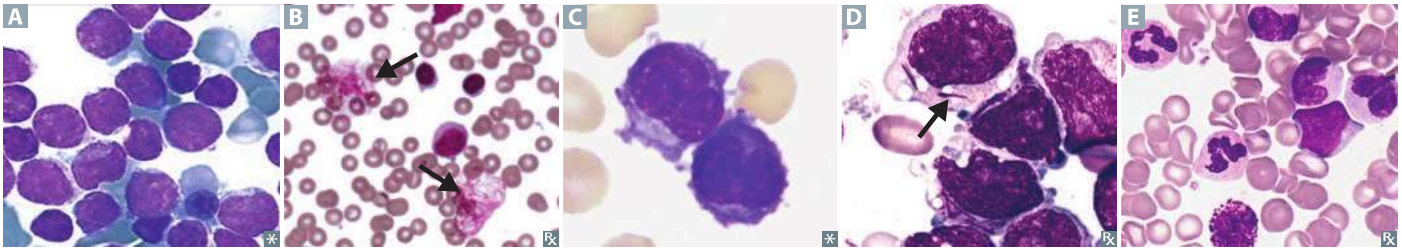
Pseudo-Pelger-Huët anomaly—neutrophils with bilobed ("duet") nuclei A. Associated with myelodysplastic syndromes or drugs (eg, immunosuppressants).

Leukemias

Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood), although some cases present with normal/↓ WBCs.

Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

TYPE	NOTES
Lymphoid neoplasms	
Acute lymphoblastic leukemia/lymphoma	Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑↑↑ lymphoblasts A. TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells). Most responsive to therapy. May spread to CNS and testes. t(12;21) → better prognosis; t(9;22) (Philadelphia chromosome) → worse prognosis.
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Age > 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. **CLL** = **C**rushed **L**ittle **L**ymphocytes (smudge cells). Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).
Hairy cell leukemia	Adult males. Mature B-cell tumor. Cells have filamentous, hairlike projections (fuzzy appearing on LM C). Peripheral lymphadenopathy is uncommon. Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia. Stains **TRAP** (**T**artrate-**R**esistant **A**cid **P**hosphatase) ⊕ (**TRAP**ped in a **hairy** situation). TRAP stain largely replaced with flow cytometry. Associated with *BRAF* mutations. Treatment: purine analogs (cladribine, pentostatin).
Myeloid neoplasms	
Acute myelogenous leukemia	Median onset 65 years. Auer rods D; myeloperoxidase ⊕ cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear. May present with leukostasis (capillary occlusion by malignant, nondistensible cells → organ damage). Risk factors: prior exposure to alkylating chemotherapy, radiation, benzene, myeloproliferative disorders, Down syndrome (typically acute megakaryoblastic leukemia [formerly M7 AML]). APL: t(15;17), responds to all-*trans* retinoic acid (vitamin A) and arsenic trioxide, which induce differentiation of promyelocytes; DIC is a common presentation.
Chronic myelogenous leukemia	Peak incidence: 45–85 years; median age: 64 years. Defined by the Philadelphia chromosome (t[9;22], *BCR-ABL*) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils E) and splenomegaly. May accelerate and transform to AML or ALL ("blast crisis"). Responds to BCR-ABL tyrosine kinase inhibitors (eg, imatinib).



Myeloproliferative neoplasms

Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines.

Polycythemia vera

Primary polycythemia. Disorder of ↑ RBCs, usually due to acquired *JAK2* mutation. May present as intense itching after shower (aquagenic pruritus). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A. Associated with hyperviscosity and thrombosis (eg, PE, DVT, Budd-Chiari syndrome).

↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).

Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor).

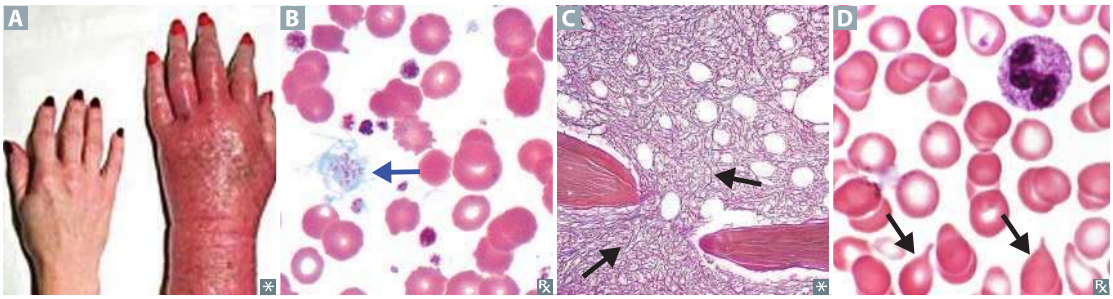
Essential thrombocythemia

Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed B. Erythromelalgia may occur.

Myelofibrosis

Atypical megakaryocyte hyperplasia → ↑ TGF-β secretion → ↑ fibroblast activity → obliteration of bone marrow with fibrosis C. Associated with massive splenomegaly and "teardrop" RBCs D. "Bone marrow cries because it's fibrosed and is a dry tap."

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	*JAK2* MUTATIONS
Polycythemia vera	↑	↑	↑	⊖	⊕
Essential thrombocythemia	–	–	↑	⊖	⊕ (30–50%)
Myelofibrosis	↓	Variable	Variable	⊖	⊕ (30–50%)
CML	↓	↑	↑	⊕	⊖



Leukemoid reaction vs chronic myelogenous leukemia

	Leukemoid reaction	Chronic myelogenous leukemia
DEFINITION	Reactive neutrophilia > 50,000 cells/mm^3	Myeloproliferative neoplasm ⊕ for *BCR-ABL*
NEUTROPHIL MORPHOLOGY	Toxic granulation, Döhle bodies, cytoplasmic vacuoles	Pseudo-Pelger-Huët anomaly
LAP SCORE	↑	↓ (LAP enzyme ↓ in malignant neutrophils)
EOSINOPHILS AND BASOPHILS	Normal	↑

Polycythemia

	PLASMA VOLUME	RBC MASS	O_2 SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	↓	–	–	–	Dehydration, burns.
Appropriate absolute	–	↑	↓	↑	Lung disease, congenital heart disease, high altitude, obstructive sleep apnea.
Inappropriate absolute	–	↑	–	↑	Exogenous EPO (athlete misuse, also called "blood doping"), androgen supplementation. Inappropriate EPO secretion: malignancy (eg, RCC, HCC).
Polycythemia vera	↑	↑↑	–	↓	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

↑↓ = 1° disturbance

Chromosomal translocations

TRANSLOCATION	ASSOCIATED DISORDER	NOTES
t(8;14)	Burkitt (Burk-8) lymphoma (c-*myc* activation)	The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, *c-myc* and *BCL-2*) are translocated next to this heavy chain gene region, they are overexpressed.
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)	
t(11;18)	Marginal zone lymphoma	
t(14;18)	Follicular lymphoma (*BCL-2* activation)	
t(15;17)	APL (formerly M3 type of AML)	
t(9;22) (Philadelphia chromosome)	CML (*BCR-ABL* hybrid), ALL (less common); Philadelphia CreaML cheese	

Langerhans cell histiocytosis

Collective group of proliferative disorders of Langerhans cells (antigen-presenting cells normally found in the skin). Presents in a child as lytic bone lesions A and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 and CD1a. Birbeck granules ("tennis rackets" or rod shaped on EM) are characteristic B.