

Bedside Hematology

Rapid Reference

A Young EHA and Young National
Societies Ambassador's initiative

About Bedside Hematology - Rapid Reference

This reference guide was created to support clinicians during hematology emergencies — those critical moments during on-calls and bedside consultations where rapid, confident decisions are essential.

It was shaped by the needs, experiences, and collaboration of a new generation of hematologists across Europe. Driven by a shared recognition: the urgent need for concise, evidence-based recommendations available at hand during acute situations in hematology, the idea arose independently in different countries. Thanks to the EHA Young National Societies Ambassador (YNSA) network, motivated young hematologists and trainees from more than ten countries were able to connect and collaborate. The goal has been to create a freely shareable, practical resource that improves access to emergency guidance, supports safer decision-making, and promotes better patient care.

Drawing inspiration from a practical emergency booklet used by hematology trainees in France, we used this model to help structure this project — ultimately revising, expanding, and adapting the contents over several rounds to fit the needs of a broader, European audience. Each topic was developed based on available evidence and reviewed by experts from European Hematology Association (EHA) Scientific Working Groups (SWGs).

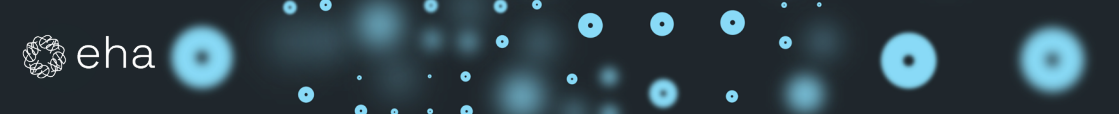
The contents are intended as a supplement to clinical training and local protocols, not a replacement. They are not official guidelines, but a practical memory aid. National and institutional guidelines — particularly those published after the release of this guide — must always take precedence.

This reference guide reflects hundreds of volunteer hours, contributed alongside clinical, academic, and personal responsibilities. It has been shaped by real-world experience, a spirit of cross-border collaboration, and a strong commitment to improving hematologic emergency care.

We invite your feedback and suggestions to help this resource continue to evolve. Our hope is that this guide becomes not just a reference, but a trusted companion for many shifts to come.

We wish you a smooth read — and safe, successful shifts ahead.

On behalf of the YoungEHA and YNSA contributors,
Michaela Essl-Gruber and Pierre-Edouard Debureau



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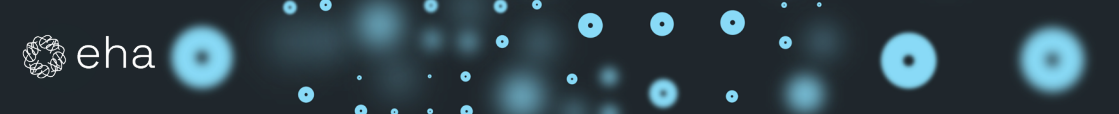
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1. Anemias

Key facts

- Anemia is a deficiency of healthy red blood cells (RBC) leading to impaired tissue oxygenation.
- Anemia may be acute or chronic, caused by excessive red cell consumption (hemorrhage or hemolysis) or inadequate production.
- Acute and chronic anemia present differently, with variable symptoms depending on onset and duration.
- Severity is determined by acuity of hemoglobin drop, co-morbidities (e.g., cardiac disease, hematologic malignancy), signs of end-organ hypoperfusion and vital status.
- Etiology can be inferred from patient history, cytopenias, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), reticulocyte count, hemolysis markers (AST, LDH, bilirubin, haptoglobin) and blood film.
- Management depends on acuity and severity; red cell transfusion in severe cases; otherwise observe or treat the underlying cause once established.
- Emergencies include acute hemorrhage, acute hemolysis, and acute marrow failure (hypoplasia or aplasia) consider ICU or high dependency care.

Important definitions:

- **Hemolysis:** accelerated RBC destruction with reduced survival; may cause life-threatening cardiovascular compromise.
- **Hypoproliferative** anemia: inadequate bone marrow production of RBCs with inappropriately low or normal reticulocyte count.
- **Classification by red cell size:**
 - microcytic: MCV below laboratory reference range;
 - normocytic: MCV within normal range;
 - macrocytic: MCV above reference range.
- **Morphologic syndromes:** specific blood film or marrow features that narrow the differential diagnosis, e.g., megaloblastic anemia due to vitamin B12 with or without folate deficiency, or sideroblastic anemias.

1.1 Clinical presentation

Appraisal of the anemic patient should promptly assess:

- **Clinical tolerance of anemia:** chronic anemia is often compensated or asymptomatic; acute anemia may cause hemodynamic compromise.
- **Etiology:** look for signs that suggest an underlying cause.

This section applies to adults and not to neonates or infants.

Parameter	Signs and symptoms
Respiratory decompensation	Dyspnea, tachypnea, cyanosis
Hypovolemia	Hypotension, hypothermia, tachycardia, pallor, mottling
Myocardial injury	Tachycardia, systolic murmur, angina
Neurological decompensation	Altered consciousness, confusion, headaches, floaters
Background and medical history	Age, cardiac or vascular disease, chronic respiratory insufficiency, malignancy

Table 1.1: Signs and symptoms of clinical severity and anemia tolerance

Parameter	Key features
General	Past medical and family history, ethnicity/heritage (if hemoglobinopathy or specific anemia syndrome suspected)
Bleeding	Signs of hemorrhage: trauma, epistaxis or mucosal, menorrhagia, upper or lower GI bleeding, hematuria, antiplatelet or anticoagulant use
Hemolysis	Acute or chronic: jaundice
	Acute intravascular: Fever, back pain or colic, dark urine, acute renal failure, shock
	Chronic: splenomegaly, gallstones
Malignancy	B symptoms, peripheral lymphadenopathy, hepatosplenomegaly, symptoms of solid malignancy
Iron and vitamin deficiency	Fatigue, asthenia, chronic blood loss, vegan or restricted diet, leukonychia, malabsorption syndrome, peripheral neuropathy, subacute combined degeneration of the spinal cord, history of bariatric surgery or diabetes

Table 1.2: Evaluation of anemia causes

1.2 Diagnostic evaluation

Basic anemia work-up:

- CBC: assess whether anemia is isolated or associated with additional cytopenias.
- Review MCV, red cell count, and MCHC for indicators of etiology. Analyzer may reveal lymphocytosis, circulating blasts (leukoerythroblastosis), or thrombocytosis or leukocytosis.
- Blood smear:
 - Schistocytes: microangiopathic hemolytic anemia or thrombotic microangiopathy
 - Polychromasia (reticulocytosis); nucleated red blood cells (NRBCs): hemolysis, recovering anemia with functional marrow, marrow infiltration
 - Red cell morphology, inclusions or dysplasia (may be multilineage)
 - Blasts or leukoerythroblastosis
 - Elliptocytes: small numbers may appear in other syndromes (e.g., thalassemia), large numbers suggest hereditary elliptocytosis
- Reticulocytes: absence of reticulocytosis may indicate impaired marrow function; note that the response is delayed after acute hemorrhage
- Biochemistry: renal and liver function tests may suggest etiology
- Iron tests: ferritin (also an acute-phase reactant), transferrin saturation, iron-binding capacity; always interpret ferritin with CRP
- Vitamin levels: vitamin B12 (cobalamin) and folate
- Hemolysis markers: bilirubin (measure conjugated and unconjugated if elevated), LDH, haptoglobin, and urine hemosiderin (if hemolysis suspected)
- Direct antiglobulin test: polyspecific and monospecific for hemolytic anemia
- Malaria test: thick and thin blood smears (pH 7.2) if suspected
- Pre-transfusion work-up: blood group and antibody screen; consider special product requirements (e.g., CMV-negative or irradiated units)

Note: Where possible, interpret laboratory results in the context of clinical findings, past medical history, and prior laboratory data. This approach enables focused work-up and management while avoiding unnecessary duplication of assays. Whenever feasible, use pre-transfusion specimens to reduce false-positive and false-negative results.

1.2.1 Consumptive anemia: secondary to blood loss or hemolysis

May present as an acutely unwell and unstable patient. Etiology is often apparent. Transfusion is generally an adjunct to definitive management.

Parameter	Key features
Clinical presentation	- Normocytic anemia; may have concurrent consumptive coagulopathy - Reticulocyte response often delayed - Signs of tissue hypoperfusion may be evident - Consider early activation of major hemorrhage protocol in the appropriate context
Clinical context	Polytrauma, external bleeding
Common causes	- Gastrointestinal bleeding - Epistaxis - Anticoagulant therapy or bleeding diathesis - Menometrorrhagia
Treatment	- Treat the cause: achieve local hemostasis where possible - Transfuse red cell concentrates with or without other components - Apply patient blood management strategies; avoid overtransfusion (Mueller et al., 2019)

Table 1.3: Acute hemorrhage: evaluation and management

Parameter	Key features
Laboratory findings	- Elevated LDH - Decreased haptoglobin - Increased unconjugated bilirubin - Hemoglobinuria (intravascular)
Extravascular causes	- Immune: warm AIHA (may also be intravascular), alloimmune, drug-induced - Infectious: malaria, <i>Clostridium perfringens</i>
Intravascular causes	- Red cell membrane abnormalities - Hemoglobinopathies (intravascular and extravascular) - Mechanical: thrombotic microangiopathy (see Chapter 3), mechanical cardiac valves - Enzymopathies (G6PD, PK) (intravascular and extravascular) - Paroxysmal disorders: paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria (PCH)

Table 1.4: Hemolysis: causes and features

Etiology	Key features
Transfusion-related	- ABO-incompatible transfusion (ICU management) - Alloimmunization with delayed hemolytic transfusion reaction (DHTR – non-consensual classification)
Drug-induced	Discontinue the causative medication (e.g., quinine, rifampin)
Autoimmune hemolytic anemia (AIHA)	- Warm antibody: anti-IgG with or without anti-complement - Cold antibody: isolated anti-complement antibodies
Causes	Warm AIHA - Cautious transfusion of “issued as suitable” red cell concentrate (Rhesus and Kell matched) - Full compatibility may take 4–6 hours - Close monitoring - Initiation of high-dose corticosteroid therapy following etiological workup - Consider IVIG or PLEX in life-threatening anemia Secondary: - Treat underlying cause in parallel with AIHA therapy CHAD: - Transfusion of RBC warmed to 37 °C (use warmer before transfusion) - Corticosteroid therapy and splenectomy usually ineffective - Consider rituximab or R-chemotherapy if LPD

Table 1.5: Approach to hemolytic anemia management: DAT positive

(Go et al., 2017; Hill et al., 2017)

Etiology	Key features
Broad differential	- Chronic hemolysis, often compensated or asymptomatic
Management	- Supportive in non-severe cases: avoid precipitants, provide folate supplementation, ensure optimal vaccination
Membranopathies (e.g., hereditary spherocytosis, elliptocytosis)	- Blood smear is often informative - Family history may be present - Targeted red cell diagnostics with or without genomics - Folate replacement
Hemoglobinopathies	- Often occur in relevant ethnic and/or geographic contexts - Blood smear informative; confirm with hemoglobin studies

	- Avoid transfusion unless strictly indicated to reduce complications, including alloimmunization
Paroxysmal Nocturnal Hemoglobinuria (PNH)	- Consider screening with flow cytometry for GPI-anchored proteins in DAT-negative hemolysis, especially if symptomatic and associated with thrombosis or cytopenias
Enzymopathies (e.g., G6PD deficiency)	- Characteristic morphology: Heinz bodies and hemi-ghosts (red cells with asymmetric hemoglobin retraction) may appear on blood smear - Oxidative hemolysis typically self-limited after exposure to oxidizing drugs - G6PD deficiency is X-linked: observed in males with variant alleles; carrier females may also be deficient. - G6PD levels may be falsely normal during acute hemolysis (due to reticulocytosis). - Consider routine G6PD screening before rasburicase in patients with blood cancer

Table 1.6: Approach to hemolytic anemia management: DAT positive

1.2.2 Hypoproliferative anemias: normocytic or macrocytic

- Normocytic anemia
 - May present with isolated or mixed hematinic deficiency;
 - May result from anemia of chronic disease or chronic inflammation (hepcidin-related; assay not routinely available);
 - In chronic, compensated cases transfusion is generally not required unless highly symptomatic;
 - Management: targeted therapy of a remediable cause; supportive care may include erythropoietin-stimulating agents (ESAs);
 - Bone marrow examination may help when diagnosis is unclear; can provide morphological and/or molecular insights;
 - Dyserythropoietic changes may suggest an underlying myeloid neoplasm (e.g., myelodysplastic syndromes) but are nonspecific and must be interpreted in the context of marrow morphology and cellularity.

Cobalamin (vitamin B12) and folate (vitamin B9) deficiency may be associated with thrombocytopenia or pancytopenia in severe cases

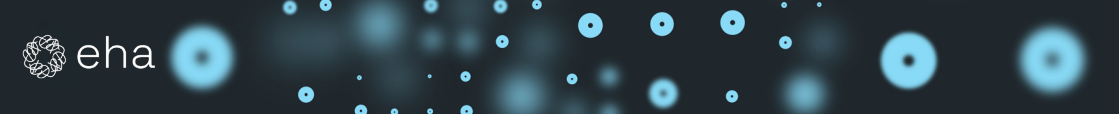
- Laboratory tests
 - First-line: serum vitamin B12 and folate;

- Second-line: plasma methylmalonic acid and serum transcobalamin in borderline cases, (where available – to clarify presence of functional deficiency) (Devalia et al., 2014);
- LDH may be elevated; blood smear may show schistocytes and hemolytic features due to intramedullary hemolysis;
- Bone marrow examination is usually unnecessary when deficiency is confirmed; if performed, it shows megaloblastosis of the erythroblastic lineage with asynchronous nucleocytoplasmic maturation.
- Causes: restricted diet (e.g., veganism), malabsorption (including pernicious anemia), inflammatory bowel disease, celiac disease, and bariatric surgery.
- Treatment: identify the cause to guide route of replacement (oral or parenteral)

1.2.3 Hypoproliferative anemias: microcytic

Iron deficiency is the most common cause of microcytic anemia.

- Laboratory tests
 - Blood smear: assess for additional features of iron deficiency (e.g., hypochromia, target cells, and pencil cells);
 - Ferritin: most commonly used test; note that ferritin is also an acute-phase reactant. Always interpret with CRP;
 - Additional tests: transferrin saturation, iron binding capacity transferrin receptor (if available);
 - Hepcidin assay (if available) may identify iron metabolism defects in microcytosis.
- Causes
 - Low dietary intake, insensible losses (e.g., menorrhagia, occult GI bleeding, chronic blood loss), malabsorption.
- Treatment
 - Oral iron is first-line, unless rapid correction is required; select formulation and frequency to minimize GI side effects;
 - Indications for IV iron: oral iron intolerance, oral iron refractoriness (no improvement after 4 weeks of therapy), severe anemia (Hb <7–8 g/dL), second and third trimesters of pregnancy, ESA treatment, chronic blood loss, postoperative anemia.
- Other causes of microcytic anemia include:
 - Anemia of chronic inflammation or chronic disease;



- Thalassemia and sickle/beta thalassemia genotypes: qualitative and/or quantitative globin chain deficiency. Characteristic smear features may include sickle or boat cells, red cell inclusions, extreme microcytosis, anisopoikilocytosis, and target cells;
- Sideroblastic anemia noted on iron and Perls' stain.

References

○ Mueller MM, et al. JAMA. 2019;321:983-997.
○ Go RS, et al. Blood. 2017;129:2971-2979.
○ Hill QA, et al. Br J Haematol. 2017;176:395-411.
○ Devalia V, et al. Br J Haematol. 2014;166:496-513.
○ Camaschella C, et al. Blood. 2019;133:30-39.

2. Thrombocytopenia

Key facts

- Main etiologies: platelet destruction mainly in the spleen and liver (primary and secondary ITP, transfusion-related), intravascular platelet consumption (DIC and other TMAs), redistribution (hypersplenism), decreased platelet production (BM toxicity, infiltration, fibrosis, MDS, AA, nutritional deficiency (vitamin B12, folic acid), inherited thrombocytopenias).
- Suspect based on: bleeding manifestations affecting the skin (petechiae, ecchymoses), mucosae (epistaxis, oral bleeding), organ systems (GI, menorrhagia, more rarely lung, CNS, hematuria).
- Reference measurement: platelet count; be alert to other blood count abnormalities (schistocytes, cytopenias), platelet size, granularity, and clumping (pseudothrombocytopenia).
- Emergency approach: CBC, blood smear, coagulation, blood chemistry; treatment is individualized based on etiology, clinical severity, and platelet count.

Important definitions:

- **Thrombocytopenia** is a condition defined by a platelet count below the normal limit $<150 \times 10^9/L$.
- Thrombocytopenia can be divided into **mild** ($100\text{--}150 \times 10^9/L$), **moderate** ($50\text{--}99 \times 10^9/L$) and **severe** ($<50 \times 10^9/L$) but these boundaries do not necessarily correlate with the bleeding risk.
- **Stable** platelet counts above $100 \times 10^9/L$ **do not** always indicate disease but require follow-up.
- **Immune thrombocytopenia (ITP)** is a disorder with an **autoimmune** background leading to the production of autoimmune antibodies against platelets and megakaryocytes resulting in increased platelet destruction and impaired platelet production.
- ITP is commonly **idiopathic**, but may also be **secondary to underlying disorders** (infections – HCV, HIV, H. pylori, CMV; autoimmunity (SLE, APS), lymphoproliferative diseases (CLL), or to drugs (quinine, antibiotics, anticonvulsants, GPIIb/IIIb inhibitors, etc.), in which cases platelets rapidly normalize after offending drug discontinuation.

2.1 Background

Main etiologies:

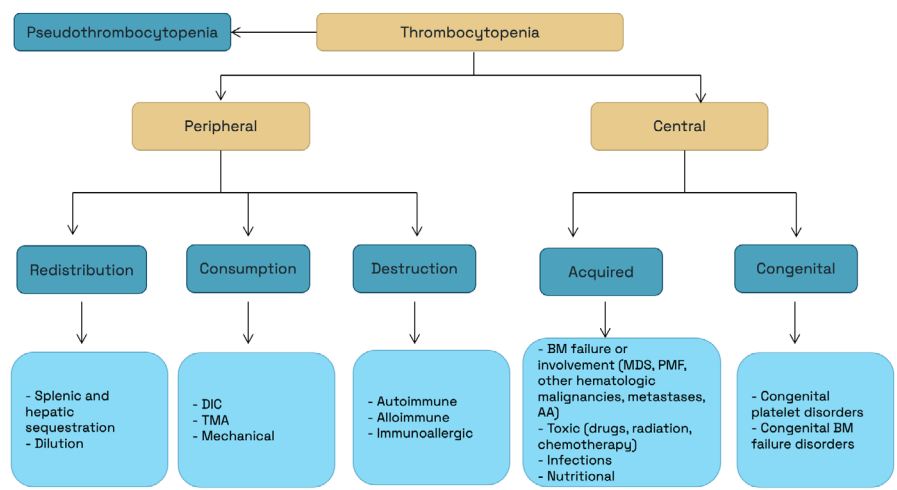


Figure 2.1: Classification of thrombocytopenia according to mechanism and site of origin.

Central origin: related to **bone marrow dysfunction**.

Acquired	Bone marrow (BM) involvement: myelodysplastic syndromes (MDS), infiltration (leukemia or metastases), myelofibrosis, aplastic anemia (AA); Toxic exposures: (alcohol-related myelotoxicity, radiation, drugs and chemotherapy, viruses) Nutritional deficiency (vitamin B12, folic acid, copper).
Congenital	Congenital BM failure syndromes (e.g., Fanconi anemia); Congenital platelet disorders: Bernard-Soulier, May-Hegglin, Wiskott-Aldrich syndromes, Gray platelet syndrome, congenital amegakaryocytic thrombocytopenia, etc.

Peripheral origin

Platelet redistribution	- Hypersplenism (splenic sequestration); - Hepatic sequestration; - Dilution (massive transfusion or pregnancy; platelet count usually >100 × 10⁹/L);
Consumption	- TMAs (TTP, aHUS, other) - DIC - HIT - VITT
Destruction	- Drug-induced thrombocytopenia (e.g., heparin-induced thrombocytopenia; new medicine started within previous 3 months; immune checkpoint inhibitors) Autoimmune - Primary ITP - Secondary ITP: autoimmune diseases (lupus, antiphospholipid syndrome), lymphoproliferative disorders, infections (viruses, malaria, H. pylori), primary immune deficiencies (CVID). Alloimmune - maternal-fetal - neonatal and fetal alloimmune thrombocytopenia - post-transfusion purpura

2.2 Clinical presentation

Hemorrhagic syndromes: heterogeneous, patients often asymptomatic:

- **Skin:** petechiae, ecchymoses, wound bleeding, subcutaneous hematomas
- **Mucosal:** epistaxis, oral (gum bleeding, oral blisters, or bullae), subconjunctival hemorrhage.
- **Organ:** GI (e.g., hematemesis, melena), menorrhagia, hematuria, more rarely lung, ocular, intracranial bleeding, other sites (e.g., peritoneum, pericardium)

Caution:

- Sudden onset of headache or focal neurologic signs should trigger evaluation for intracranial bleeding, despite a <2% overall rate (and an even lower rate in children).

- In ITP, oromucosal hemorrhage may predict CNS bleeding, particularly with platelet count $\leq 20 \times 10^9/L$
- Thrombocytopenia with microangiopathic hemolytic anemia (MAHA), renal failure, neurologic abnormalities, fever, other organ failure, or nonspecific symptoms (e.g., nausea, weakness, abdominal pain) **should raise suspicion for TMA.**

Use bleeding assessment tools to evaluate **severity of bleeding** (ITP-BAT, Modified Buchanan bleeding score); note their limited predictive value for future bleeding and always interpret alongside the platelet count.

Infectious syndrome: if purpura is present, rule out purpura fulminans (necrotic lesions, rapid spread, or fever) suggestive of meningococcal infection; **start antibiotics immediately.**

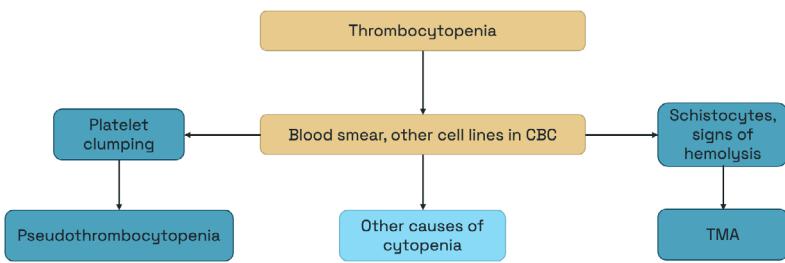
Signs of etiology: sepsis, autoimmune disease, lymphadenopathy, splenomegaly, etc.

Patient interview	Medical history: underlying pathology that may be associated with thrombocytopenia (HIV, HCV, HBV, autoimmune diseases, hematologic disorders, neoplasms, etc.)
	Drug history: use of anticoagulants, antiplatelet agents, recent addition of a new drug
	Detailed family history of thrombocytopenia, leukemia, bone marrow failure, bleeding disorders, and syndrome-specific issues
	Intake of alcohol and other toxic substances
	Disease history, associated symptoms (hemorrhagic syndrome), rate of progression, availability of previous blood counts, other comorbidities
	Pregnancy (gestational thrombocytopenia, ITP during pregnancy, TMA)

2.3 Diagnostic evaluation

- Always:
- CBC and blood smear: check for associated cytopenias, abnormal circulating cells (blasts, abnormal lymphocytes), platelet morphology, schistocytes (TMA)
 - Platelet clumping on blood smear is suggestive of EDTA-dependent pseudothrombocytopenia (exclude by sampling with a citrate tube, and/or peripheral blood smear analysis)

- Coagulation tests: PT, aPTT, fibrinogen, D-dimer (DIC)
- Blood chemistry: hemolysis tests: haptoglobin, LDH, bilirubin; creatinine



If TMA is suspected, refer to the corresponding section.

Figure 2.2: Diagnostic approach to thrombocytopenia.

- Circumstantial:
- Blood cultures if fever. Thick and thin films at pH 7.2 in the appropriate context, to evaluate for malaria
 - Bone marrow aspiration: perform immediately if abnormal circulating cells are present to exclude marrow infiltration. If ITP is suspected, bone marrow aspiration is indicated only if the patient is >60 years old, has abnormalities of other blood lines, organomegaly or lymphadenopathy or resistance to primary treatment
 - Blood group and direct antiglobulin test (DAT; Coombs) (Evans syndrome)
 - Platelet aggregation (if qualitative disorder suspected), von Willebrand disease (VWD) type 2B, genetic testing (if strong suspicion of inherited form)
 - Vitamin B12, folate

Isolated thrombocytopenia with no other biological and clinical abnormalities should be regarded as ITP.

Assess the severity of thrombocytopenia (in the absence of hemostatic disorders). Risk is exacerbated by concurrent treatment with antiplatelet drugs or anticoagulants.

No risk of spontaneous bleeding	$\geq 80 \times 10^9/L$
Low risk of spontaneous bleeding	$20\text{--}50 \times 10^9/L$ usually asymptomatic thrombocytopenia
Risk of spontaneous bleeding	$<20 \times 10^9/L$ High risk when $<10 \times 10^9/L$

2.4 Clinical management

Caution: all newly presenting febrile purpuras should be considered **purpura fulminans** until proven otherwise (**emergency antibiotic treatment** – i.e., ceftriaxone 100 mg/kg per 24 h or cefotaxime 50 mg/kg per 24 h, alternatively amoxicillin 25–50 mg/kg per 24 h)

Platelet transfusion

Central etiology	Presence of bleeding and/or platelets < 20 × 10 ⁹ /L
Peripheral etiology	For ITP , transfusions are of scarce and very brief efficacy and are indicated only in cases of life-threatening bleeding for their immediate but temporary hemostatic effect. Other emergency treatments (IVIG, high dose corticosteroids) must be added.

Note: Thresholds of <10 × 10⁹/L in patients without additional risk factors or no prophylactic platelet transfusion for asymptomatic cases with chronic BM failure not receiving intensive therapy can also be acceptable: consult local protocols.

In rare cases, platelet transfusions may afterwards be fractionated every 8 hours (more effective for obtaining a platelet increase at 1 hour) or less in order to reach the desired platelet threshold (100 × 10⁹/L for intracerebral bleeding or 50 × 10⁹/L for any other active bleeding).

Principles of ITP Treatment

Initial treatment depends on the severity of thrombocytopenia and the associated hemorrhagic signs.

- Initial treatment (first line therapy) should be initiated in cases of newly diagnosed ITP with a platelet count of < 20–30 × 10⁹/L or in the presence of significant bleeding such as multiple petechiae, oral hemorrhagic bullae, hematuria, menorrhagia or other organ bleeding. First-line therapy consists of either steroids or IVIg, and is dependent on the grade of emergency and the need for rapid platelet increase, such as in severe bleeding.
- Emergency treatment should be initiated in case of massive bleeding, intracerebral bleeding, other major organ bleeding, or in patients with < 10 × 10⁹/L with bleeding manifestations.
- If imminent risk for life, consider platelet transfusion together with high dose corticosteroids and intravenous immunoglobulin (IVIg) 1 g/kg per day for 1–2 days or 400 mg/kg per day for 5 days. If bleeding is not immediately life-threatening, dexamethasone at 40 mg per day for 4 days plus IVIg may be sufficient and safe.

Surgery. Most surgical intervention require > 50–80 × 10⁹/L; in these cases, IVIG at the doses above may be the best option. When platelet count is 50–80 × 10⁹/L, antithrombotic prophylaxis can be given.

In patients with recurrence of thrombocytopenia <20–30 × 10⁹/L after initial treatment, thrombopoietin receptor agonists (TPO-RA) may be an option.

References

- Neunert C, et al. Blood Adv. 2019;3:3829–3866.
- Rodeghiero F, et al. Blood. 2013;121:2596–2606.
- Kaufman RM, et al. Ann Intern Med. 2015;162:205–213.
- Estcourt LJ, et al. Br J Haematol. 2017;176:365–394.
- Liu XG, et al. J Hematol Oncol. 2023;16:4.

3. Thrombotic microangiopathies

Key facts

- Very rare; diagnostic and therapeutic emergency.
- Treatment in an intensive care unit.
- Platelet transfusion contraindicated unless symptomatic bleeding.

Important definitions:

- Thrombotic microangiopathies (TMA): syndrome characterized by mechanical hemolytic anemia (presence of schistocytes on blood smear with negative Coombs test) and peripheral thrombocytopenia, with or without associated organ failure.

3.1 Etiology

TMA have diverse causes, including congenital or acquired enzyme deficiencies, infections, complement dysregulation, systemic disorders, drug exposure, and malignancy.

Thrombotic thrombocytopenic purpura (TTP):

- Congenital ADAMTS13 deficiency due to biallelic mutations
- Acquired ADAMTS13 deficiency due to anti-ADAMTS13 autoantibodies

Hemolytic uremic syndrome (HUS):

- Shigatoxin-associated HUS caused by certain strains of Escherichia coli (STEC+)
- Typically affects children with gastroenteritis and bloody diarrhea

Atypical HUS:

- Disorders of the alternative complement pathway

Other conditions associated with TMA:

- HELLP syndrome
- Malignant hypertension
- Catastrophic antiphospholipid syndrome (CAPS)

- Post-HSCT TMA
- Iatrogenic: anticalcineurins, rapamycin, ticlopidine, clopidogrel, emicizumab with aPCC, chemotherapy (mitomycin C, gemcitabine, anti-VEGF, proteasome inhibitors)
- Metastatic cancer with marrow infiltration
- HIV infection

3.2 Clinical symptoms

Patients with TMA may present with diverse symptoms reflecting multi-organ involvement.

Typical pentad of TTP

(rarely all present; brain involvement more frequent than kidney involvement)

1. **Thrombocytopenia:** low platelet count causing bleeding symptoms such as petechiae (small red or purple spots on the skin), easy bruising, bleeding gums, or nosebleeds
2. **Microangiopathic hemolytic anemia:** fatigue, weakness, pallor, jaundice (yellowing of the skin or eyes), or dark urine
3. **Neurological symptoms:** can range from mild (headache, confusion, difficulty speaking) to severe (seizures, stroke-like symptoms, coma)
4. **Kidney dysfunction:** decreased urination, blood in urine, elevated creatinine
5. **Fever:** usually low-grade

More frequently a triad of thrombocytopenia, hemolytic anemia, and neurological symptoms.

Typical triad of HUS

(Kidney involvement more frequent than brain involvement)

1. **Microangiopathic hemolytic anemia:** fatigue, pallor, jaundice, or dark urine
2. **Thrombocytopenia:** low platelet count causing bruising, petechiae, or bleeding
3. **Acute kidney injury:** hallmark feature distinguishing HUS from TTP

Typical HUS (more common in children than adults): often preceded by (bloody) diarrhea, typically 5–10 days before onset; severe abdominal pain and cramping; facial swelling or edema, oliguria or anuria; hypertension

Atypical HUS (more common in adults than children): gradual onset of fatigue, fluid retention and swelling, hypertension.

Other symptoms may include signs of organ ischemia (e.g., cardiac involvement, hepatic dysfunction).

3.3 Diagnosis

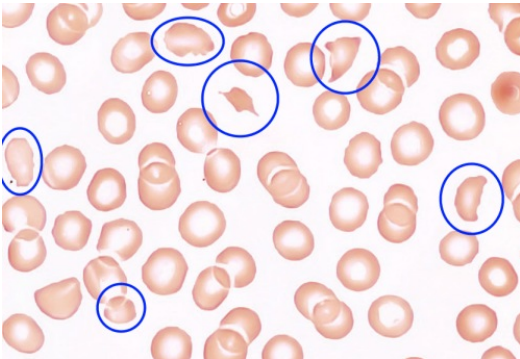
The diagnosis of TMA, particularly TTP, should be considered in the presence of hemolytic anemia with thrombocytopenia, especially when organ failure is present (e.g., cerebral damage, abdominal pain, renal failure). Repeated examination of the peripheral smear for schistocytes is essential. Validated scoring systems, such as the PLASMIC score, can assist in diagnosis.



To access the scoring system (mdcalc.com), follow this [link](#) or scan the QR code.

Urgent investigations

- CBC
- Peripheral smear test for schistocytes
- Reticulocyte count
- Coombs test and hemolysis work-up
- Standard coagulation screening (aPTT, PT, fibrinogen – distinguish from DIC)
- Renal function test and proteinuria
- Liver function tests
- ECG and troponin (to detect underdiagnosed myocardial damage)
- Clinically relevant brain imaging
- HIV and hepatitis serology



Credit:
Central Hematology Laboratory
Hemostasis Research Laboratory
Bern University Hospital & University
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Figure 3.1: Peripheral blood smear showing schistocytes (fragmented red blood cells) in a patient with thrombotic microangiopathy

Tests before treatment

- ADAMTS13 activity (<10% confirms TTP diagnosis) and anti-ADAMTS13 antibodies (check local lab policies; results may be confounded by prior plasma transfusion or plasma exchange)
- If infectious syndrome suggests STEC+ HUS: blood cultures, urine test, and stool sample (or rectal swab) stored at +4°C to test for enteropathogenic *Escherichia coli* and shigatoxins
- If syndrome suggests atypical HUS: explore the alternative complement pathway (biochemical and genetic tests)
- Blood group and antibody screen (IAT, direct Coombs test)
- Height and weight (for plasma volume calculation before plasmapheresis)

3.4 Initial therapeutic management

TMA are associated with very high mortality. Early initiation of treatment is critical and should not be delayed while awaiting confirmatory tests. Management includes urgent supportive care and, where appropriate, disease-specific therapy.

General management

- Refer patient to an apheresis unit without delay
- Ensure central venous line access and prepare plasma (defrosting)
- No systematic platelet transfusion
- Red blood cell transfusion and folate supplementation as required
- Initiate thromboprophylaxis with mechanical measures; start LMWH once platelet count is $>50 \times 10^9/L$

Specific therapy

Regulatory approvals, drug availability, and clinical guidelines may differ between countries. Clinicians should always consult local guidance to tailor management.

- **Autoimmune TTP**
 - Daily plasma exchange of 1.5 plasma volume ($\approx 60 \text{ mL/kg}$) until platelet count normalizes and hemolysis markers decrease
 - Start treatment while awaiting ADAMTS13 results if clinical score is highly suggestive
 - Immunosuppression: corticosteroids (methylprednisolone IV or prednisone PO 1–2 mg/kg per day) plus rituximab as soon as severe ADAMTS13 deficiency is confirmed
 - Caplacizumab: 10 mg IV before first plasma exchange, then 10 mg SC after each exchange until ADAMTS13 activity normalizes

- Note: Caplacizumab is a monoclonal antibody against VWF and may increase bleeding risk; VWF-containing concentrates may be required
 - If concurrent VTE is present, therapeutic anticoagulation dose may need adjustment when used with caplacizumab
 - Platelet transfusion should be avoided unless life-threatening bleeding occurs
- **Congenital TTP**
 - Plasma infusions until thrombocytopenia and hemolysis resolve
 - **STEC+ HUS**
 - Symptomatic management: volume expansion and rehydration, blood pressure control, renal replacement therapy if required
 - Antibiotic therapy (bacteriostatic) may be considered on a case-by-case basis
 - **Atypical HUS**
 - Symptomatic management: renal replacement therapy, blood pressure control
 - Anti-complement therapy (eculizumab)
 - **TMA in specific contexts**
 - Management directed at underlying cause (e.g., HELLP, malignant hypertension, drug-induced, post-HSCT, malignancy, HIV)

References

- George JN, Nester CM. N Engl J Med. 2014;37:654–666.
- Scully M, Goodship T. Br J Haematol. 2014;164:759–766.
- Bendapudi PK, et al. Lancet Haematol. 2017;4:e157–e164.
- Subhahn M, Scully M. Blood Rev. 2022;55:100945.
- Scully M, et al. Br J Haematol. 2023;203:546–563.
- Zheng XL, et al. J Thromb Haemost. 2020;18:2486–2495.

4. Disseminated Intravascular Coagulation

Key facts

- Disseminated Intravascular Coagulation (DIC) is always secondary to an underlying condition (e.g., severe infections, trauma, malignancies [solid or hematologic], obstetric complications).
- Laboratory features: thrombocytopenia, prolonged PT and aPTT, low fibrinogen, increased D-dimer.
- Scoring systems (e.g., ISTH) can aid diagnosis.
- ICU transfer may be required.
- Treatment is primarily etiological.
- In case of active bleeding: transfuse platelets to maintain $>50 \times 10^9/L$; give fresh frozen plasma (FFP) if PT $>1.5 \times$ normal or fibrinogen <1.5 g/L.
- Avoid invasive procedures if possible.
- Compression therapy and LMWH or UFH are recommended for thromboprophylaxis if no bleeding; therapeutic dosing for overt thrombosis.

Important definitions:

- DIC is a syndrome of systemic activation of coagulation.
- DIC is characterized by ongoing stimulation of the coagulation cascade, eventually leading to depletion of coagulation factors and platelets.
- It is associated with widespread clot deposition (thrombotic complications and organ failure) followed by fibrinolysis and consumption of platelets and coagulation factors (bleeding).
- DIC may be acute or chronic (in cases of malignancy or large vascular malformations).
- In hematologic patients, DIC is commonly observed in the setting of promyelocytic leukemia (M3), but may also develop in the course of AML with monocytic differentiation, sepsis and incompatible transfusion.

4.1 Underlying conditions

A wide variety of conditions can trigger disseminated intravascular coagulation (DIC). The most frequent underlying etiologies are listed below.

- **Malignancy:** hematologic malignancies, especially acute leukemias. Acute myeloid leukemia (AML) is more often associated with DIC than acute lymphoblastic leukemia (ALL). Among AML subtypes, AML-M3 accounts for approximately 75% of cases and is more frequent than AML-M4 and AML-M5. Solid tumors may also trigger DIC.
- **Infections:** bacterial sepsis (e.g., respiratory, genitourinary), protozoa (malaria), viral hemorrhagic fevers (e.g., Marburg, yellow fever), CMV, COVID-19.
- **Transfusion or transplantation:** incompatible blood product transfusion, graft rejection.
- **Biological or chemical agents:** drugs, venoms (e.g., snake bite).
- **Vascular malformations:** large aneurysms, arteriovenous malformations, congenital vascular tumors (e.g., Kasabach-Merritt syndrome).
- **Tissue damage:** major trauma, crush syndrome, extensive burns, hypo- or hyperthermia.
- **Pregnancy complications:** preeclampsia, eclampsia, placental abruption, amniotic fluid embolism, postpartum hemorrhage.

Main mechanisms:

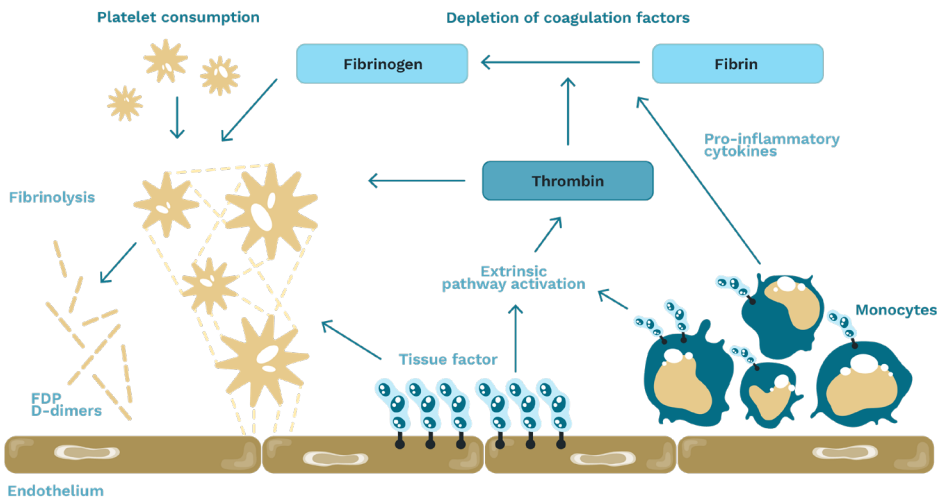


Figure 4.1. Pathophysiology of disseminated intravascular coagulation (DIC)

- Thrombin generation in DIC is most commonly triggered by induced expression of tissue factor on endothelial cells, monocytes, or cancer cells in response to the underlying condition.
- Activation of coagulation then induces a physiologic fibrinolytic response. This may eventually lead to depletion of coagulation and anticoagulation factors and platelets through consumption, inhibition, and defective hepatic synthesis, manifesting as prolonged clotting times and thrombocytopenia.
- The predominant symptom may either be **bleeding, thrombosis, or neither** (subclinical DIC with only laboratory abnormalities, often seen in many solid cancers).
- When **hyperfibrinolysis** predominates (**AML-M3, vascular abnormalities**), **bleeding** is the primary manifestation.
- When hypercoagulation with impaired **fibrinolysis** predominates (**sepsis, some solid tumors**), thrombosis of small- and medium-sized vessels occurs, contributing to organ failure.
- When both hypercoagulation and hyperfibrinolysis are present (obstetric complications, surgery), consumption of coagulation factors dominates, leading to massive bleeding and possible death, if not promptly treated with transfusions.

4.2 Clinical presentation

Depends on the underlying disorder, DIC subtype (procoagulant, hyperfibrinolytic, or subclinical; see above), severity, and duration.

- **Bleeding:** mucocutaneous hemorrhages, persistent bleeding at puncture sites.
- **Thrombosis:** mainly disseminated, affecting the microcirculation and leading to organ failure (acute renal failure with cortical necrosis, liver insufficiency, encephalopathy, acute respiratory distress syndrome, skin necrosis, shock).

Note

- Severe infections: primarily thrombotic consequences.
- APL (M3) and AML with monocytic differentiation (M4, M5): primarily bleeding consequences.
- Solid tumors: primarily thrombotic consequences.
- Trauma and burns: primarily bleeding, followed by thrombosis.
- Obstetric complications: primarily bleeding in combination with thrombosis.
- Large vascular malformations: primarily bleeding consequences.

4.3 Diagnostic evaluation

Diagnosis of DIC requires consideration of the clinical context (associated condition), symptoms, and laboratory abnormalities over time. No single laboratory test is diagnostic, so repeat testing (from monthly to daily, depending on the case) is essential to assess dynamics.

Core laboratory tests

- **CBC:** Thrombocytopenia with a downward trend in serial measurements. An abrupt drop, even within the normal range, may indicate early DIC. Thrombocytopenia may also reflect the underlying disorder (e.g., impaired production in leukemia, destruction or impaired production in sepsis).
- **Coagulation:**
 - **PT and aPTT:** Classically prolonged but may be normal. Worsening trends add diagnostic value. Consider confounders such as liver disease, vitamin K deficiency, paraproteinemias, or acquired inhibitors.
 - **Fibrinogen:** Typically decreased, especially in hyperfibrinolytic forms, but can be normal or increased (in procoagulant DIC or as an acute-phase reactant). Declining values are informative.
 - **FDPs and D-dimers:** Usually increased (especially in hyperfibrinolytic forms), but elevations may also result from trauma, surgery, bleeding, venous thromboembolism, or impaired kidney or liver function. Worsening trends add diagnostic value.

Additional tests (supportive)

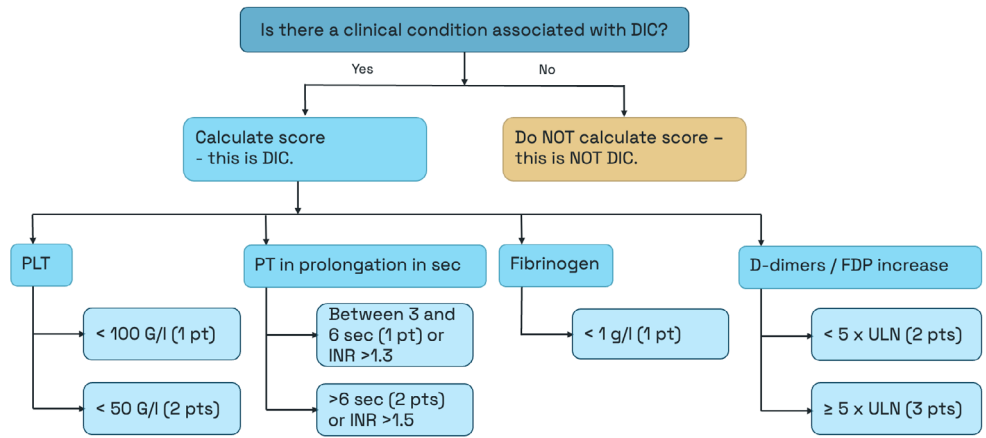
- **Blood smear:** Schistocytes may be present but are non-specific, and can also suggest thrombotic microangiopathy.
- **Coagulation factor assays:** If available, reduced activity of factors such as V and II supports the diagnosis. Acute-phase factors (e.g., VIII) may remain normal or be increased. Serial testing can help differentiate from liver disease or vitamin K deficiency.

Considerations for differential diagnosis

- **Liver failure:** Decreased synthesis of coagulation factors and fibrinogen due to impaired hepatic function (except factor VIII and von Willebrand factor). FDPs may be only mildly elevated because fibrinolysis is also impaired. Thrombocytopenia may occur from hypersplenism and reduced thrombopoietin production, but is usually stable, unlike in DIC.

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- **Primary activated fibrinolysis:** Rare condition with isolated activation of fibrinolysis leading to fibrinogen degradation. Laboratory features include markedly increased FDPs, marked reduction in fibrinogen, and prolonged PT. Seen in some malignant tumors (e.g., prostate cancer, after surgery) and in amniotic fluid embolism.
- **Thrombotic microangiopathies (TMA):** Thrombocytopenia with schistocytes may indicate TTP or HUS. Unlike DIC, clotting times are normal and D-dimers are normal or only slightly elevated.
- **Heparin-induced thrombocytopenia (HIT):** Presents with thrombocytopenia and thrombosis (hence, elevated D-dimers) but normal clotting times. Typically occurs 5–10 days after exposure to heparin, often after prophylactic low-dose use.

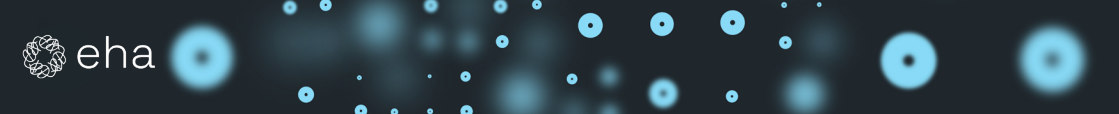
The International Society of Thrombosis and Haemostasis (ISTH) DIC score can facilitate the diagnostic process and estimate the severity of DIC (overt vs non-overt):



Score ≥ 5 pts: consistent with overt DIC – repeat every 24h
 Score < 5 pts: not suggestive of DIC – may be non-overt DIC – repeat every 24-48h

Figure 4.2: International Society on Thrombosis and Haemostasis (ISTH) scoring system for disseminated intravascular coagulation (DIC).

Toh CH, Hoots WK; SSC on Disseminated Intravascular Coagulation of the ISTH. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. J Thromb Haemost. 2007 Mar;5(3):604-6. doi: 10.1111/j.1538-7836.2007.02313.x. Epub 2006 Nov 10. PMID: 17096704.



4.4 Clinical management

Summary

- The cornerstone of DIC treatment is management of the underlying disorder, which may lead to spontaneous resolution of the coagulopathy (e.g., ATRA in acute promyelocytic leukemia).
- Supportive treatment should be considered in patients with active bleeding or at high risk of bleeding, based on symptoms, laboratory data, and the need for invasive procedures.

Supportive therapy

- **Platelet concentrate:**
 - In bleeding patients if platelet count $<50 \times 10^9/L$.
 - In non-bleeding patients if platelet count $<10\text{--}20 \times 10^9/L$ (threshold may be higher in acute promyelocytic leukemia).
 - If high risk of bleeding (e.g., invasive procedure): transfuse 1–2 doses if platelet count $<30 \times 10^9/L$ in APL, or $<20 \times 10^9/L$ in most other conditions.
 - In the presence of bleeding: maintain platelet count $>50 \times 10^9/L$.
- **Fresh frozen plasma (FFP):** In bleeding patients if PT or aPTT $>1.5 \times \text{ULN}$, or fibrinogen $<1.5 \text{ g/L}$. Dose 15–30 mL/kg (adjusted for severity). Aim for fibrinogen $>1.0 \text{ g/L}$ and factor activity $>40\%$ if available.
- **Prothrombin complex concentrate:** Consider instead of FFP if volume overload is a concern.
- **Fibrinogen concentrate:** If fibrinogen remains $<1.5 \text{ g/L}$ despite other measures, especially in bleeding. Dose: 2–4 g IV.
- **Heparin:**
 - Consider pharmacologic anticoagulation in procoagulant and subclinical DIC. Contraindicated in hyperfibrinolytic DIC and in cases of active bleeding with platelet count $<20 \times 10^9/L$.
 - Isolated clotting screen abnormalities are not a contraindication.
 - LMWH preferred over UFH.
 - Uses:
 - Thromboprophylaxis in non-bleeding patients with DIC.
 - Therapeutic anticoagulation for overt arterial or venous thrombosis; may also be considered for purpura fulminans or acral ischemia.

- **Antifibrinolytics:** Not generally recommended. May be considered in DIC patients with severe bleeding due to marked hyperfibrinolysis (e.g., leukemia, trauma). Avoid combining ATRA with tranexamic acid due to risk of severe thrombosis.

References

- Wada H, et al. J Thromb Haemost. 2013;11:761–767.
- Wada H, et al. J Intensive Care. 2014;2:15.
- Thachil J, et al. J Thromb Haemost. 2015;13:671–675.
- Squizzato A, et al. J Thromb Haemost. 2020;18:2400–2407.
- Levi M, et al. Blood. 2018;131:845–854.
- Toh CH, et al. Hematology. 2013;2013:286–291.
- Iba T, et al. J Thromb Haemost. 2019;17:1989–1994.

5. Management of bleeding in patients with inherited bleeding disorders

Key facts

- Most common inherited bleeding disorders: von Willebrand disease (VWD) and hemophilia A/B.
- VWD: mainly mucocutaneous bleeding; hemophilia: joint and muscle bleeding.
- Desmopressin effective in type 1 VWD and mild hemophilia A; contraindicated in type 2B VWD.
- Factor replacement is standard in hemophilia and severe VWD
- Inhibitors in hemophilia A generally require bypassing agents in case of hemorrhage; avoid aPCC in the context of emicizumab.
- Always consult a specialized coagulation/hemophilia center for emergency management.

Important definitions:

- **Von Willebrand factor (VWF):** Protein needed for platelet adhesion and FVIII stability.
- **Von Willebrand disease (VWD):** Most common inherited bleeding disorder; quantitative or qualitative VWF defect.
- **Hemophilia A/B:** Congenital FVIII or FIX deficiency; X-linked.
- **Severity (hemophilia):** Severe <1%, moderate 1–5%, mild >5%.
- **Inhibitors:** Neutralizing antibodies against FVIII or FIX.
- **Bypassing agents:** rFVIIa or aPCC used in inhibitor-positive hemophilia.
- **Desmopressin (DDAVP):** Drug releasing endogenous VWF and FVIII.

5.1 Von Willebrand disease

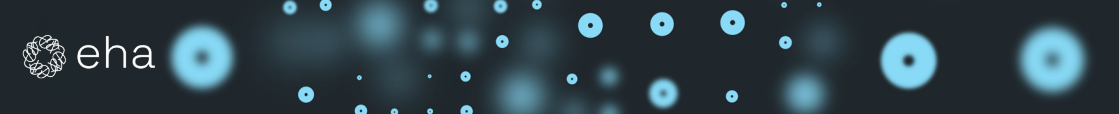
Von Willebrand disease (VWD) is the most common inherited bleeding disorder, caused by quantitative or qualitative abnormalities of von Willebrand factor (VWF).

5.1.1 Pathophysiology

- VWF has two main roles:
 - Platelet adhesion to the injured vessel wall and subsequent aggregation
 - Transport and stabilization of factor VIII
- Inheritance is usually autosomal dominant with variable penetrance and expression; severe forms (type 3) are recessive.
- Main types of VWD:
 - **Type 1:** partial quantitative deficiency (≈60–70% of cases)
 - **Type 2:** qualitative binding abnormalities (≈25% of cases)
 - Type 2A: absence of high-molecular-weight multimers (HMWM)
 - Type 2B: hyper-affinity for platelet GPIb, with variable thrombocytopenia and loss of HMWM; RIPA test shows increased platelet aggregation at low ristocetin concentrations
 - Type 2M: decreased affinity of VWF for platelet GPIb
 - Type 2N: reduced binding of VWF to factor VIII
 - **Type 3:** near-total deficiency (<5% of cases)

5.1.2 Clinical–biological picture

- Bleeding pattern:
 - Predominantly mucocutaneous bleeding (ecchymosis, epistaxis, gum bleeding, menorrhagia)
 - Gastrointestinal bleeding, especially small-bowel angiodysplasia
 - Hemarthrosis and muscle hematomas in type 2N and type 3
 - Post-traumatic and surgical bleeding
- Diagnostic work-up:
 - aPTT: normal in ~50% of cases
 - PFA-100: sensitive for most deficiencies (except type 2N), but non-specific
 - Platelet count: usually normal; thrombocytopenia may occur in type 2B
 - First-line assays: VWF antigen (VWF:Ag), ristocetin cofactor activity (VWF:RCo), factor VIII activity (FVIII:C)



Von Willebrand disease types differ substantially for triage and initial management. Check Table 5.1 for more information

Feature / Test	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
Inheritance	50–75% Dominant		20–30% Dominant or recessive			≤5%, Recessive
Platelet count	Normal	Normal	Fluctuating thrombocytopenia	Normal	Normal	Normal
aPTT	Normal or mildly prolonged	Normal or mildly prolonged	Normal or mildly prolonged	Normal or mildly prolonged	Prolonged	Markedly prolonged
VWF:Ag	Low	Normal or low	Normal or low	Normal or low	Normal or low	Very low/ undetectable
VWF:RCo	Low	Decreased (disproportionate to Ag)	Decreased	Decreased	Normal (or slightly decreased)	Very low/ undetectable
FVIII:C	Normal or low	Normal or low	Normal or low	Normal or low	Low	Very low
VWF multimers (HMWM)	Normal pattern, low concentration	Absent	Decreased	Normal pattern or mildly decreased	Normal pattern	Absent
RIPA	Normal or decreased	Decreased	Increased at low ristocetin	Decreased	Normal	Absent response
Desmopressin response	Usually effective	Rarely effective	Contraindi- cated	Rarely effective	Often effective	Ineffective

Table 5.1. Key diagnostic features and expected desmopressin response across von Willebrand disease types.

Notes: “Decreased” indicates lower than the laboratory reference range; “very low/undetectable” typically indicates <10 IU/dL. Increased RIPA at low ristocetin concentrations supports type 2B and desmopressin is contraindicated in type 2B.

5.1.3 Specific emergency treatments

Desmopressin (DDAVP)

- Perform a DDAVP trial in routine care and assess response at 1 h and 4 h; this facilitates planning for elective surgery and treatment of acute bleeding.

- Perform a DDAVP trial in routine care and assess response at 1 h and 4 h; this facilitates planning for elective surgery and treatment of acute bleeding.
- Fluid restriction 1 L in 24 h in adults, especially with repeated doses.
- **Absolute contraindications:** type 2B VWD; history of seizures; age ≤2 years.
- **Not indicated:** type 3 VWD.
- **Relative contraindications:** coronary artery disease, pregnancy, inability to comply with fluid restriction, hypertension.
- **Adverse effects:** hyponatremia, headache, flushing, tachycardia.

Replacement therapy

- Recombinant VWF for baseline FVIII >40% or for minor bleeding not requiring FVIII correction within 6–12 h.
- Plasma-derived combined VWF and FVIII concentrates, or recombinant VWF with recombinant FVIII, when baseline FVIII <40% or in emergencies.
- Repeat dosing every 24 h for 1 day to 2 weeks depending on indication (e.g., surgery).
- For multi-day therapy, monitor FVIII:C and VWF to avoid over-treatment.
- In severe bleeding, repeat the initial dose after 12 h.
- Rare (<10%) anti-VWF alloimmunization in type 3; manage in specialized centers (e.g., with recombinant FVIII or rFVIIa).

5.1.4 General clinical management

Initial steps

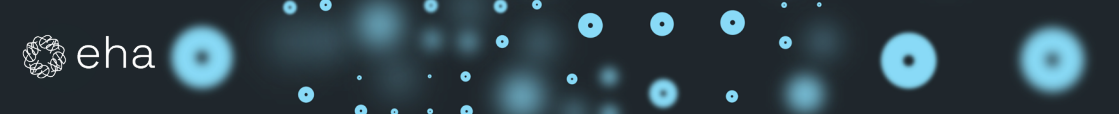
- Retrieve the “Care and Emergency Card”: type of bleeding disorder, DDAVP responsiveness, contact details of the referral center.
- Seek referral center input when specific treatment is required.

Minor bleeding / local hemostasis

- Examples: epistaxis; menorrhagia.
- Local measures: manual compression for 10 min (“watch in hand”), hemostatic wick or nasal packing.
- Antifibrinolytics: tranexamic acid 15 mg/kg orally or IV three times daily; may be used as a mouthwash for gingival bleeding or after oral surgery.
- Caution: avoid tranexamic acid in hematuria.
- Preventive measures: avoid NSAIDs and intramuscular injections; consider hormonal therapy to manage menorrhagia.
- If local care fails or symptoms worsen: use specific therapy based on clinical severity and DDAVP responsiveness (DDAVP if known responder; otherwise replacement therapy).

Severe bleeding or bleeding not controlled by local measures

- Examples: gastrointestinal hemorrhage.



- VWF with or without FVIII replacement therapy; obtain referral center advice when possible.
- Standard hemorrhage management.

High-risk situations outside scheduled surgery

- Head or abdominal trauma: give preventive replacement therapy immediately, before imaging.
- Surgical emergency: administer replacement therapy without delay.

5.2 Hemophilia

Hemophilia A and B are congenital coagulation disorders caused by factor VIII (FVIII) or factor IX (FIX) deficiency, respectively. Emergency care hinges on rapid assessment of severity and inhibitor status, plus timely access to factor replacement or bypass therapy.

5.2.1 Pathophysiology basics

- Congenital deficiency of FVIII (hemophilia A, HA) or FIX (hemophilia B, HB).
- X-linked recessive transmission (~30% de novo). Primarily affects men; female carriers may have low factor levels with a usually minor hemorrhagic phenotype due to X-chromosome inactivation.
- Bleeding severity correlates with factor level (often similar within families):
 - Mild: FVIII or FIX >5%; provoked bleeding; sometimes undiagnosed.
 - Moderate: FVIII or FIX 1–5%; frequent provoked bleeding; rare spontaneous bleeding.
 - Severe: FVIII or FIX <1%; frequent provoked and spontaneous bleeding; early diagnosis.
- Clinical picture: predominantly internal bleeding (hemarthroses, muscle hematomas, intracranial hemorrhage); external bleeding is less common. Recurrent hemarthrosis in a “target” joint leads to hemophilic arthropathy.
- Treatment principles: severe and some moderate cases require prophylaxis (replacement or non-replacement) from early childhood to prevent severe bleeding and arthropathy; provide education for self-management and on-demand treatment. Emicizumab (bispecific FIXa–FX antibody) is approved for HA with and without inhibitors.

5.2.2 Specific emergency treatments

- Use the patient’s usual product first.
- **DDAVP (desmopressin):** for non-severe bleeding in **mild HA** if a known responder (DDAVP trial required, as in type 1 VWD).

Replacement therapy

- **Factor VIII (HA):** recombinant preferred where available; plasma-derived also effective. Extended half-life products lengthen dosing intervals.
 - Recovery: 1 IU/kg ≈ 2 IU/dL FVIII.
 - Half-life: 8–12 h (up to ~18 h with extended half-life).
 - Dose to target based on age (shorter half-life in children), weight, and clinical context.
- **Factor IX (HB):**
 - Recovery: 1 IU/kg ≈ 0.7–1 IU/dL FIX.
 - Half-life: 12–20 h (up to 75–90 h with extended half-life).
- Repeat dosing every **12–72 h** according to bleed severity and product half-life.
- Major complication: **inhibitors** (anti-FVIII or anti-FIX), usually within the first **20–50 exposure days**; renders replacement ineffective. Occurs in about **one-third** of severe HA and **~5%** of severe HB (in HB, often preceded or accompanied by immune-allergic reactions).

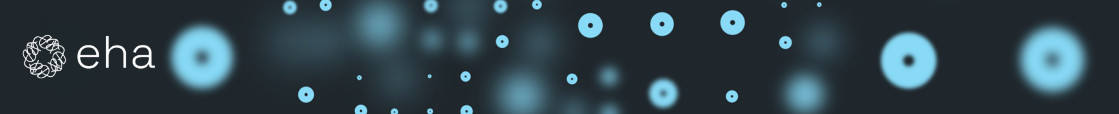
Non-replacement therapy

- **Emicizumab (Hemlibra®):** bispecific monoclonal antibody bridging FIXa and FX; prophylaxis for HA with and without inhibitors; subcutaneous every **1, 2, or 4 weeks**.
- **If emicizumab is not possible, give rFVIIa (NovoSeven®)** 90 µg/kg.
- If a patient on emicizumab bleeds, prefer **rFVIIa (NovoSeven®)** and avoid aPCC (FEIBA®) because high or prolonged aPCC dosing (e.g., ≥100 U/kg per day for >24 h) increases the risk of thrombotic microangiopathy and thrombosis. If not on emicizumab, rFVIIa or aPCC may be used per referral-center guidance.

5.2.3 General clinical management

Initial steps

- Retrieve the “Care and Emergency Card”: type and severity, inhibitor status, usual treatment, prophylaxis use, DDAVP responsiveness in mild HA, and referral-center contacts; consider the patient’s disease knowledge.
- In patients on emicizumab, aPTT and one-stage FVIII may appear normal; **use a chromogenic FVIII assay**.
- Contact the reference center whenever possible, especially when specific treatment is required.



Assessment of bleeding

- Assess hemodynamic status.
- Determine location and extent: life-threatening (brain, pharynx/neck, iliopsoas hematoma) or function-threatening (joint, periorbital area, axillary fossa, forearm, hand, inguinal, popliteal fossa).
- Maintain high suspicion for **iliopsoas hematoma** (can mimic a surgical abdomen; may present with back or hip pain).
- **Do not perform invasive procedures without prior replacement therapy.**

Minor bleeding and local hemostasis

- Examples of minor bleeding: bruises, small subcutaneous hematomas, small muscular hematomas, epistaxis.
- Small hematomas or bruising: analgesics, compression, icing.
- Epistaxis: evacuate clots, then manual compression for 10 min (“watch in hand”); hemostatic wick or nasal packing as needed.
- Mucocutaneous bleeding: tranexamic acid 15 mg/kg orally or IV three times daily; may be used as a mouthwash for gingival bleeding or after oral surgery.
- Caution: avoid tranexamic acid in hematuria.
- If local care fails or symptoms worsen: escalate to specific therapy based on severity and DDAVP responsiveness (DDAVP if known responder; otherwise replacement therapy).
- Preventive measures: avoid NSAIDs and intramuscular injections; consider hormonal therapy to manage menorrhagia.

Hemarthrosis

- Clinical diagnosis (joint ultrasound helpful if hip involvement suspected).
- Short immobilization **24–48h**, icing, then physiotherapy.
- **Systematic replacement therapy;** dose based on weight, age, and target factor level.

Severe bleeding, head or abdominal trauma, or surgical emergency

- Administer **replacement therapy immediately, before further examination;** if an inhibitor is present or suspected, give a **bypassing agent** (e.g., rFVIIa) as first-line. **Pre-hospital administration is appropriate if the patient or the parents/caregivers have the product at home.**
- **Iliopsoas hematoma:** dose every **8h (HA)** or **12h (HB)** for ~1 week, then taper to maintain trough levels **>50%** (e.g., FVIII **50 IU/kg**, then **30 IU/kg** every **8h**; FIX **100 IU/kg**, then **50 IU/kg** per center protocol).
- **Major surgery or cerebral hemorrhage:** maintain FVIII or **FIX >80–100%** (e.g., FVIII **70 IU/kg**, then **50 IU/kg** every **8–12h**; FIX **50 IU/kg**, then **70 IU/kg** every **12–24h**).

- **Hematuria:** no replacement initially due to risk of clot formation; hydration and rest. If bleeding persists, consider replacement at usual doses. **Avoid tranexamic acid.**

Suspected inhibitor with life-threatening hemorrhage

- Treat immediately with a **bypassing agent** while awaiting inhibitor testing (e.g., spontaneous intracranial hemorrhage in a patient with severe HA recently started on prophylactic replacement).

5.3 Urgent management at a glance

Clinical pearls

Involve a coagulation specialist as soon as possible

Observe the patient and consult with other specialties to better adjust the next dose

Always remember tranexamic acid 10–15mg/kg IV (except in high urinary hemorrhages)

In trauma, do not wait for exams (e.g., CT scan) to start replacement or bypass treatment

Von Willebrand Disease	
DDAVP	First-line for type 1 (limited effect in type 1C); variable in types 2A and 2M; little effect in type 2N; no effect in type 3; contraindicated in type 2B
	Do not administer with a history of seizures or at age ≤2 years
	IV: 0.3 µg/kg in 50–100mL of saline over 30 min
	Intranasal: 2 sprays if weight >50 kg, 1 spray if weight <50 kg
Replacement	Repeat every 8–12 hours; tachyphylaxis after ≥3 doses
	Preferred for types 2 and 3, or type 1 without DDAVP response
	Dose (IU) = weight (kg) × desired increase from baseline (IU/dL × 0.5)

	Products vary in vWF:RCo units and may contain FVIII at different concentrations; consult the pharmacist.
	Target (day 1 in major bleed or surgery): >80–100 IU/dL (~40–50 IU/kg)

Hemophilia without inhibitors

Replacement	Recovery FVIII: 1IU/kg ≈ 2 IU/dL; FIX: 1IU/kg ≈ 0.7–1 IU/dL
	Target for joint, muscle, renal, deep wound: FVIII 40–60 IU/dL, FIX 40–60 IU/dL
	Target for Iliopsoas, nerve compression, CNS, GI, major surgery or trauma FVIII/FIX: 80–100 IU/dL Same target dose can be used for those on emicizumab

Hemophilia with inhibitors

Replacement	Only for low-responding inhibitor
	FVIII dose (IU) = weight(kg) × 80 × [(1–hematocrit) × antibody titer(BU)] + 50 IU/kg
Bypass	General recommended treatment
	rFVIIa initial dose 90 µg/kg; repeat every 2–6 h according to clinical course
	PCC initial dose ≤50 IU/kg (25 IU/kg may suffice), then 12–25 IU/kg every 6–8 h; do not exceed 100 IU/kg per day. Best avoided in patients on emicizumab (risk of TMA/venous thrombosis)

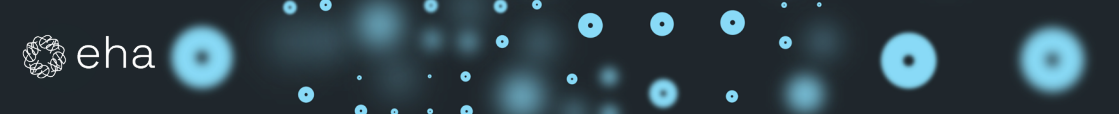
Rare Factor Deficiencies

Good phenotype–laboratory correlation: fibrinogen, prothrombin, FX, FXIII
Poor correlation: FV, FVII, FXI

General replacement	For the initial management. Afterwards, adjustments are necessary. ○ PCC 20–30 IU/kg (1 IU/kg ≈ 2 IU/dL) — prothrombin, FVII, FX. ○ FFP 15–25 mL/kg — FV, FXI (for FXIII use 3–5 mL/kg).
Specific replacement	Products generally available in hospitals for the initial management (ask your pharmacist if there are more; e.g. pd-FXIII, pd-FX) ○ Fibrinogen 50–100 mg/kg ○ rFVIIa 15–30 µg/kg every 4–6 h
Prophylaxis	○ Recommended for severe FXIII deficiency and afibrinogenemia; consider based on clinical phenotype for other deficiencies (usually not recommended for severe FXI deficiency)

References

- Srivastava A, et al. Haemophilia. 2020;26 Suppl 6:1–158.
- Connell NT, et al. Blood Adv. 2021;12;5:301–325.
- Mumford AD, et al. Br J Haematol. 2014;167:304–326.



6. Febrile neutropenia

Key facts

- Infection risk increases as ANC decreases, particularly $<0.5 \times 10^9/L$ or if neutropenia lasts ≥ 7 days.
- Febrile neutropenia is a medical emergency in patients with cancer: broad-spectrum antibiotics should be started immediately after blood cultures are taken.

Important definitions:

- **Fever:** single oral temperature of $\geq 38.3^\circ C$ or $\geq 38^\circ C$ sustained for ≥ 1 h.
- **Neutropenia:** ANC $<1.5 \times 10^9/L$; severe $<0.5 \times 10^9/L$.
- **Febrile neutropenia:** fever with ANC $<0.5 \times 10^9/L$, or ANC expected to fall $<0.5 \times 10^9/L$ within 48 h.

6.1 Clinical presentation and diagnostic evaluation of febrile neutropenia

1. General considerations

- Patients with febrile neutropenia (FN) must be examined within 1 h; diagnostic measures must not delay antibiotics.
- In clinically unstable patients, start antimicrobial therapy immediately after blood cultures
- Repeat careful clinical examination daily in all hospitalized febrile patients
- Persistent neutropenia (≥ 7 –10 days) increases the risk of fungal infection

2. Assessment

- Vital signs: look for shock or respiratory failure
 - Example scores: qSOFA score (respiratory rate $\geq 22/min$, systolic blood pressure ≤ 100 mmHg, altered mental status) or NEWS.
- Risk factors for complications: MASCC score (see below), anticipated severe neutropenia >7 days

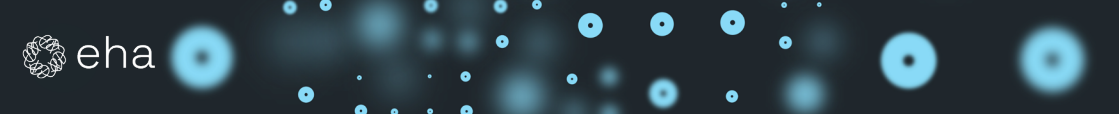
- Patient background: age, comorbidities (e.g., COPD, splenectomy)
- Physical examination: look for signs of infection at common sites
 - Pulmonary: cough, dyspnea, crackles, respiratory insufficiency
 - Urogenital: dysuria, flank pain
 - Central line: swelling, pain, secretion
 - Gastrointestinal: mucositis, diarrhea, abdominal pain, constipation
 - Liver: jaundice
 - CNS: headache, neurological symptoms
 - ENT and face: mucositis, tonsillitis, pharyngitis, facial pain, rhinorrhea, impaired vision or hearing
 - Skin and soft tissue: erythema, swelling, pain, pustule, indwelling catheters or devices
 - Spine and joints: swelling, pain

3. Diagnostic work-up

- Laboratory: CBC, CRP, renal and liver function, electrolytes
 - additionally, if indicated by severity: coagulation tests, serum lactate, arterial blood gas
- Microbiology: at least 2 sets of blood cultures (1 set: 1 aerobic and 1 anaerobic, ≥ 10 mL each); if central line in place, include 1 set from the line for differential time to positivity
Add according to clinical signs:
 - Respiratory: sputum for bacteriology and fungi, Legionella antigen (urine), viral swab or multiplex PCR
 - Diarrhea: stool cultures including Clostridioides difficile
 - UTI suspected: urine culture
 - Suspected fungal infection: serum galactomannan, fungal PCR, β -d-glucan
- Imaging:
 - Non-contrast chest CT (preferred over X-ray) if respiratory symptoms
 - CT sinuses if sinusitis symptoms
 - Ultrasound or CT if neutropenic colitis suspected
 - If fever persists ≥ 3 days in a high-risk patient, consider chest and sinus CT even without localizing signs

4. Additional considerations

- Check for colonization with resistant bacteria
- Review ongoing antibacterial or antifungal prophylaxis
- Persistent fever, new pulmonary infiltrates, or rising inflammatory markers: repeat microbiology and consider change in therapy; consult infectious disease or senior physician



6.2 Clinical management

General approach

- Risk stratification using the MASCC score and evaluation of risk factors for high-risk neutropenia to decide if hospitalization is necessary

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms*	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms*	3
Outpatient status	3
Age <60 years	2

Table 6.1: MASCC score

*based on the evaluation of the attending physician, only one of these may be applied

- MASCC score <21 points identifies patients requiring hospitalization

Additional risk factors for high-risk febrile neutropenia

- Expected prolonged neutropenia (>7 days) with ANC <0.1 × 10⁹/L
- Significant comorbidities (e.g., hemodynamic instability, hypoxemia, severe mucositis, abdominal or neurologic symptoms, central line-associated infection)
- Liver or renal failure, chronic pulmonary diseases

Other considerations for hospitalization

- Patient-intrinsic: previous compliance, mobility, presence and duration of prior neutropenic episodes
- Patient-extrinsic: treatment protocol, distance to nearest health care facility

General recommendations for therapy

- Immediate treatment with broad-spectrum antibiotics including a pseudomonas-active agent, started after microbiological sampling
- Review and adapt prophylaxis according to protocol (HSV, PCP, fungal prophylaxis, and G-CSF)

- Consider empirical antifungal therapy in high-risk patients with persistent fever
- Choose antimicrobial regimen according to local guidelines, availability and prevalence of resistant organisms
- Escalate therapy based on positive cultures and susceptibility testing
- Duration of antibiotics:
 - If an infectious source is identified: treat the standard duration for that infection or longer if clinically warranted
 - If no infectious source is identified:
 - If neutrophil recovery (>0.5 × 10⁹/L) occurs, empirical antibacterial therapy may be discontinued after ≥ 48h of defervescence.
 - In patients who remain clinically stable, empiric therapy may also be discontinued after 3–5 days of defervescence and clinical recovery, irrespective of neutrophil count.
 - Reinstitution of systemic antibacterial prophylaxis, if it had been administered prior to the onset of fever, may be considered until marrow recovery.

Consult infectious disease specialist for patients with renal failure, liver disease, β-lactam allergy, or recurrent fever during empirical therapy

Management of low-risk neutropenia

- Can be managed as inpatient or outpatient
- Oral broad-spectrum antibiotics are first line
- If patient is on fluoroquinolone prophylaxis, intravenous agents are recommended,
- Common oral regimens:
 - Amoxicillin-clavulanic acid 875/125 mg, 2–3 times daily, plus ciprofloxacin 750 mg twice daily
 - Amoxicillin-clavulanic acid 875/125 mg, 2–3 times daily, plus levofloxacin 750 mg once daily
 - If penicillin allergy: clindamycin 600 mg 3–4 times daily plus ciprofloxacin 750 mg twice daily

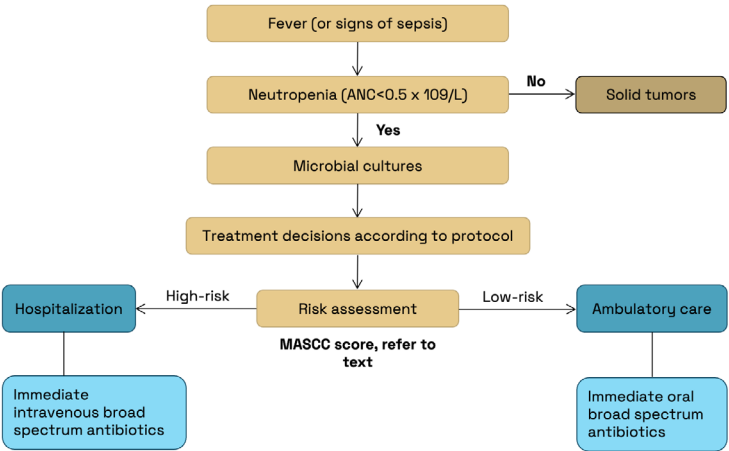


Table 6.1: Clinical management algorithm for febrile neutropenia

Management of high-risk neutropenia

- Should be managed in inpatient setting
- Intravenous broad-spectrum antibiotics are first line agents
- Frequently used regimes include:
 - Piperacillin-tazobactam (iv. 4 × 4.5 g)
 - First dose unchanged; adjust subsequent doses according to creatinine clearance
 - Use extended-infusion b-lactam antibiotics if possible
 - Meropenem (iv 3 × 1 g) or imipenem (iv 4 × 500 mg) in case of patients colonized with Gram-negative bacteria resistant to aminopenicillins
 - Cefepime (iv 3 × 2 g)
- Consider Gram-positive coverage if signs of cellulitis, mucositis, or central line infection are present
- Added empirical coverage should be considered and later tailored based on culture results or local epidemiology, for example:
 - MRSA: vancomycin (iv 2 × 1 g), linezolid (iv 2 × 600 mg) or daptomycin (iv 6 mg/kg per day)(e.g. central-line associated infection)
 - ESBL: meropenem (iv 3 × 1 g) or imipenem (iv 4 × 500 mg) (e.g. urinary or abdominal sepsis)
 - Other multidrug resistant bacteria: consult infectious disease specialist (e.g., MDR *Pseudomonas*)

References

- Freifeld AG, et al. Clin Infect Dis. 2011;52:e56-93.
- Sandherr M, et al. Lancet Reg Health Eur. 2025;51:101214.
- Ullmann AJ, et al. Clin Microbiol Infect. 2018;24(Suppl 1):e1-e38.
- Heinz WJ, et al. Ann Hematol. 2017;96:1775-1792.
- Klastersky J, et al. J Clin Oncol. 2000;18:3038-3051.
- Cotner SE, et al. Antimicrob Agents Chemother. 2017;61:e00871-17.
- Vardakas KZ, et al. Lancet Infect Dis. 2018;18:108-120.
- Yang H, et al. PLoS One. 2015;10:e0116769.
- ECIL. 2024. Available at: https://ecil-leukaemia.com/images/ecil-10/ECIL_10_-_bacterial_group_final_recommendations.pdf
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prevention and Treatment of Cancer-Related Infections. Version 1.2025. Available at: <https://www.nccn.org>

7. Hypercalcemia

Key facts

- The main hematological causes for hypercalcemia are: multiple myeloma, B-cell non-Hodgkin lymphoma, Hodgkin lymphoma, HTLV-1-associated T-cell lymphomas.
- Suspect in patients with: extracellular dehydration, confusion, acute renal failure, cardiac arrhythmias, constipation, elevated corrected calcium.
- Reference test: ionized calcium.
- Emergency management: ECG (conduction abnormalities), hydration with isotonic saline, treat underlying cause, bisphosphonates, intensive care or renal replacement therapy if severe.
- Differential diagnosis: endocrine disorders (e.g., hyperparathyroidism), drug-induced (e.g., thiazides, vitamin D, immune checkpoint inhibitors), prolonged immobilization.

Important definitions:

- **Normal total calcium:** 2.1–2.6 mmol/L (or 8.5–10.5 mg/dL).
- **Normal ionized calcium:** 1.16–1.31 mmol/L (or 4.65–5.25 mg/dL).
- **Hypercalcemia:** ionized calcium above the normal range (ionized calcium is the metabolically active fraction).
- **Corrected calcium:** estimated from total calcium, usually > 2.6 mmol/L
Formula: $\text{Corrected Ca (mmol/L)} = \text{Total Ca (mmol/L)} + 0.025 \times (40 - \text{albumin [g/L]})$.
Caution: correction formulas may be unreliable in multiple myeloma with marked paraproteinemia.

7.1 Background

The main causes of hypercalcemia can be divided into hematologic malignancies and non-hematologic conditions, as outlined below.

Hematological malignancies:

- Multiple myeloma (MM)
- Hodgkin lymphoma (HL)
- Non-Hodgkin lymphoma (NHL)
- HTLV-1-associated T-cell lymphomas (ATLL)

Non-hematological conditions:

- Hyperparathyroidism (should not be overlooked, particularly in early hematological malignancies; 6–25% of cancer cases)
- Hypercalcemia of malignancy (paraneoplastic or bone metastases)
- Granulomatous diseases (sarcoidosis, tuberculosis)
- Excess calcium or vitamin D supplementation
- Immobilization
- Medication: diuretics, lithium
- Endocrine diseases: hyperthyroidism, adrenal insufficiency

In addition to the underlying causes, it is important to understand the disease types and mechanisms through which hypercalcemia develops

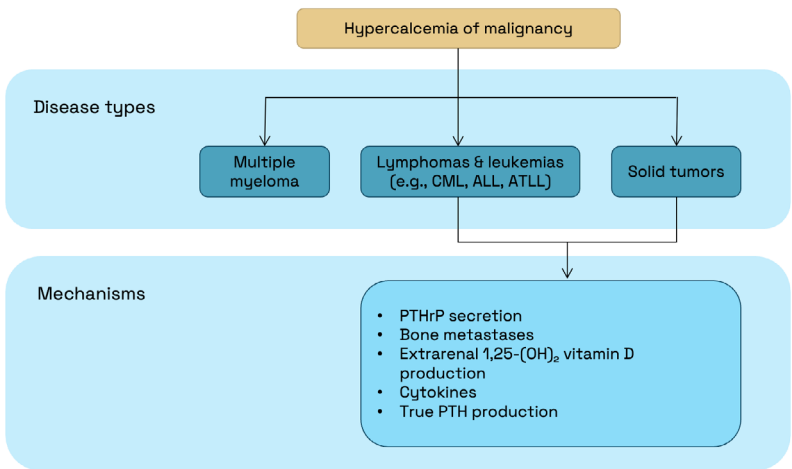
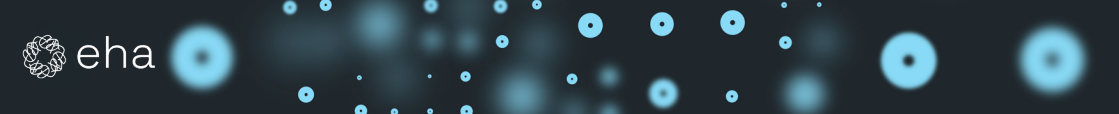


Figure 7.1: Disease types and mechanisms of hypercalcemia of malignancy



In most patients with hematologic malignancies or solid tumors, hypercalcemia is driven by elevated PTHrP. In MM, it results from local secretion of bone-resorbing factors (e.g., IL-6, DKK-1) and disrupted signaling pathways, causing bone resorption without new bone formation.

7.2 Clinical presentation

Hypercalcemia presents with a broad range of manifestations, most often affecting the cardiovascular, renal, gastrointestinal, neuromuscular, and neuropsychiatric systems:

- **Cardiac:** rhythm disturbances; ventricular tachycardia (VT), ventricular fibrillation (VF), QT shortening, tachycardia, PR prolongation.
- **Renal:** acute renal failure, extracellular dehydration, polyuria-polydipsia syndrome
- **Gastrointestinal:** abdominal pain, vomiting, constipation
- **Neuromuscular:** cramps, spasms
- **Neuropsychiatric:** confusion, disturbed mental state
- **Bone:** bone pain

7.3 Diagnostic evaluation

Diagnostic evaluation aims to confirm true hypercalcemia and identify the underlying mechanism.

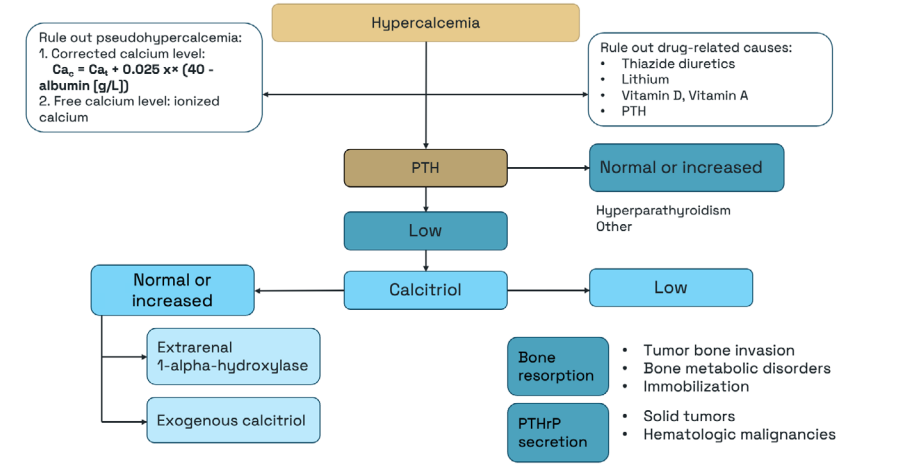


Figure 7.2: Diagnostic evaluation of hypercalcemia

Always measure total calcium with serum albumin; use ionized calcium when indicated.

Optional tests to determine etiology (must not delay treatment):

- Phosphate
- Urine calcium
- PTH
- 25-OH Vitamin D
- 1,25-(OH)₂ vitamin D
- serum protein electrophoresis
- immunofixation
- serum free light chains

Albumin effect: total calcium varies with albumin concentration (e.g., in dehydration), whereas ionized calcium remains stable. Corrected calcium formulas can be applied, but accuracy is limited.

Classification by corrected calcium level:

- Mild (usually asymptomatic): 2.6–3.0 mmol/L (10.5–12 mg/dL)
- Moderate: 3.0–3.4 mmol/L (12–14 mg/dL)
- Severe: ≥3.5 mmol/L (≥14 mg/dL)

7.4 Clinical management

- Check for cardiac rhythm disorders
- Adjust drug doses in the event of associated acute renal failure
- Treat underlying cause

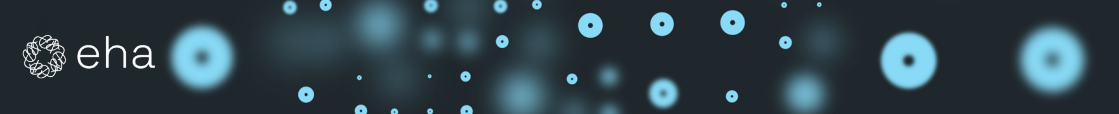
Withdrawal of aggravating drugs

Infuse with caution:

- Digitalis medicines
- Diuretics
- Calcium
- Vitamin D supplementation

Correction of hypercalcemia:

- **Hydration with isotonic saline (1–2 L):** adjust for dehydration based on clinical signs (weight, tachycardia, urine output) and biological signs (urea, creatinine)



- **If calcium >3.5 mmol/L or >3.0 mmol/L with clinical signs:**
 - Bisphosphonates: zoledronic acid 4 mg (preferred) or pamidronic acid 60 mg (adjust for renal function)
 - Alternatively: denosumab
- Calcitonin: 4 units/kg every 12 h for 24–48 h only (tachyphylaxis risk)
- Renal replacement therapy: in very severe cases (ECG changes or blood calcium >4.5 mmol/L)

References

Dickens LT, et al. JAMA Oncol. 2023;9:430–431.
El-Hajj Fuleihan G, et al. J Clin Endocrinol Metab. 2023;108:507–528.
Goltzman D, et al. Endotext. 2000. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK279129/>.
Izzedine H, et al. Nephrol Dial Transplant. 2022;37:1598–1608.
Sargent JTS, et al. Br J Haematol. 2010;149:465–477.

8. Hyperviscosity

Key facts

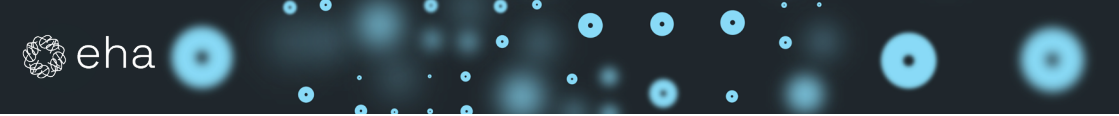
- Hyperviscosity most commonly arises in secretory lymphoproliferative neoplasms.
- Clinical and laboratory features reflect to reduced tissue oxygenation, thrombosis and hemorrhage.
- Prompt treatment is essential to reduce the risk of life-threatening complications.

Important definitions:

- Viscosity is a fluid's resistance to flow based on shear stress; it reflects its "thickness".
- Symptomatic hyperviscosity is a clinical diagnosis in the appropriate context; treatment should not be delayed while awaiting e serum viscosity results marked paraproteinemia.

Background

- Plasma viscosity can be measured directly by mechanical methods or using a viscometer (e.g., Ostwald tube)
- Blood viscosity measurements are not routinely available and do not reliably correlate with clinical severity.
- Absolute immunoglobulin levels, hematocrit, or leukocyte counts do not directly correlate with symptom burden.
- Symptomatic hyperviscosity is a medical emergency.



8.1 Clinical presentation

Hyperviscosity may present with a classical triad of mucosal or skin bleeding, visual disturbance and neurological symptoms.

Other signs and symptoms:

- **General:** asthenia, anorexia
- **Neurological:** headache, hearing loss, tinnitus. May present emergently with intracranial hemorrhage, reduced consciousness or coma, seizure, ataxia.
- **Visual:** blurred vision, reduced visual acuity, ophthalmoplegia, vitreous floaters, papilloedema, retinal hemorrhage or thrombosis
- **Mucosal hemorrhage** (may be recurrent): epistaxis, gingival bleeding, gastrointestinal bleeding
- **Thrombosis:** arterial or venous
- **Cardiac:** may present with right-sided cardiac failure.

8.2 Diagnostic evaluation

Hyperviscosity is most often associated with hematological diseases characterized by a monoclonal protein (M-band), reflecting an underlying plasma cell dyscrasia or other lymphoproliferative neoplasm, or with extreme hyperleukocytosis due to newly diagnosed acute leukemia (most often myeloid). The nature and concentration of the M-protein inform the risk of hyperviscosity but do not predict symptom severity in an individual patient.

Causes

Monoclonal hypergammaglobulinemia

- Elevated IgM
 - Most often in Waldenström macroglobulinemia (lymphoplasmacytic lymphoma)
 - IgM is a large pentameric protein with five Fc regions
 - Symptoms most often when the IgM peak is >30 g/L
 - May occur due to an IgM flare after anti-CD20 monoclonal antibody monotherapy; many protocols omit anti-CD20 from cycle 1 or delay administration after chemotherapy infusion to mitigate this risk

- Elevated IgA or IgG
 - IgA multiple myeloma (dimeric); hyperviscosity usually when the peak is >60 g/L
 - IgG multiple myeloma rarely causes hyperviscosity
- Cryoglobulinemia (type 1 or 2)
 - Temperature-dependent gelling in the peripheral circulation increases serum viscosity
 - Often due to an underlying smoldering lymphoproliferative disorder

Polyclonal hypergammaglobulinemia (rare cause of serum hyperviscosity)

- Autoimmune conditions, including rheumatoid arthritis and Sjögren syndrome
- Uncontrolled HIV infection
- Following intravenous immunoglobulin (IVIg) infusion in neonates

Cellular causes

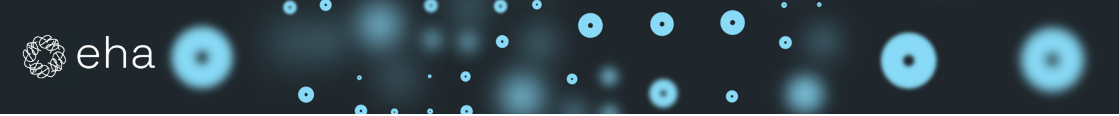
- Polycythemia or elevated hematocrit (primary or secondary)
- Hyperleukocytosis in acute leukemia (see Chapter 10); rarely in chronic myeloid leukemia, sometimes presenting with priapism

Hyperviscosity is a clinical diagnosis in the appropriate context; treatment should not be delayed while awaiting serum viscosity results. Serum viscosity does not reliably reflect symptom severity.

Fundoscopy is essential when hyperviscosity is suspected. Common features include retinal venous tortuosity, hemorrhages, exudates, and papilledema.

Investigations

- Complete blood count (CBC) and peripheral blood smear: assess for polycythemia or anemia, thrombocytosis, leukocytosis, red-cell rouleaux, abnormal lymphoid cells or blasts
- Hemostasis tests: prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen
- Biochemistry: creatinine, electrolytes (including corrected calcium), albumin
- Serum protein electrophoresis and immunofixation; serum free light-chain assay; urine immunofixation as available; quantify total IgG, IgA, and IgM
- Serum viscosity: baseline if available; not decisional for treatment



- Workup for plasma exchange: viral serology and blood type
- ECG
- Record height and weight to calculate plasma volume for potential therapeutic plasma exchange; assess venous access

8.3 Clinical management

Prompt treatment is essential to reduce the risk of life-threatening complications, including hemorrhage, thrombosis, myocardial infarction, and multiorgan failure due to systemic hypoperfusion.

- **Stabilization and temporizing measures**
 - Judicious intravenous fluid administration while preparing for plasma exchange
- **Definitive acute therapy**
 - Therapeutic plasma exchange (plasmapheresis) is the standard of care for symptomatic hyperviscosity
 - Urgent indications: neurological symptoms, uncontrolled hemorrhage, respiratory compromise, thrombotic manifestations, and IgM flare following monoclonal anti-CD20 therapy
 - Prophylactic plasma exchange may be considered when the monoclonal protein level approaches the patient's usual symptomatic threshold
- **Treatment of the underlying cause**
 - Lymphoproliferative disorders (e.g., Waldenström macroglobulinemia, multiple myeloma): systemic corticosteroids with or without chemoimmunotherapy
 - Cellular hyperviscosity: cytoreductive therapy as appropriate
- **General measures**
 - Avoid unnecessary red-cell transfusions (anemia may be dilutional; transfusion can increase blood viscosity)
 - Optimize fluid balance and correct electrolyte abnormalities carefully

Follow-up

- Monitor for progression or recurrence of the causative disorder
- Identify and manage long-term sequelae (eg, deafness, reduced visual acuity)

References

○ Debureaux et al. Rev Med Interne. 2024;45(12):759–766.
○ Treon SP, et al. Ann Oncol. 2004;15(10):1481–1483
○ Mehta J, Singhal S. Semin Thromb Hemost. 2003;29(5):467–472.

9. Symptomatic hyperleukocytosis or leukostasis

Key facts

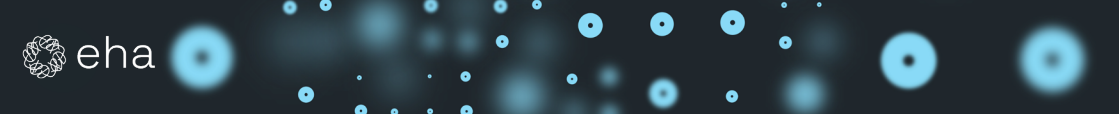
- Symptomatic hyperleukocytosis/leukostasis generally occurs in a subset of patients with leukemia. Risk increases with higher white cell counts.
- Most commonly manifests with pulmonary and/or neurological symptoms.
- Hyperleukocytosis in acute myeloid leukemia (AML) is associated with inferior outcomes, associated with complications of leukostasis, tumor lysis syndrome, and disseminated intravascular coagulopathy (DIC).

Important definitions:

- **Hyperleukocytosis** is a laboratory abnormality typically defined as a white cell count $>100 \times 10^9/L$.
- **Symptomatic hyperleukocytosis** or **leukostasis**, is a clinical manifestation that occurs in a subset of patients with leukemia, most frequently acute leukemia, and is characterized by white cell plugs in the microvasculature. It is more common in AML, especially monoblastic subtypes, than in acute lymphoblastic leukemia (ALL).

Background

The pathophysiology of symptomatic hyperleukocytosis is not fully defined. Contributing factors include blast size, shape, and phenotype. Additional factors include parenchymal leukemic blast infiltration, microvascular thrombi, endothelial activation, hyperviscosity, cytokines (IL-1, TNF α) and coagulopathy. The condition is associated with poor outcomes, with mortality in AML around 40%.



9.1 Clinical presentation and diagnostic evaluation

As a result of leukostasis, the clinical features are characterized by reduced perfusion of end organs, tissue hypoxia, and ultimately organ dysfunction with frequently occurring organ infarctions, coagulation disorders, thrombosis, and central nervous system (CNS) bleeding.

Leukostasis or symptomatic hyperleukocytosis is diagnosed based on clinical, biological, and radiological features. Diagnosis should be made in an appropriate clinical context (e.g. a new presentation or relapse of acute leukemia or chronic myeloid leukemia [CML]). It is often associated with a dramatically elevated white cell count ($> 100 \times 10^9 /L$), although symptoms can occur with lower WBC counts. In AML, especially monocytic subtypes (AML FAB M4 and M5), symptoms can appear with $50\text{--}100 \times 10^9/L$ leukocytes. In contrast, leukostasis usually appears at higher blood counts in ALL ($>400 \times 10^9/L$) and chronic lymphocytic leukemia [CLL] ($>1,000 \times 10^9/L$).

Clinical features suggestive of leukostasis:

- Neurological: headache, vertigo, tinnitus, psychomotor retardation, impaired level of consciousness, focal sensorimotor deficits, intracranial hemorrhage, ataxia, deterioration of vision
- Pulmonary: cough, dyspnea, hypoxemia, chest pain, pulmonary hemorrhage, pulmonary embolism, acute respiratory failure
- Systemic: pyrexia, constitutional symptoms
- Unexplained hemorrhage or new arterial or venous thrombosis: retinal thrombosis or hemorrhage, myocardial infarction, bowel ischemia, acute limb ischemia, deep venous thrombosis
- Psychiatric: restlessness, delirium, vigilance disorder
- Other: renal dysfunction, heart failure
- Special cases: priapism (more frequent in CML)

Investigations guided by clinical presentation:

- General: laboratory testing to examine for coagulopathy (DIC, hyperfibrinolysis) and tumor lysis syndrome [TLS] (PT, APTT, fibrinogen, D-dimer, creatinine, electrolytes [phosphate, calcium, potassium], urate, LDH).
- Hyperkalemia (raised K⁺) must be interpreted with caution. Pseudohyperkalemia can be due to in vitro leukemic cell lysis. If hyperkalemia present: confirm with new sample: ideally with a heparinized arterial blood gas syringe at the point of care (process sample promptly and no pneumatic tube transport).
- Pseudohypoxemia on arterial blood gas samples may be observed due to continued consumption of oxygen by malignant cells in the blood sample after collection. Oxygenation is best assessed with non-invasive pulse oximetry.

- Pulmonary symptoms: CT thorax features include diffuse or multifocal interstitial pulmonary infiltrates, ground glass with blurred boundaries, parenchymal hemorrhage. Assessment of oxygenation should also be undertaken.
- Neurological symptoms: CT brain to assess for infarction or hemorrhage.

9.2 Clinical management

Consideration should be given to continuous monitoring and treatment of the patient in an intensive care unit (ICU) with the primary goal of rapidly reducing leukocyte levels to prevent multi-organ failure.

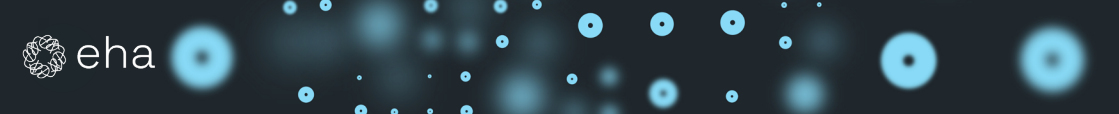
Supportive management of the patient includes:

- Supplementary oxygen therapy and consideration of non-invasive or invasive ventilation in cases of acute respiratory distress syndrome/acute respiratory failure.
- Hyperhydration with intravenous fluids (3 L/m² per day), maintaining urine output $>100 \text{ mL/m}^2/\text{h}$.
- Close monitoring of the patient's fluid balance.
- Monitoring for and treatment of associated TLS with electrolytes and uric acid levels checked initially every 6 h. Treat hyperuricemia with allopurinol or rasburicase (see relevant chapter for details).
- Treat coagulopathy with platelet transfusions, fresh frozen plasma, and fibrinogen concentrate or cryoprecipitate according to clinical context.
- Avoid red cell transfusion unless clinically necessary, due to the risk of increased viscosity.
- Consider early antimicrobials as superimposed infection may be present (e.g., fever, pulmonary or neurologic symptoms).

Cytoreductive options:

Management requires prompt induction therapy to treat the underlying leukemia with cytoreduction as supportive treatment.

- Hydroxyurea $50\text{--}100 \text{ mg/kg}$ per day in 2–4 divided doses (1–2 g every 6 h) is the most commonly used cytoreductive agent alongside induction therapy or to temporize patients before induction is started.
- Glucocorticoids (e.g. dexamethasone $20\text{--}40 \text{ mg IV}$ daily for 2–3 days) are effective in leukostasis, particularly for cytoreduction in lymphoid tumors and acute promyelocytic leukemia (APL).
- Leukapheresis reduces leukocyte count by 20–50% and can be considered in critical cases as a bridging therapy to induction. It reduces early mortality but not overall survival. If induction therapy is delayed, leukapheresis may be repeated due to the re-accumulation of leukemic blasts. Contraindicated in APL.



- Bridging chemotherapy: use rapid onset chemotherapy for cytoreduction in leukostasis. Cytarabine 100–200 mg IV daily for up to 2 days is most commonly used. Lower doses, starting at 100 mg per day, may be administered according to institutional practice. Low dose cytarabine is typically given as a continuous infusion, whereas higher doses are administered as short intravenous infusions over 1–3 h.

10. Tumor lysis syndrome

Key facts

- Discharge of uric acid, calcium, phosphorus (which chelates calcium), potassium, and elevated LDH levels.
- Renal insufficiency is linked to the intratubular formation of uric acid and calcium phosphate crystals, which exacerbates metabolic abnormalities.
- Life-threatening risk is associated with renal insufficiency and metabolic irregularities.
- Therapeutic intervention is an urgent priority.

Important definitions:

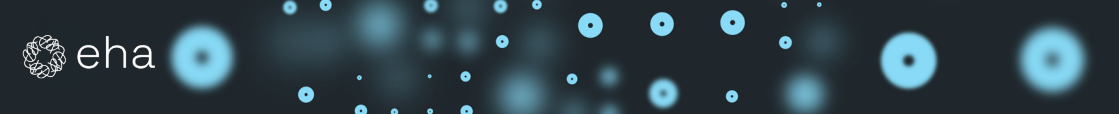
- **Tumor lysis syndrome (TLS):** a metabolic syndrome induced by the abrupt release of intracellular components following the lysis of malignant cells, either spontaneously or post-chemotherapy.

Pathophysiology

DNA released from lysed cells is metabolized into adenosine and guanosine, which are further converted to xanthine. Xanthine oxidase then generates uric acid, excreted by the kidneys. The release of electrolytes with high intracellular concentrations can trigger life-threatening disturbances (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia). TLS may cause acute kidney injury via precipitation of uric acid, xanthine, and calcium phosphate crystals, as well as crystal-independent mechanisms.

References

- Macaron W, et al. Leuk Lymphoma. 2022;63:1780-1791.



10.1 Diagnostic criteria

The diagnosis of TLS is based on internationally established laboratory thresholds, supplemented by clinical features that reflect organ involvement. The Cairo-Bishop criteria remain the standard reference and distinguish between biological TLS and clinical TLS.

Biological TLS

Presence of 2 or more of the following between day -3 and day +7 from day 1 of chemotherapy:

- Uric acid: either increase >25% or >476 $\mu\text{mol/L}$
- Potassium: either increase >25% or >6 mmol/L
- Phosphate: either increase >25% or >1.45 mmol/L
- Calcium: either decrease >25% or <1.75 mmol/L

Clinical TLS

Biological TLS plus one of the following:

- Acute renal failure
- Cardiac rhythm or conduction disorder
- Seizure or coma

10.2 Complications

- Hyperkalemia can cause serious arrhythmias
- Hyperphosphatemia can:
 - cause secondary hypocalcemia (neuromuscular irritability, arrhythmia, seizure)
 - lead to formation of calcium phosphate crystals in various organs (e.g., kidneys)
- Uric acid can induce renal insufficiency by intrarenal crystallization and crystal-independent mechanisms.
- Tumor lysis also triggers inflammatory cytokine release, which may lead to multiorgan failure.

10.3 Risk factors and monitoring

- **Patient-related:**
 - Intracellular or extracellular dehydration

- Preexisting renal insufficiency
- Hyperuricemia
- Obstructive uropathy
- **Disease-related:**
 - High tumor burden
 - Rapidly growing tumor
- **Antitumor therapy-related:**
 - Very effective cytotoxic treatment
- **Laboratory risk markers:**
 - Significant increase in LDH
 - Marked elevation of uric acid

Monitoring

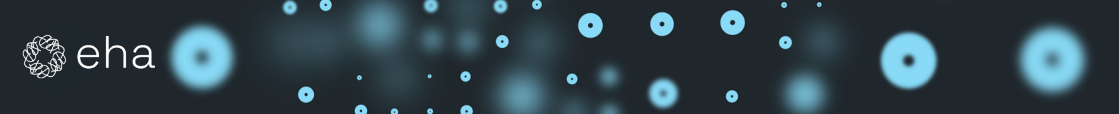
Patients at high-risk of TLS, whose risk is not considered to be sufficiently reduced by preventive measures, should be carefully monitored for laboratory and clinical signs. In these patients, uric acid, electrolyte panel, phosphate, calcium, blood urea nitrogen (BUN), and creatinine should be checked regularly after treatment initiation. Any discrepancy between fluid intake and urine output, or even a minimal increase in creatinine ($\geq 26 \mu\text{mol/L}$ or $\geq 50\%$ from baseline), should be considered renal insufficiency that increases the risk of mortality.

10.4 Therapeutic management

Prevention of TLS is the most important aspect of management and should ideally start 48 hours before initiation of aggressive antitumor therapy.

Preventive measures

- Intravenous hydration: 2500–3000 mL/m^2 per day:
 - improves renal perfusion and glomerular filtration
 - minimizes acidosis (which lowers urine pH and promotes the formation of uric acid crystals) and oliguria
- Diuretics: may be required to maintain urine output
- Dietary restriction: limit potassium and phosphorus intake during the risk period
- Allopurinol: 300 mg daily (may be increased to 600 mg) or febuxostat 80–120 mg daily



- inhibits xanthine oxidase, preventing conversion of hypoxanthine and xanthine to uric acid
- does not reduce existing uric acid levels
- Urine alkalization: previously used, now considered controversial due to increased risk of calcium and/or xanthine precipitation in renal tubules
- Rasburicase: recommended for high-risk patients when risk is not sufficiently reduced by other measures; 0.2 mg/kg per day
 - prevents xanthine accumulation
 - removes uric acid by enzymatically degrading it into allantoin, a highly soluble non-toxic metabolite
 - contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency (risk of acute hemolysis and methemoglobinemia)
- Steroid prephase (± vincristine or cyclophosphamide): often used in high-risk lymphoid malignancies, to reduce complications from sudden tumor cell death

Management of biological TLS

- Intravenous hydration 2500–3000 mL/m² per day
- Diuretics as needed
- Rasburicase. Dose: 0.2 mg/kg per day (for 1–7 days)

Management of acute kidney injury

- Continue hydration
- Rasburicase if not previously administered
- Renal replacement therapy if uncontrolled hypocalcemia or hyperkalemia

References

- Howard et al., N Engl J Med 2011;364:1844-1854.
- Durani U, Br J Haematol. 2020 Feb;188(4):494-500.

11. Main complications of chemotherapies

Key facts

- Chemotherapy complications may be acute or delayed, ranging from organ-specific toxicity to systemic syndromes.
- Methotrexate toxicity, hemorrhagic cystitis, and extravasation injuries are among the most critical and potentially life-threatening complications.
- Early recognition and preventive strategies (hydration, protective agents, drug monitoring) are essential to reduce morbidity and mortality.
- Certain complications (e.g., extravasation, gross hematuria, acute methotrexate toxicity) require immediate intervention to prevent irreversible damage.
- Management is often protocol-driven; awareness of local and institutional guidelines is crucial.

Important definitions:

- **Chemotherapy complication:** Any adverse clinical effect directly attributable to the pharmacologic action, metabolism, or administration route of cytotoxic agents.
- **Methotrexate toxicity:** Excessive systemic exposure to methotrexate resulting in hematologic, hepatic, renal, or mucosal injury.
- **Hemorrhagic cystitis:** Bladder mucosal injury, often due to oxazaphosphorine metabolites such as acrolein, presenting with hematuria of variable severity.
- **Extravasation:** Accidental leakage of a cytotoxic drug from the vasculature into surrounding tissue, which may cause local necrosis or systemic complications.
- **Vesicant:** A drug capable of causing severe tissue injury and necrosis if extravasated.

11.1 Excessive exposure to methotrexate (MTX)

Background

Methotrexate inhibits folate metabolism by blocking dihydrofolate reductase. This leads to impaired synthesis of purines and pyrimidines, thereby reducing DNA and RNA synthesis.

Clinical presentation

Methotrexate toxicity can manifest with a wide spectrum of adverse events, ranging from mild to life-threatening, as outlined below.

Common adverse events	Severe adverse events
- stomatitis - oral ulcers - hair loss - fatigue - headache - gastrointestinal upset - nausea - diarrhea	- bone marrow suppression - severe infections - severe liver and lung disease - lymphomas - severe skin reactions - tumor lysis syndrome - fetal death - congenital abnormalities

Table 11.1: Methotrexate toxicity

Clinical management

Preventive management of methotrexate toxicity consists of hospital-based procedures, summarized below.

Intervention	Details
Drug interactions	- Stop implicated treatments 24–48 h before MTX. - Contraindicated: proton pump inhibitors, cotrimoxazole, NSAIDs, penicillins (e.g., tazocillin), probenecid, fluoroquinolones, nephrotoxic agents
Hyperhydration	3 L per day
Urine alkalization	IV bicarbonate ± acetazolamide; monitor urinary pH and correct if acidic; initiate if pH >7
Monitoring	Measure MTX levels per protocol (typically ≥24 h after infusion start; earlier measurements not interpretable)

Leucovorin (folinic acid) rescue	Start at protocol-defined time; adjust dose according to MTX levels
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Table 11.2: Preventive management of methotrexate toxicity

Curative treatment

If methotrexate toxicity develops despite preventive management, curative treatment follows a stepwise approach, illustrated in the flowchart below

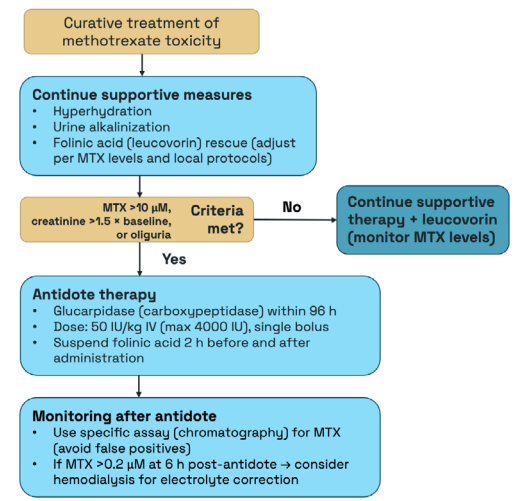


Figure 11.1: Curative treatment pathway for methotrexate toxicity

11.2 Hemorrhagic cystitis induced by oxazophosphorines (cyclophosphamide and ifosfamide)

Background

Oxazophosphorines are metabolized into several molecules, including acrolein, which exerts direct bladder toxicity. BK virus infection may facilitate onset in the setting of allogeneic transplantation.

Clinical presentation

- Ranges from microscopic hematuria to gross hematuria with clot formation and acute renal insufficiency
- May be aggravated by BK virus infection (especially post-allograft)

Clinical management: preventive treatment

Preventive management is required in all patients receiving oxazophosphorines, as summarized in the table below.

Intervention	Details
Hydration	- 0.9% NaCl, 3 L per 24 h, starting 6 h before and continuing ≥6 h after administration - alkaline water intake recommended the day before and day of high-dose treatment
Mesna	60–120% of oxazophosphorine dose
Urine alkalinization	IV bicarbonate ± acetazolamide; monitor urinary pH and correct if acidic; initiate if pH >7
Mode of administration	Either continuous infusion from start of chemotherapy to 8–12 h after completion, or three short doses at H0, H4, H8
Oral switch	Double the mesna dose if switching to oral administration

Table 11.3: Preventive management in patients on oxazophosphorines

Clinical management: curative treatment

If hemorrhagic cystitis develops despite preventive measures, curative management should be initiated promptly to avoid clot retention and obstructive renal injury. The main steps are outlined below and can be represented in a flowchart for clarity.

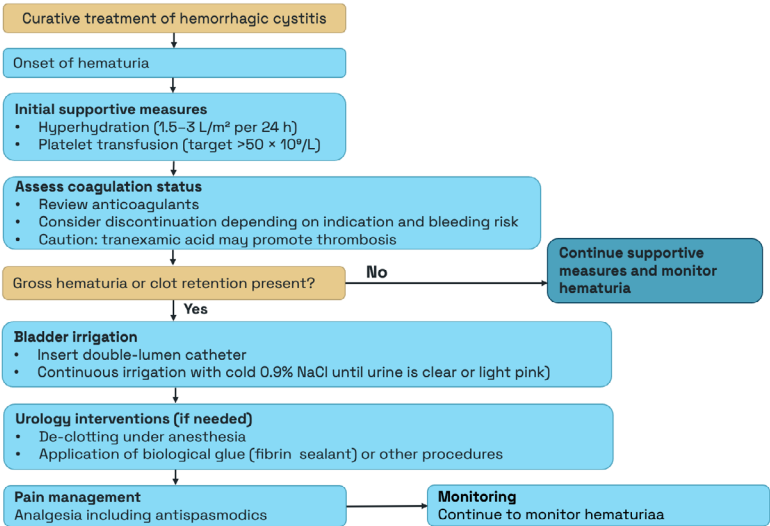


Figure 11.2: Curative management pathway for hemorrhagic cystitis

11.3. Extravasation of chemotherapy

Extravasation of cytotoxic drugs may range from mild local irritation to severe necrosis; early identification and immediate management are essential.

Clinical presentation

Extravasation of vesicant chemotherapy can cause progressive vascular and tissue necrosis.

- Early symptoms: pain, erythema, local swelling
- Late symptoms: ulceration, necrosis, and persistent lesions lasting weeks
- Mechanism: continuous release of cytotoxic drug from necrotic cells (endocytolysis)
- Potential progression: extension to fascia, muscle, tendons, and bone, causing irreversible functional damage.

Severity factors

The urgency and extent of intervention depend on:

- **Type of drug:**
 - Vesicants: cause severe tissue necrosis (e.g., anthracyclines, mitomycin C, vinca alkaloids)
 - Irritants: may cause pain, phlebitis, or local reactions; high-volume extravasation or hyperosmolar solutions can mimic vesicant damage
 - Non-toxic agents: local damage in specific organs
- **Extent of extravasation**
- **Location of extravasation** (e.g., elbow crease, back of hand)

Vesicants	Irritants	Non-toxic
○ Anthracyclines • epirubicin • idarubicin • doxorubicin • daunorubicin ○ actinomycin ○ mitomycin C ○ carmustine (BCNU) ○ dacarbazine ○ mitoxantrone ○ plicamycin ○ mechlorethamine ○ vinblastine ○ vincristine ○ vindesine ○ trabectedine ○ streptozotocin	○ busulfan ○ carboplatin ○ etoposide ○ cisplatin ○ cladribine ○ irinotecan ○ 5-FU ○ docetaxel ○ oxaliplatin ○ topotecan	○ methotrexate ○ cytarabine ○ bleomycin ○ gemcitabine ○ asparaginase ○ cyclophosphamid ○ melphalan ○ fludarabin ○ mitoguazone ○ paclitaxel ○ ifosfamide ○ thiotepa ○ cladribine

Table 11.3: Examples of chemotherapy drugs by extravasation risk (non-exhaustive list)

Clinical management

Extravasation must be treated as an urgent complication. Management steps include:

- 1. Stop infusion immediately**, leaving the needle/catheter in place
- 2. Record time of event** and estimate volume extravasated
- 3. Aspirate** using a syringe to remove as much extravasated drug and 3–5 mL blood as possible via the catheter
- 4. Mark and document:** outline the affected area with a pen and take a photo for follow-up
- 5. Elevate** the area above heart level, if possible
- 6. Keep the patient fasting** and record last oral intake
- 7. Call the surgery team for therapeutic discussion.**
Management depends on the drug and amount extravasated:
 - Non-toxic drugs: monitoring
 - Irritants in small quantities in non-sensitive areas: local topical treatment (antihistamines, analgesics, corticosteroids)

- Irritants or vesicants in large quantities: surgical treatment (emergency liposuction under general anesthesia)
 - Vesicant drugs in small quantities: apply cold sterile compress for 1 h (exceptions: warm compress for vinca alkaloids; room-temperature compress for oxaliplatin)
- 8. Documentation:** complete extravasation form and update patient record

References

- Howard SC, et al. Oncologist. 2016;21:1471–1482.
- Ramsey LB, et al. Oncologist. 2018;23:52–61.
- Gonella S, et al. Clin J Oncol Nurs. 2015;19(1):E8–E14.
- Pérez Fidalgo JA, et al. Ann Oncol. 2012;23(Suppl 7):vii167–vii173.
- Bielack SS, et al. J Cancer Res Clin Oncol. 2024;150:441.
- Emadi A, et al. Nat Rev Clin Oncol. 2009;6:638–647.
- Hensley ML, et al. J Clin Oncol. 2009;27:127–145.

12. Complications of classic immunotherapy

Key facts

- Infusion reactions to intravenous immunoglobulins (IVIG) are common but usually mild; severe anaphylaxis occurs mainly in patients with congenital IgA deficiency and anti-IgA antibodies.
- Antithymocyte globulin (ATG) may cause cytokine release syndrome or serum sickness; pre-medication with corticosteroids, antihistamines, and antipyretics reduces risk.
- Monoclonal antibodies can trigger cytokine release reactions, hypersensitivity, and infusion-related symptoms, particularly during the first doses.
- Antibody-drug conjugates carry risks similar to monoclonal antibodies, with additional risk of sinusoidal obstruction syndrome (SOS/VOD) in the post-transplant setting.

Important definitions:

- **Cytokine release syndrome (CRS):** Acute inflammatory reaction caused by massive cytokine release during immunotherapy infusion, presenting with fever, chills, hypotension, rash, and respiratory compromise.
- **Serum sickness:** Delayed immune complex-mediated reaction that may occur after ATG therapy, characterized by fever, rash, arthralgia, and lymphadenopathy.
- **Aseptic meningitis:** Meningeal syndrome with headache, neck stiffness, and pleocytosis in cerebrospinal fluid without infection, sometimes occurring after IVIG infusion.
- **Sinusoidal obstruction syndrome (SOS/VOD):** Hepatic vascular complication defined by painful hepatomegaly, jaundice, ascites, and weight gain; may follow antibody-drug conjugate treatment or hematopoietic stem cell transplantation.

12.1 Reactions to intravenous immunoglobulins

Background information

Blood-derived medication, prepared from pooled human plasma (from 1000 healthy individuals).

Clinical presentation and diagnosis

- Minor acute reactions are common and include headache, fever, chills, myalgia/arthralgia, lower back pain, nausea/vomiting, and rash with itching. Typically begin 30–60 min after infusion start, often due to excessive infusion rate. Mechanism unknown.
- Severe anaphylactic reactions are rare and life-threatening, occurring in patients with congenital IgA deficiency and anti-IgA antibodies.
- Aseptic meningitis: meningeal syndrome 1–36 h after infusion, with pleocytosis and elevated protein in cerebrospinal fluid (CSF) but no microbes. Resolves in 3–5 days. Mechanism unknown.
- Acute renal injury: onset 2–4 days after infusion; usually regresses within 2–4 weeks. Mechanism poorly understood.
- Other (rare): thrombosis, arrhythmia, hemolytic anemia, and transfusion-related acute lung injury (TRALI).

Clinical management

The management of IVIG reactions relies on rapid recognition and immediate supportive measures. Preventive strategies aim to reduce infusion-related risk, while treatment focuses on stopping the reaction, symptomatic control, and escalation in severe cases.

Prevention	- Start slowly and gradually increase the infusion rate (do not exceed 4 mL/kg per h). - Peri-infusion hyperhydration. - Avoidance of nephrotoxic medications.
Treatment	Mild to moderate reaction: - decrease infusion rate or stop the infusion - administer antihistamine - administer corticosteroids if needed (dexamethasone 10 mg IV slow injection). - in repeated severe reactions, consider switching to a different IVIG product.

Treatment	Severe reaction: - contact ICU specialist - begin symptomatic resuscitative measures - administer adrenaline for signs of shock - give IV corticosteroid: dexamethasone 10 mg or hydrocortisone 100 mg IV slow injection - for subsequent infusions, use polyvalent immunoglobulins depleted in IgA under medical supervision. Neurotoxicity: - headache: improves after reducing the infusion rate and/or simple analgesics. - aseptic meningitis: symptomatic treatment. Renal toxicity: - hyperhydration - correction of electrolyte imbalances - renal replacement therapy if necessary
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Table 12.1: Clinical management of IVIG reactions

12.2 Reactions to antithymocyte globulin (ATG)

Background information

ATG is composed of polyclonal antibodies generated from animals after inoculation with human thymocytes. Preparations are derived from rabbits or horses and are used in allograft conditioning and in the management of idiopathic bone marrow aplasia.

Clinical presentation and diagnosis

- Cytokine release reaction during ATG administration may cause fever, chills, hypotension, rash, and mucosal swelling or congestion.
- Serum sickness can occur after the injection, although it is rare in the context of allografting.

Clinical management	
Pre-medication	Follow hospital-based protocols, which usually include: - antipyretic (acetaminophen) - antihistamine - corticosteroids (except hydrocortisone): 1 mg/kg the day before, 2 mg/kg on the first day of ATG administration, and 1 mg/kg on subsequent days - slow initial infusion (6–12 h), gradually increased according to tolerance
Treatment	- discontinue the infusion and provide symptomatic treatment (antihistamines, corticosteroids, bronchodilators) as required - after clinical signs resolve, resume the infusion at half rate, and increase gradually - in neutropenic patients: consider broad-spectrum antibiotic therapy if fever, chills, or signs of shock are present

Table 12.2: Clinical management of ATG reactions

Possible interactions with medications

- For ATG-Fresenius, ATG should not be administered with IVSE heparin.
- Transfusions and parenteral nutrition are not administered during ATG treatment.
- Extremely rare anaphylactic reactions can occur in patients with severe allergies to horses or rabbits; always verify allergy history.

Note: In bone marrow aplasia, corticosteroid therapy is extended for a few days to reduce the risk of serum sickness.

12.3 Reactions to monoclonal antibodies

Background information

CD20 is expressed on B lymphocytes, and CD38 is expressed on plasma cells.

Clinical presentation and diagnosis

- Reactions under monoclonal antibody therapy may include:
- Cytokine release (distinct from anaphylaxis; more frequent with obinutuzumab than rituximab)
 - Hypersensitivity

- Tumor lysis syndrome (see chapter 10)
- Delayed hypersensitivity

	Cytokine release (frequent)	Hypersensitivity (rare)
Risk factors	Bulky disease or lymphocytes count >50 × 10 ⁹ /L	History of allergies
Shared clinical signs	- Skin: flush, itching, rash - Cardiac: tachycardia, atrial fibrillation, hypotension - Pulmonary: shortness of breath, chest tightness, angioedema - Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea Anti-CD38-specific signs - Predominance of ear, nose, throat (ENT) symptoms (rhinitis, laryngeal edema) - Predominance of respiratory symptoms (cough, shortness of breath, bronchospasm, pulmonary edema, hypertension)	
Distinctive clinical signs	Fever, chills, body aches	Hives, repeated cough, wheezing
Timing	First infusion, within the first 2 h, then decreasing with subsequent treatments	Second dose, occurring within a few minutes, with an increase in reactions
At infusion resumption	Symptoms improve when infusion is slowed or stopped	Symptoms improve when infusion is slowed or stopped
Differential diagnosis when fever and chills	Sepsis (particularly if rituximab given via a catheter). Obtain blood cultures (catheter and peripheral). Start antibiotics only in cases of incipient shock, neutropenia, or no improvement after corticosteroid administration and cessation of infusion.	

Table 12.3: Clinical presentation of infusion reactions to monoclonal antibodies

Clinical Management

Management of reactions is based on whether symptoms are due to cytokine release or hypersensitivity. Preventive strategies reduce the risk of infusion-related complications, while treatment requires rapid recognition, infusion adjustment, and supportive measures.

	Cytokine release (frequent)	Hypersensitivity (rare)
Pre-medication	Usual pre-medications include the following: - corticosteroids (except hydrocortisone). - antipyretic (acetaminophen). - antihistamine. - gradual increase in infusion rate during administrations. - option to divide the initial dose.	
Treatment	Mild to moderate reaction: halve infusion rate; give antipyretic/antihistamine; stop infusion if no improvement. Resume only after symptoms resolve. Severe reaction: Immediate cessation. Consider appropriate resuscitative measures. Symptomatic treatment: Oxygen therapy, repeat dose of antihistamine, bronchodilator 5 mg via aerosol if bronchospasm occurs.	Stop infusion permanently. Symptomatic treatment: - oxygen therapy - adrenaline - corticosteroid - antihistamine - fluid replacement - bronchodilator
	For anti-CD38 antibodies: consider adding montelukast to reduce bronchospasm risk	

Table 12.4: Clinical management of infusion reactions to monoclonal antibodies

Other reactions

- Thrombocytopenia during cytokine release reactions: monitor platelet count and consider withholding antiplatelet and anticoagulant therapy during initial treatments.
- Prolonged,fluctuating neutropenia after anti-CD20 therapy: responsive to granulocyte colony-stimulating factor (G-CSF).

- Anti-CD38 antibodies may cause panagglutination in the indirect antiglobulin test (IAT), leading to false-positives results.

12.4 Reactions to antibody-drug conjugates

Background information

Antibody-drug conjugates (immunoconjugates) are monoclonal antibodies coupled to a cytotoxic drug. Examples include gemtuzumab ozogamicin and inotuzumab ozogamicin. CD33 is expressed on myeloid cells and CD22 on B lymphoid cells.

Clinical presentation and diagnosis

Reactions under monoclonal antibody therapy may include:

- Reactions similar to those with monoclonal antibodies (topic 12.3).
- Delayed toxicities:
 - Hepatic cytolysis and hyperbilirubinemia.
 - Sinusoidal obstruction syndrome (SOS) with diagnostic criteria as described below (EBMT 2023 criteria):

Probable	Clinical criteria	Proven
Two of the following criteria must be present: ○ Bilirubin $\geq$ 2 mg/dL ○ Painful hepatomegaly ○ Weight gain $>$ 5% ○ Ascites ○ Ultrasound and/or elastography suggestive of SOS/VOD	Bilirubin $\geq$ 2 mg/dl and two of the following criteria must be present: ○ Painful hepatomegaly ○ Weight gain $>$5% ○ Ascites	Histologically proven SOS/VOD or hemodynamically proven (HVPG $\geq$ 10 mmHg)
Classical SOS/VOD In the first 21 days after HSCT Late onset SOS/VOD >21 days after HSCT		

Table 12.5: Diagnostic criteria for sinusoidal obstruction syndrome/veno-occlusive disease (SOS/VOD) according to EBMT 2023

If criteria are met, perform same-day ultrasound-Doppler/elastography to assess for ascites, hepatosplenomegaly, gallbladder wall thickening, pseudo-portal flow, reduced portal velocity, decreased hepatic vein size, and increased elastography values.

Clinical management

Management involves preventive measures, close monitoring, and treatment tailored to specific toxicities.

Pre-medication	Pre-medication: - corticosteroids (except hydrocortisone) - antipyretic (acetaminophen) - antihistamine 1 hour prior to infusion Pre-medication: - corticosteroids (except hydrocortisone) - antipyretic (acetaminophen) - antihistamine 1 hour prior to infusion
Treatment	- Hepatic cytolysis and hemostasis disturbance: interrupt treatment - SOS/VOD: defibrotide 25 mg/kg per day for 14–21 days, continued until resolution of all symptoms. • Stop anticoagulants (increased risk of bleeding). • Stop 6 h before liver biopsy or ascites tapping • This complication carries a risk of respiratory and renal failure.

Table 12.6: Clinical management of toxicities related to antibody-drug conjugates

References

- Guo Y, et al. Front Immunol. 2018;9:1299.
- Freeman CL, et al. Blood. 2015;126:2646–2649.
- Fouda GE, Bavbek S. Front Pharmacol. 2020;11:572863.
- Mohty M, et al. Bone Marrow Transplant. 2023;58:749–754.

13. Toxicities of CAR-T and BiTE therapies

Key facts

- Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are common and potentially life-threatening toxicities of CAR T cells and BiTEs; early recognition, grading, and rapid intervention are essential.
- CAR T and BiTE therapies trigger inflammatory reactions that resemble severe immune activation; vigilance is needed to differentiate them from infection and other complications.
- Cytopenias and infections are frequent adverse events and require early monitoring, prevention, and treatment.
- Risk factors for severe CRS include high tumor burden, CAR T construct (e.g., CD28 co-stimulatory domains), pre-existing inflammation, and younger age.
- With BiTEs, CRS usually develops within hours to 3 days after the first administration; incidence and severity decrease in later cycles.

Important definitions:

- **CAR T cells:** T cells genetically engineered to express a chimeric antigen receptor (CAR) that targets and kills malignant cells.
- **Bispecific T-cell engagers (BiTEs):** bi-specific antibodies that link T cells (commonly via CD3) to tumor cells, triggering T-cell activation. BiTEs can cause inflammatory reactions resembling those of CAR T cells and monoclonal antibodies.
- **Cytokine release syndrome (CRS):** a systemic inflammatory response caused by activation and proliferation of CAR T cells and bystander immune and non-immune cells, leading to rapid release of cytokines (e.g., IL-6, TNF- α , IFN- γ , IL-10).

- **Immune effector cell-associated neurotoxicity syndrome (ICANS):** a neurotoxic syndrome following CAR T-cell activation and cytokine release, associated with disruption of the blood-brain barrier and neuroinflammation.
- **Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS):** a hyperinflammatory syndrome with excessive macrophage activation, considered distinct from CRS. Characterized by rapidly rising ferritin, hepatic transaminase elevation, hypofibrinogenemia, cytopenias, and/or hemophagocytosis in tissues.
- **Immune effector cell-associated hematologic toxicity (ICAH):** Hematologic adverse events (most often cytopenias) occurring after CAR T infusion, related to inflammatory responses, direct marrow effects, or impaired hematopoietic recovery.

13.1 Chimeric Antigen Receptor (CAR) T-cells toxicity

13.1.1 Cytokine Release Syndrome

Prevention

- High tumor burden
- CAR T dose and construct (e.g., CD28 co-stimulatory domains)
- Proliferation under lymphodepleting therapy
- Pre-existing inflammation (e.g., active infections, elevated CRP, or ferritin).
- Other factors to consider for the severity of CRS:
 - type of disease (aggressive lymphomas or leukemias)
 - younger age
 - comorbidities
 - prior therapies (e.g., checkpoint inhibitors).

Prophylaxis with tocilizumab and/or corticosteroids should be used only in the context of a clinical trial.

Clinical Presentation

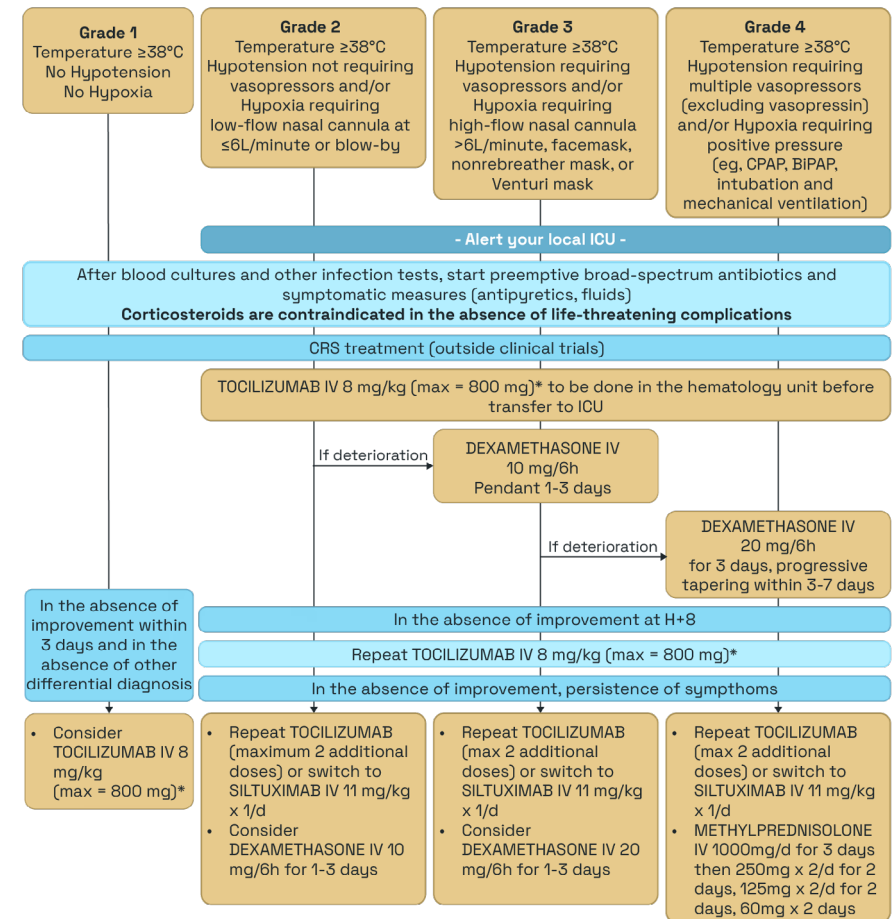
CRS usually develops within 1–14 days after infusion and lasts 1–10 days. Incidence varies; grade ≥ 3 occurs in fewer than 30% of cases. Early onset is associated with more severe presentations, whereas delayed CRS is rare.

Symptoms typically appear gradually, beginning with fever and followed by hypotension, hypoxemia (capillary leak), and organ failure. CRS can progress rapidly, making severity grading (table 13.1) essential for treatment decisions.

	Grade 1	Grade 2	Grade 3	Grade 4**
Fever*	Temperature ≥ 38 °C in absence of other identifiable causes (e.g., sepsis)			
And				
Hypotension	No	Yes, without vasopressor	With 1 vasopressor +/- vasopressin	≥ 2 vasopressors (except vasopressin)
And				
Hypoxia	No	Low-flow oxygen (< 6 L/min)	High-flow oxygen (≥ 6 L/min)	Positive airway pressure (either invasive or non-invasive)

** The grade of CRS is determined by the most severe event.

- Always consider infection in the differential diagnosis
- Do not delay antipyretics, cultures, fluids, and antibiotics.
- CRS/MAS may require additional treatment with anakinra, methylprednisolone, or etoposide.
- Mandatory consultation with a senior physician and/or intensivist is essential to define the optimal management strategy.



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doi: 10.1016/j.annonc.2021.12.003.

IEC-HS may overlap clinically with CRS and macrophage activation syndrome (MAS) but is now recognized as a distinct entity with different treatment implications.

Diagnosis

IEC-HS is a hyperinflammatory syndrome distinct from CRS, with important therapeutic implications. It usually manifests after CRS has improved or resolved, with recurrence or worsening of inflammation despite CRS-directed therapies. The incidence is estimated at <5%.

Key diagnostic features include:

- Elevated ferritin ($\geq 2 \times$ baseline or upper level of normal, or rapidly rising levels)
- Hepatic transaminase elevation ($\geq 5 \times$ baseline or upper level of normal)
- Hypofibrinogenemia
- New or worsening cytopenias
- Hemophagocytosis in bone marrow or other tissue
- Other organ dysfunction may also be present

Fever is not part of the diagnostic criteria. Severity grading should not guide treatment.

Treatment

- Early consultation with a senior physician and/or intensivist is mandatory to define the optimal strategy.
- First line therapy: anakinra (anti-IL-1), in combination with corticosteroids.
- Refractory cases: consider ruxolitinib, low-dose etoposide or emapalumab.

13.1.3 Immune effector cell-associated neurotoxicity syndrome

Background

ICANS often occurs in association with CRS and reflects cytokine-mediated disruption of the blood–brain barrier, resulting in neuroinflammation.

Prevention

- Control risk factors as for CRS; CRS itself is a risk factor for ICANS.
- No validated preventive therapy is available.
- Prophylaxis should be considered only in a clinical trial setting.

Clinical presentation

- Onset: typically 2–8 days after infusion; duration 1 day to 3 weeks.
- Can occur concurrently with CRS, shortly after CRS, or rarely before CRS.
- Grade ≥ 3 develops in fewer than one third of patients.
- Delayed ICANS beyond 3 weeks may occur, particularly neurocognitive or movement disorders with BCMA CAR T cells.

Symptoms include:

- Tremor
- Dysgraphia
- Oral communication difficulties (e.g., naming objects, monosyllabic speech, unintelligible speech, perseveration)
 - which may rapidly progress to complete aphasia
- Attention deficits
- Apraxia
- Lethargy
- Clouding of consciousness progressing to coma, sometimes with seizures
- Headache (non-specific, often with fever)
- Motor deficits or higher cortical dysfunction
- Symptoms suggestive of cerebral edema (Grade 4), which require prompt evaluation

Diagnosis

ICANS is a clinical diagnosis. Other causes (hemorrhage, malignant hypertension, liver failure, infection, stroke, CNS disease) must be excluded. Supportive tests may include brain imaging, EEG, and lumbar puncture.

Global severity assessment

ICE score (10 points total):

- Orientation: ability to give year, month, city, hospital (4 points)
- Description: ability to name 3 objects (e.g., clock, pen, button) (3 points)
- Commands: ability to follow simple commands (e.g., “smile”) (1 point)
- Writing: ability to write a standard sentence (e.g., The cat is gray) (1 point)
- Attention: ability to count backwards from 100 to 0 by tens (1 point)

Symptoms	Grade 1	Grade 2	Grade 3	Grade 4*
ICE score (/10)	7–9	3–6	0–2	0
Consciousness	Spontaneous awakening	Awakening to speech	Awakening to touch	No awakening
Seizures			Focal, generalized, or subclinical seizure responsive to treatment	Focal, generalized, or subclinical seizure responsive to treatment

Symptoms	Grade 1	Grade 2	Grade 3	Grade 4*
Motor impairments				Hemiparesis or paraparesis
Consciousness			Localized on imaging	Diffuse cerebral edema, or decerebrate or decorticate posturing, or cranial nerve VI palsy, or papilledema, or Cushing triad

Table 13.2: ASTCT consensus criteria for ICANS grading.
* The grade is determined by the most severe event, after excluding other potential causes of the episode

Treatment

- Early intervention is essential due to the risk of rapid deterioration particularly when the diagnosis is uncertain.
- Mandatory consultation with a senior physician and/or intensivist to define the management strategy.
- Early involvement of a neurologist is recommended whenever possible.

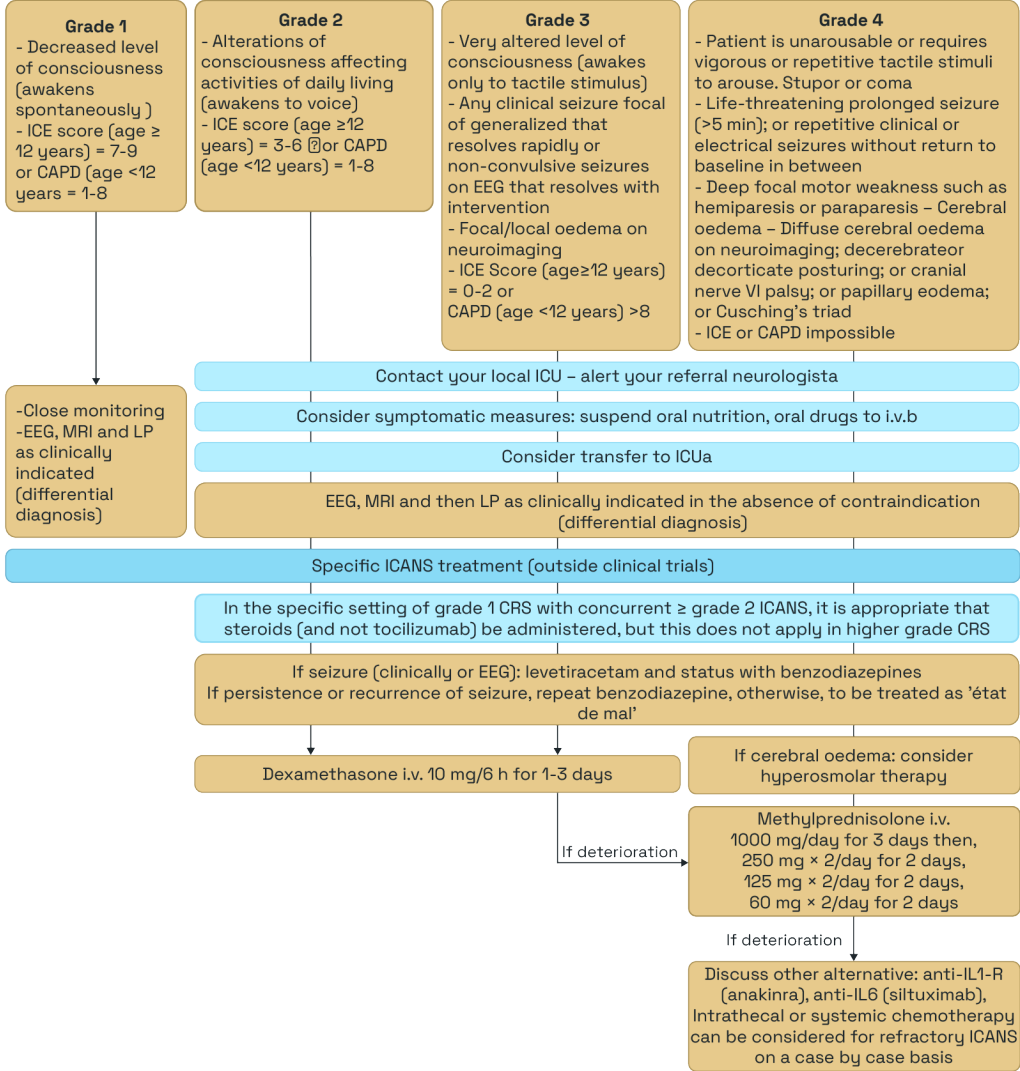


Figure 13.2: EHA/EBMT algorithm for grading and management of ICANS.
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doi: 10.1016/j.annonc.2021.12.003.

13.1.4 Immune effector cell-associated hematology toxicity

Background

ICAHT refers to hematologic adverse events after CAR T-cell infusion. Although the pathophysiology is incompletely understood, it may result from inflammatory reactions, direct marrow effects of CAR T cells, or reduced hematopoietic reserve due to prior therapies or disease infiltration.

Clinical presentation

ICAHT is classified as early or late, and graded according to Table 13.3.

- Incidence of grade ≥3 varies between 13–85%.
- Prolonged neutropenia of any grade occurs in 10–74%.
- Manifestations are secondary to cytopenia: asthenia, infections, hemorrhages, etc.
- Risk-prediction scores such as CAR-HEMATOTOX may help identify high-risk patients (not validated for lymphoblastic leukemias).
- Differential diagnosis should include:
 - drug side effects
 - vitamin deficiencies
 - infections (especially viral)
 - CRS/MAS
 - IEC-HS
 - disease relapse
 - secondary hematological disorders

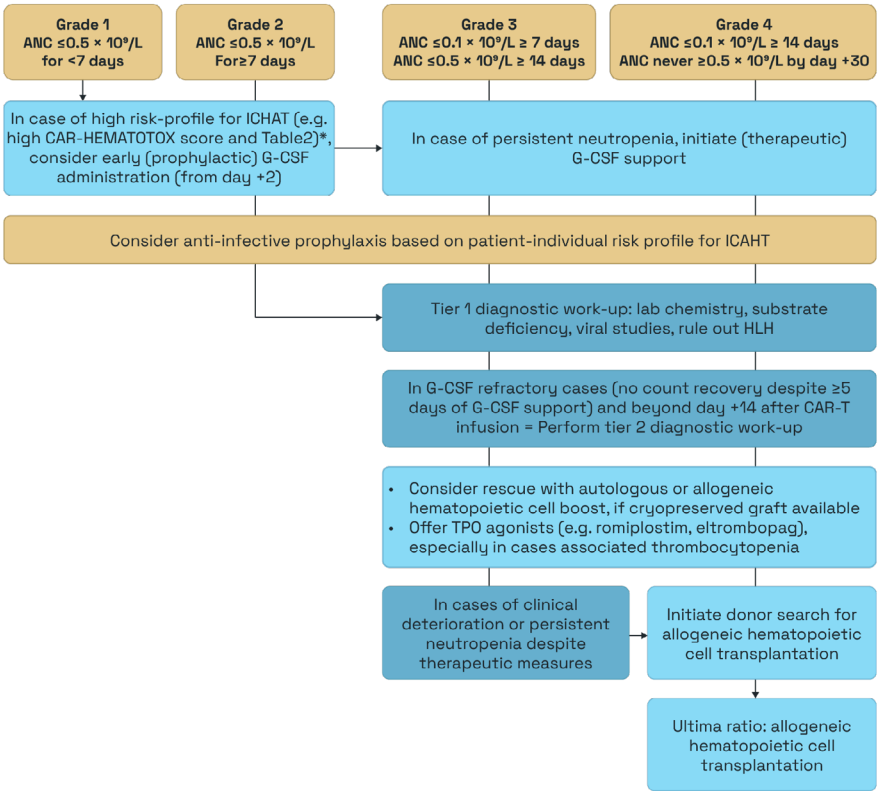


Figure 13.3: EHA/EBMT algorithm for grading and management of ICAHT
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13.2 Toxicities of bispecific T-cell engagers

13.2.1. Clinical presentation and diagnosis

Cytokine release syndrome

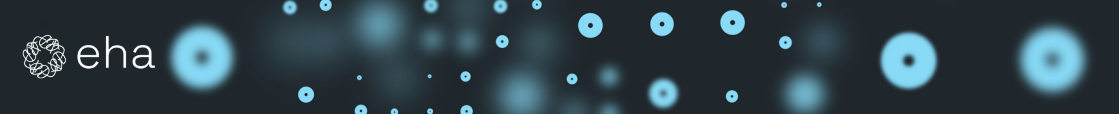
CRS is a systemic inflammatory reaction triggered by BiTE-mediated T-cell activation. Diagnosis, grading, and management generally follow those established for CAR T cells (see 13.1.1), although BiTEs have a distinct toxicity profile.

Symptoms	Grade 1	Grade 2	Grade 3	Grade 4
Early ICATH (day 0–30)				
ANC ≤0.5 × 10 ⁹ /L	<7 days	7–13 days	≥14 d	Never >0.5 × 10 ⁹ /L
ANC ≤0.1 × 10 ⁹ /L	-	-	≥7 d	≥14 d
Late ICATH (after day +30; measured ≥2 time points)				
ANC	≤1.5 × 10 ⁹ /L	≤1.0 × 10 ⁹ /L	≤0.5 × 10 ⁹ /L	≤0.1 × 10 ⁹ /L

Table 13.3: EHA/EBMT consensus criteria for ICAHT grading

Treatment

Possible underlying factors for cytopenias should be corrected. Before the use of early G-CSF, it is mandatory to discuss the case with a senior physician, due to the theoretical risk of CRS. If CRS/MAS or IEC-HS is suspected, a senior physician must be consulted before treating.



- CRS usually develops within the first hours to 3 days after infusion, with a duration of <7 days. After this period CRS/MAS should be considered.
- Overall incidence ranges from 15 –90%; grade ≥3 occurs in <10%.
- CRS is most frequent with the first administrations of BiTE, and incidence decreases after the second cycle.

Neurologic toxicity

Neurologic adverse events are less common with BiTEs and may result from endothelial activation and blood-brain barrier disruption. Diagnosis and grading follow the criteria for ICANS for CAR T cells (see 13.1.3).

- Most frequent symptoms: headache and dizziness.
- ICANS-like symptoms may occasionally occur
- Neurologic adverse events occur in 10–65% of patients; grade ≥3 occurs in ≤15%.
- Imaging and lumbar puncture should be considered in the differential diagnosis.

Other adverse events

- Tumor lysis syndrome (see Chapter 10).
- Rare tumor flare reactions, mainly after first doses.
- Cytopenias, especially neutropenia (see Chapter 6).
- T-cell exhaustion and target cell depletion (e.g., B cells and plasma cells with hypogammaglobulinemia), leading to increased risk of infections, including fungal and viral opportunistic agents.

13.2.2 Clinical management

The management of BiTE-related toxicities largely parallels that of CAR T cells, with emphasis on early recognition and rapid intervention. Preventive measures are aimed at reducing the risk of CRS and neurologic events, while treatment strategies focus on supportive care and timely escalation when complications arise.

Preventive treatment

- Premedication: corticosteroids (dexamethasone preferred), acetaminophen, and an antihistamine (as per manufacturer’s recommendations).
- Corticosteroids can usually be discontinued after 2 cycles if CRS has not occurred.
- Routine neurological testing is not required in asymptomatic patients with normal baseline assessments.
- Antimicrobial prophylaxis and infection monitoring are recommended.

Treatment

- Early intervention for CRS and neurologic toxicity is essential due to the risk of rapid deterioration.
- Management should be discussed with a senior physician.
- For CRS and neurologic toxicities, follow recommendations in sections 13.1.1 and 13.1.3.
- Consider levetiracetam prophylaxis at the onset of neurologic symptoms.
- Dose modifications or treatment interruption after a serious adverse event should follow the manufacturer’s instructions.

References _____

- Hayden PJ, et al., Ann Oncol. 2022;33:259–275.
- Hines MR, et al., Transplant Cell Ther. 2023;29:438.e1–438.e16.
- Rejeski K, et al., Blood. 2023;142:865–877.
- Crombie LJ, et al. Blood. 2024;143:1565–1575.

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14.1 Clinical presentation

Adverse events related to ICIs occur in approximately 70% of treated patients. Presentations are heterogeneous and may mimic pre-existing autoimmune conditions. Although any organ can be affected, the skin, gut, thyroid, lungs, liver, and joints are most frequently involved. Onset typically occurs within the first few months of therapy, in contrast to chemotherapy where toxicities appear within days. Late events may also develop after ICI discontinuation. In terms of severity, most events are grade 1 or 2 in severity.

Certain toxicities – especially myocarditis, pneumonitis, myositis, colitis, adrenal insufficiency, and encephalitis – can be life-threatening. Treatment should be discussed in cases with highly suggestive clinical signs before the full diagnostic work-up is complete. Clinicians must rapidly distinguish immune-related events from cancer progression, or alternative causes (e.g., infection, paraneoplastic syndromes). Treatment-related mortality has been reported in about 1% of ICI-treated patients.

14.2 Clinical management

Management of irAEs is guided by severity, as defined in the CTCAE v5 grading system. Even mild or new symptoms during immune checkpoint inhibitor (ICI) therapy should be investigated, as they may signal potentially severe toxicity. In general, grade 1 toxicities can be managed with close monitoring and symptomatic care, while grade 2 or higher toxicities often require treatment modification and systemic corticosteroids. The table below provides a summary of treatment decisions and additional interventions by grade.

Grade	Clinical manifestations (per CTCAE v5)	ICI treatment decision	Additional management
1 (mild)	Mild symptoms or diagnostic observations only; intervention not indicated	Continue ICI with close monitoring; consider temporary hold if persistent or organ-specific	Symptomatic care only (e.g., topical corticosteroids for rash, loperamide for mild diarrhea)

Grade	Clinical manifestations (per CTCAE v5)	ICI treatment decision	Additional management
2 (moderate)	Moderate symptoms; minimal, local, or noninvasive intervention indicated; limits instrumental ADLs	Hold ICI until recovery to grade ≤ 1	Start corticosteroids (prednisone 0.5–1 mg/kg per day or equivalent); taper when improved
3 (severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; limits self-care ADLs	Usually permanently discontinue ICI (exception: endocrine irAEs manageable with hormone replacement)	High-dose corticosteroids (prednisone or methylprednisolone 1–2 mg/kg per day); taper over ≥ 4 –6 weeks. If steroid-refractory, consider additional immunosuppressants (e.g., infliximab for colitis — avoid in myocarditis). Alternative or adjunctive options include anti-cytokine therapies (tocilizumab), JAK inhibitors, or anti-TNF therapies.
4 (life-threatening)	Life-threatening consequences; urgent intervention required	Permanently discontinue ICI	As for grade 3. For refractory cases, other agents may be required (e.g., mycophenolate mofetil, abatacept, tacrolimus, cyclosporine, anti-thymocyte globulin). Treatments targeting humoral immunity (e.g., rituximab, IVIG, plasma exchange) are generally less effective in these T-cell-mediated events. Specialist consultation strongly recommended.

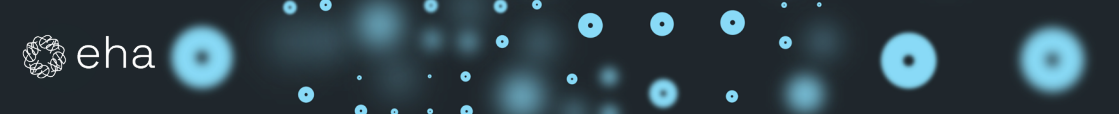


Table 14.1: Management of immune-related adverse events by grade (CTCAE v5)

Additional considerations

High-dose corticosteroids should be tapered over at least 4–6 weeks once symptoms are controlled, as early tapering increases the risk of recurrence. Endocrine irAEs are a notable exception, as patients can often continue ICI therapy with appropriate hormone replacement. In all cases, infection and tumor progression must be excluded before attributing symptoms to irAEs. Specialist consultation is strongly recommended for severe, refractory, or atypical presentations.

14.3 Special circumstances (focus on severe forms)

○ **Myocarditis**

- Frequency: ~1% of patients; mortality 30–50%; median onset ~1 month
- Symptoms: chest pain, dyspnea, pulmonary edema, syncope, cardiogenic shock, sudden death
- Work-up: EKG, CT angiography, NT-proBNP, troponin assay, echocardiography; consider cardiac MRI or endomyocardial biopsy
- Management: intensive care; cardiology consultation; often associated with myositis (~90% of cases)

○ **Encephalitis**

- Frequency: <1% of patients
- Symptoms: confusion, seizures, focal neurological signs
- Work-up: immediate contrast-enhanced MRI, lumbar puncture (to distinguish tumor invasion, paraneoplastic syndromes, infection), EEG (to rule out subclinical seizures)
- Management: empiric antibiotics or antivirals until infection results available; initiate methylprednisolone 1–2 mg/kg per day if infectious causes are ruled out

○ **Pneumonitis**

- Frequency: ~10% of patients (including ~50% grade 1 cases)
- Symptoms: unexplained dyspnea, cough, hypoxaemia, inspiratory crackles
- Work-up: high-resolution CT with contrast; consider bronchoscopy with BAL to exclude infection (if respiratory status allows)
- Management: suspend ICI in progressive grade 1 or higher cases

○ **Diabetes mellitus**

- Frequency: rare; often severe

- Symptoms: frequently presents with diabetic ketoacidosis
- Work-up: screen for type 1 diabetes antibodies and C-peptide
- Management: rapid initiation of insulin when hyperglycemia is detected

○ **Hypophysitis**

- Frequency: rare; median onset ~6 months for anti-PD-1; earlier and more frequent with anti-CTLA-4
- Symptoms: severe headache, diplopia, other neurological signs
- Management: prednisolone 1 mg/kg per day

○ **Colitis**

- Frequency: rare with monotherapy; up to 30% with dual anti-PD(L)1 + anti-CTLA-4; often within first month
- Symptoms: abdominal pain, nausea, mucus or blood in stools, systemic inflammation. Increased risk in patients with pre-existing inflammatory bowel disease
- Work-up: metabolic and thyroid panels, CBC, inflammatory markers, stool cultures (parasites, Clostridioides difficile, cytomegalovirus, other viruses). For ≥grade 2 symptoms, endoscopy and abdominal CT are strongly recommended; colonoscopy or flexible sigmoidoscopy shows inflammatory lesions in >50% of cases; biopsies required even if macroscopic findings are normal. Gastroscopy if upper GI symptoms present
- Management: steroid treatment guided by biopsy results; escalate in severe cases

○ **Adrenal insufficiency**

- Frequency: ~1% of patients; onset from days to 12 months (median ~4 months)
- Symptoms: adrenal crisis, vasodilatory shock; resembles secondary adrenal insufficiency
- Work-up: CT to rule out adrenal metastasis or hemorrhage; ACTH measurement to determine central vs peripheral origin
- Management: corticosteroid therapy during acute phase

References

- Lyon AR, et al. Eur Heart J. 2022;43:4229–4361.
- Brahmer JR, et al. J Immunother Cancer. 2021;9:e002435.
- Haanen JB, et al. Ann Oncol. 2017;28(Suppl 4).
- Jurlander RS, et al. Eur J Cancer. 2024;115053.
- Ramos-Casals M, et al. Nat Rev Dis Primers. 2020;6:38.

15. Catheter-related complications

Key facts

- Always verify central venous catheter (CVC) tip position after insertion; malposition increases thrombosis and arrhythmia risk.
- Loss of blood return with normal infusion suggests a fibrin sheath; confirm with contrast study, treat with fibrinolysis or interventional radiology stripping.
- For complete occlusion, first rule out technical issues, avoid syringes <10 mL, and use unit protocol fibrinolysis if simple measures fail.
- Catheter-related bloodstream infection (CRBSI): remove the catheter if sepsis, local infection or other complications (e.g., septic thrombophlebitis, endocarditis, septic emboli); otherwise combine systemic antibiotics with an antibiotic lock when appropriate. Do not use antibiotic lock therapy for *Staphylococcus aureus*, *Staphylococcus lugdunensis* regardless of leukocyte count, or *Pseudomonas aeruginosa* in the presence of neutropenia.
- Catheter-associated thrombosis: treat with anticoagulation for at least 3 months; remove catheter if non-functional, mal positioned, no longer needed, in case of septic thrombophlebitis, catheter must be removed.
- Air embolism is a medical emergency: clamp the line, place patient in supine Trendelenburg position, administer high flow oxygen, initiate IV fluid resuscitation, aspirate air if possible, and arrange urgent transfer for hyperbaric oxygen therapy.

Important definitions:

- Central venous catheter (CVC): a catheter with the tip in a central vein (e.g., superior vena cava).
- Peripherally inserted central catheter (PICC): a centrally terminating catheter inserted via a peripheral vein.
- Midline catheter: a peripherally inserted catheter with the tip remaining in a peripheral vein.
- Catheter-related bloodstream infection (CRBSI): laboratory-confirmed bloodstream infection where the intravascular catheter is the suspected source.
- Antibiotic lock: instillation of a concentrated antimicrobial solution into the catheter lumen and dwelling for a defined period while the catheter is not in use.

15.1 Central catheter tip position

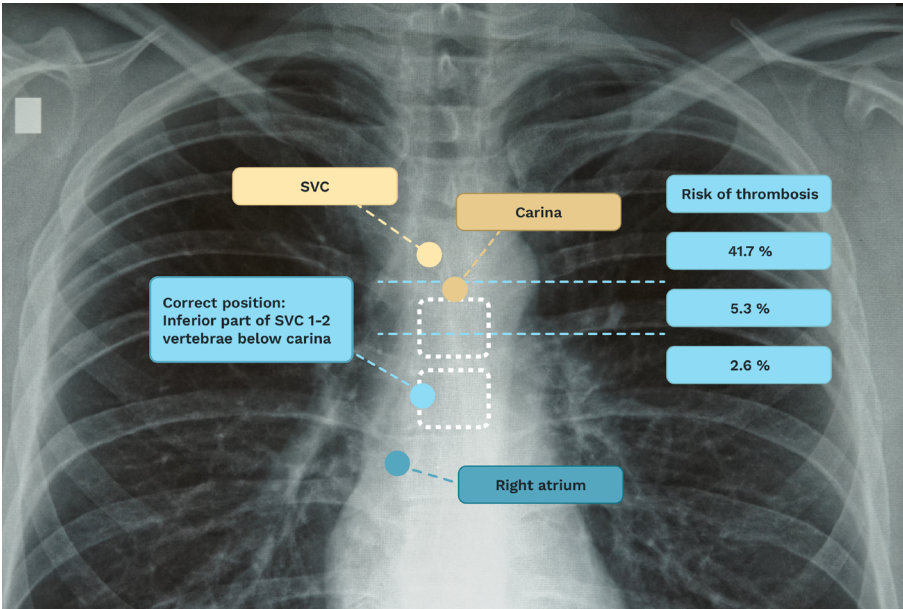
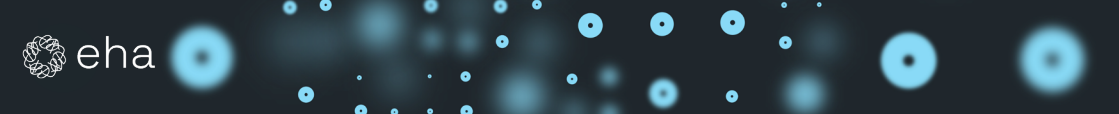


Figure 15.1: Optimal central catheter tip position

It is important to verify the position of the catheter tip after insertion. The optimal location is at the cavoatrial junction, corresponding to approximately 1.5–2.5 vertebral body units below the carina. The tip should not project into the right atrium, as this increases the risk of thrombosis and arrhythmia. When feasible, a lateral chest radiograph helps confirm placement in the superior vena cava and excludes rare malpositions (e.g., azygos or internal mammary vein).

15.2 Type of catheter

Several types of vascular access catheters are used in hematology. Their characteristics differ in terms of insertion site, dwell time, care requirements, and removal procedure. The table below summarizes the most common types.



Catheter type	Insertion site	Tip location	Continuous use by week	Typical dwell time	Iodinated contrast	Removal procedure	Specific characteristics
Non-tunneled central catheter	Central	Central	7/7 days	up to ~21 days	Yes	Nursing setting	Multiple lumens possible; regular nursing care
Tunneled central catheter	Central	Central	7/7 days	Years	Model dependent	Nursing setting	Regular nursing care
Tunneled cuffed central catheter	Central	Central	7/7 days	Years	Model dependent	Surgical	Reduced accidental removal; Regular nursing care
Implantable port	Central	Central	5/7 days	Years	Model dependent	Surgical	Use a Huber needle; change needle at appropriate interval
Peripherally inserted central catheter (PICC)	Peripheral	Central	7/7 days	3-6 months	Yes	Nursing setting	Regular nursing care
Mid-line catheter	Peripheral	Peripheral	7/7 days	≤28 days	Yes	Nursing setting	Regular nursing care
Peripheral venous catheter	Peripheral	Peripheral	7/7 days	≤3 days	Yes	Nursing setting	Regular nursing care

Table 15.1: Characteristics of most common catheter types

15.3 Common central catheter malfunctions

Central catheters can fail through loss of blood return, obstruction, infection, thrombosis, or rupture. Prompt identification and standardized management reduce complications.

15.3.1 No backflow (blood return) with normal infusion

Work-up

- No blood return on aspiration while infusion remains possible.
- Step 1: obtain a chest x-ray (anteroposterior, and lateral if possible) to check for malposition, looping, or migration.
- For implantable ports, confirm that the Huber needle is correctly placed.

If the catheter is well positioned

- Perform an opacification (contrast study).
- The only indication is to look for a fibrin sleeve at the tip.

Management

- If a fibrin sleeve is present, fibrinolytic instillation can be attempted (variable success, per unit protocol).
- If unsuccessful, consider referral to interventional radiology for catheter stripping.

Remarks

- Infusion may still function despite absent backflow.
- Document the finding and reassess catheter function before high-risk infusions.

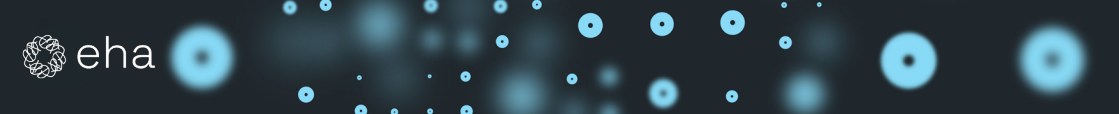
15.3.2 Central Catheter obstruction (no infusion flow or backflow)

Work-up

- No infusion flow and no blood return.
- First step: contact the person who inserted the catheter.
- Check for obstruction:
 - For implantable ports, verify needle position and re-insert at a different puncture site if needed.
 - Attempt to aspirate the clot with a 10 mL syringe using the POP-UP technique.
 - Reposition the patient (turn head away from the catheter, arms by sides) and ask the patient to cough to relieve positional occlusion.
- Warning:** small-volume syringes (<10 mL) are prohibited because of high intraluminal pressure.

Management

- If obstruction persists, instil a fibrinolytic agent according to unit protocol.
- If the catheter is completely blocked and difficult to access:
 - Connect two syringes in parallel or use two Huber needles for an implantable port.
 - Close the stopcock on the syringe with the fibrinolytic.
 - Aspirate firmly on the second syringe to create negative pressure.
 - Open the stopcock to the first syringe and inject the fibrinolytic solution, which enters the catheter under negative pressure.
 - Leave in place for 60 minutes.
 - If needed, repeat once, with the second attempt left in place for up to 24 hours.



Remarks

- Document the obstruction episode and the measures taken.
- Re-evaluate catheter function before high-risk infusions.

15.3.3 Catheter-related infection

Work-up

- Local signs such as pus, cellulitis, or tunnelitis are mandatory indications for catheter removal.
- Other suggestive signs include fever, chills, and bacteremia with no obvious portal of entry.
- A >2 h growth differential between catheter-drawn and peripheral vein blood cultures has sensitivity and specificity >90% for diagnosing catheter-related bacteremia, except:
 - *Staphylococcus aureus*: sensitivity only 42%.
 - *Candida*: sensitivity also low.

Management of bacteremia and candidemia associated with central venous catheters

1. After catheter removal and first negative blood culture

- Coagulase-negative staphylococcus: 3 days (without complications) if apyrexial and no endovascular material; in some cases catheter removal alone may suffice (with specialist advice).
- *Streptococcus*, *Enterococcus*, and gram-negative bacilli: 7 days.
- *Staphylococcus aureus*: 14 days (longer if bacteremia persists or complications occur).
- *Septic thrombophlebitis*: 21 days
- *Candida species*: 14 days (longer if fungemia persists or complications occur).

2. If the catheter remains in place (with antibiotic lock)

- *Streptococcus*, *Enterococcus*, coagulase-negative staphylococcus, and gram-negative bacilli: 10 days of systemic therapy plus 10 days of lock therapy.

What to do with the catheter?

- Remove the catheter if:
 - Sepsis.
 - Local signs contraindicating lock therapy.
 - Other complications eg., septic thrombophlebitis, endocarditis, septic emboli.

Contraindications to lock therapy

- **Absolute**
 - Uncontrolled infection/sepsis.
 - Local infection.
 - Pathogens: *Staphylococcus aureus* and *Candida*.
 - Septic thrombophlebitis, distant complications such as endocarditis or septic emboli.
- **Relative**
 - *Stenotrophomonas*, *Pseudomonas*, or other gram-negative bacilli (consider degree of aplasia, time to aplasia, tolerance of infection; catheter removal recommended if neutropenia is present or imminent).

If no indication for catheter removal

- Keep the catheter in place, combining systemic antibiotics with lock therapy:
 - Do not use the port during lock treatment.
 - Instil 3 mL of antibiotic solution:
 - Vancomycin 12.5 mg/mL for gram-positive cocci.
 - Amikacin 5 mg/mL for gram-negative bacilli.
 - Gentamicin 5 mg/mL if resistant to amikacin, and sensitive to gentamicin
 - Change the Huber needle as usual (maximum 7 days).
 - Change the lock solution every 48 h.
 - Flush with pulsed saline before each reinjection.
 - Total duration: 10 days.
 - Control blood cultures after recovery of the old lock at days 4 and 11, and prior to catheter reuse.
 - Remove the port in case of persistent fever, microbiological failure at day ≥4, or septic emboli (20%–30%).

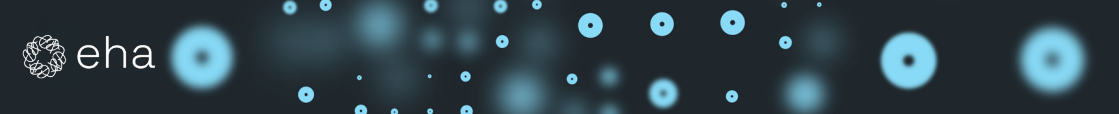
15.3.4 Catheter-related thrombosis

Work-up

- Symptoms may include pain, edema, superior vena cava syndrome, or fever.
- Incomplete thrombosis may be asymptomatic and present only as absent reflux or mild signs (50%–75% of cases).

Confirmation of diagnosis

- Do not screen for asymptomatic thrombosis.
- First-line test: Doppler ultrasonography.
- If intrathoracic involvement is suspected: contrast-enhanced CT scan.
- Clinical scoring and D-dimer testing are not useful because of low positive predictive value, especially in oncology.
- Note: Thrombosis is more frequent in patients with cancer, after traumatic insertion, with larger catheter diameter, with extrinsic tumor compression, or when the catheter is too short.



Management

- Therapeutic anticoagulation with LMWH or a DOAC for 3 months; extend to 6 months in oncology or as long as the cancer is active/treated and the catheter remains in place.
- Vitamin K antagonists (VKA) are reserved for contraindications to LMWH and DOAC.
- Switching to a DOAC should be considered when therapy continues beyond 6 months or in cases of low adherence with LMWH.
- Remove the catheter only if:
 - It is no longer needed.
 - It is non-functional.
 - The catheter tip is malpositioned.
 - Fever persists beyond 72 h despite anticoagulation.
- In the absence of infection, many experts recommend removing the catheter after 2 days of effective anticoagulation.
- If a poorly tolerated superior vena cava syndrome persists beyond 72h of treatment, discuss fibrinolysis, thrombus aspiration, or stent placement.

15.3.5 Catheter rupture

Management (emergency)

- This is a medical emergency because of the risk of bleeding, air embolism, or catheter migration.
- Clamp the catheter immediately to prevent air entry and migration.
- Follow the air embolism management steps (see Section 15.4).
- If rupture occurs in a central CVC without a cut tip, removal can be performed during exhalation.

15.4 Air embolism

Work-up

- Air embolism is the entry of air into the bloodstream after a vascular breach. It may occur during catheter insertion, removal, rupture, or from air in the tubing system.
- A few milliliters of venous air are usually asymptomatic (e.g., small bubbles in infusion).
- In patients with a right-to-left shunt (e.g., patent foramen ovale, present in ~30% of the population), arterial air embolism may occur and cause cerebral or coronary occlusion.

Clinical features

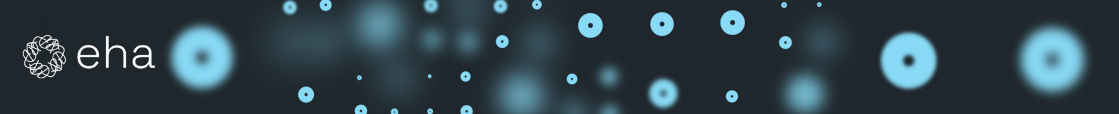
- Cardiorespiratory: tachycardia, bradycardia, dyspnea, cough, desaturation, chest tightness or pain
- Hemodynamic: hypotension, cardiac arrest
- Neurologic: sensory or motor deficits

The association of these nonspecific signs with the clinical context (e.g., visible air bubbles in tubing) should raise suspicion of air embolism. Clinical signs may appear immediately or be delayed after catheter manipulation.

Management

Air embolism must be managed as a treatment emergency. Immediate recognition and action are essential.

1. Clamp the catheter.
2. Assess severity and call the resuscitation/critical care team if:
 - Shock or cardiac arrest.
 - Acute respiratory failure.
 - Any neurological deficit.
3. Position the patient supine with Trendelenburg.
4. Administer oxygen at 15 L/min via non-rebreather mask.
5. Attempt aspiration via the central catheter until blood is obtained, then reclamp.
6. Begin fluid resuscitation with 2000 mL crystalloids in the first 6 h.
7. Provide supportive treatment for symptoms.
8. Transfer urgently to a facility with a hyperbaric chamber for hyperbaric oxygen therapy.
9. If air embolism is suspected without clinical signs, perform an urgent CT thorax. If confirmed, transfer for hyperbaric oxygen therapy.



16. Homologous (allogeneic) transfusions and complications

Key facts

- Red blood cells: use a restrictive transfusion policy; usually 1 unit at a time with clinical reassessment.
- Platelets: transfuse according to bleeding risk and clinical context, not just platelet count.
- Plasma: indicated only in specific settings (eg, DIC, TTP, severe liver dysfunction, massive transfusion).
- Granulocytes: rarely used; reserved for selected patients with refractory infection and expected marrow recovery.
- Transfusion is a medical act: monitor all patients closely and be prepared to manage acute or delayed reactions.

Important definitions:

- **Packed red blood cell (PRBC)** unit: ~275 mL (± 75 mL) containing ≥ 40 g hemoglobin; hematocrit 0.6 (± 0.1).
- **Platelet concentrate (PC)**: 1 unit ~200–300 mL containing $\geq 2.4 \times 10^{11}$ platelets; pool and single-donor units are considered bioequivalent.
- **Fresh-frozen plasma (FFP)**: 200–300 mL per unit; provides all plasma proteins including clotting factors and complement.
- **Granulocyte concentrate**: 200–650 mL apheresis product, collected after donor stimulation (eg, corticosteroids).
- **ABO compatibility**: Matching rules vary by component; plasma and platelets may be transfused across groups with caution.
- **Irradiated products**: Cellular components treated to prevent transfusion-associated graft-versus-host disease.
- **Washed/deplasmatised products**: Components processed to remove plasma proteins, used in IgA deficiency or severe allergic reactions.
- **Extended matching**: Providing RBC units matched beyond ABO/RhD for selected patients (alloimmunization, sickle cell disease, thalassemia).

References

- Blot F, et al. Lancet. 1999;354(9184):1071–1077.
- Böll B, et al. Ann Hematol. 2021;100(1):239–259.
- Sous les Verrous Study Group. Infect Dis Now. 2021;51(3):236–246.

16.1 Red blood cell transfusion

Packed red blood cell (PRBC) concentrates, provided in leukoreduced form, are the most frequently used blood component in hematology. They are administered to correct symptomatic anemia and to maintain adequate hemoglobin levels in a wide range of clinical settings. This section outlines the principles of indication, transfusion policy, and special handling considerations.

Background

- **Indications and thresholds (general principles):**
 - Hb <7 g/dL in patients <80 years without cardiovascular disease or poor tolerance (exception for well-tolerated deficiencies).
 - Hb 7–8 g/dL in hematology patients in general.
 - Hb up to 10 g/dL in case of cardiovascular disease (begin with 1 unit to reduce transfusion associated cardiac overload [TACO] risk).
 - No fixed threshold for hemolytic anemias and hemoglobinopathies; transfuse according to clinical tolerance.
 - Patients with hemoglobinopathies may have individual transfusion targets.
 - In the event of cold agglutinins, warm the blood bag using a dedicated device.
- **Transfusion policy:**
 - In general, adopt a single-unit transfusion strategy with clinical reassessment.
 - For outpatient hematology care (e.g., myelodysplastic syndromes), a more liberal approach may be considered.
- **Compatibility and definitions (broad context):**
 - Adult dosage: 1 PRBC unit ~275 mL (±75 mL), ≥40 g hemoglobin, Hct 0.6 (±0.1).
 - ABO compatibility: standard matching rules apply; O blood group as universal donor in emergencies.

Management and treatment

- **Pretransfusion testing**
 - Before the first transfusion of any blood component: perform two independent determinations of ABO–RhD blood group and Rh C, E, c, e, and Kell (K) phenotype.
 - For PRBCs, an irregular agglutinin test/indirect antiglobulin test (IAT) dated within 72 h is mandatory (may be extended to 21 days if no transfusion, pregnancy, or transplant in the past 6 months).

- Regardless of urgency, blood samples for blood group and IAT must always be collected.
- Depending on the level of urgency, transfusion may be initiated before results are available (see table below).
- After any transfusion episode: repeat IAT within 1–3 months.
- All transfused patients should be issued a blood group card.

	Relative urgency	Vital emergency	Immediate life- threatening emergency
Time to deliver	2–3h	<30 min	Without delay
ABO–RhD blood group and Rh–Kell phenotype determinations	Identical or compatible transfusion	Identical or compatible transfusion	Draw blood for testing but transfuse group O PRBCs (preferably Kell-negative). For women with childbearing potential: O D-negative Kell-negative is preferred if available.
IAT	Mandatory result before transfusion. If positive: perform direct laboratory compatibility test.	Collected, but transfusion may proceed without waiting for results	Collected, but transfusion may proceed without waiting for results

Table 16.1: Urgency categories and testing requirements

Compatibility and dosage

Adult dosage: 1 PRBC unit: 275 mL (±75 mL), containing ≥ 40 g hemoglobin; hematocrit 0.6 (± 0.1).
Quantity transfused should be the minimum needed to eliminate poor tolerance and/or raise Hb to an acceptable level.

Recipient blood group	1st choice	2nd choice	3rd choice	4th choice
Unknown	O	-	-	-
O	O	-	-	-
A	A	O	-	-
B	B	O	-	-
AB	AB	A	B	O

Table 16.2: ABO compatibility rule for PRBCs

Special issues in testing

Three main causes of false-positive irregular antibody test (IAT):

- Autoantibodies with a positive direct Coombs test.
- Treatment with monoclonal antibodies (inform the blood bank systematically):
 - Anti-CD38 (e.g., daratumumab, isatuximab, indicated in myeloma because plasma cells express CD38, but RBCs also carry CD38 at low levels).
 - Anti-CD47
- Anti-D treatment: passive anti-D leads to a positive IAT for ≥3 weeks; confirm negativity at a later date.

RhD compatibility

- Must be respected for transfusion of red blood cells, platelets, and leukocytes (not for plasma).
- If RhD-incompatible platelet transfusion is unavoidable in women of childbearing potential: administer ≥100 µg anti-D immunoglobulin (eg, Rhophylac®, Rhogam®) within 72 h. Residual anti-D can be retested at 3 weeks to confirm protection.

Special Circumstances

- **Irradiated PRBC**
 - From 7 days before HSC collection, including CAR T (marrow or blood donor); also discussed for lymphapheresis.
 - Before and after autologous HSC transplantation, including CAR T therapy (≥6 months after; up to day 365 if TBI).
 - Post allograft from day 0 to day 365 (longer if ongoing immunosuppression or chronic GvHD).
 - Up to 1 year after treatment with purine or pyrimidine analogues (fludarabine, bendamustine, pentostatin, cladribine).

- Any profound T-cell deficiency other than HIV (eg, ATG, anti-CD52, congenital deficiency).
- Intra-family directed donations (requires exemption).
- HLA-matched products.

○ Deplasmated/washed PRBC

- IgA deficiency with anti-IgA antibodies in the recipient's plasma.
- History of severe or repeated allergic transfusion reactions (eg, shock, angioedema).

○ Matched for Rh and Kell (moderate matching may suffice in patients >80 years or in palliative care)

- Patients with clinically significant anti-erythrocyte alloantibodies against Rh (C, E, c, e), Kell, Fy, Jk, S, U, or other rare antigens.
- Women from birth until end of reproductive age.
- Patients with thalassemia.
- Patients requiring lifelong transfusion support (eg, thalassemia, MDS, congenital dyserythropoietic anemia).
- Patients with rare blood types.

○ Extended matching (Fy/JK/MNS)

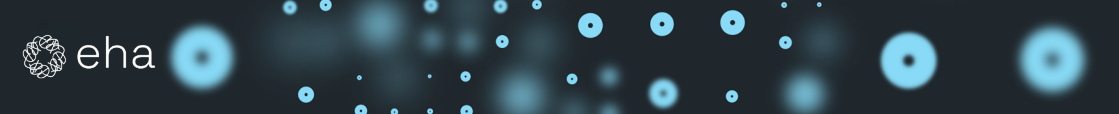
- Patients with one or more alloantibodies against antigens outside Rh and Kell, requiring ongoing transfusion support.
- Patients with sickle cell anemia.

○ Compatibility testing

- Sickle cell patients, regardless of IAT result.
- Patients with a positive IAT or history of positive IAT.

○ Anti-CD38/anti-CD47 treatment

- False-positive IAT results may persist for up to 6 months after the end of treatment.
- Possible approaches:
 - Use DTT-treated test cells (note: destroys Kell antigens).
 - Use an anti-daratumumab neutralizing reagent (anti-idiotypic antibody fragment).
 - Select compatible PRBCs based on extended phenotyping or genotyping performed before initiation of anti-CD38 therapy.



16.2 Platelet transfusion

Platelet concentrates (PC), either pooled or single-donor, are transfused to prevent or treat bleeding due to thrombocytopenia or platelet dysfunction. Transfusion policy is guided not only by platelet count but also by the clinical setting and the patient's bleeding risk.

Background

- Platelet product: 1 PC unit $\approx$ 200–300 mL, containing $\geq 2.4 \times 10^{11}$ platelets.
- Pooled and single-donor concentrates are considered bioequivalent; single-donor units are preferred in HPA/HLA alloimmunization.
- Platelet antigens are carried in several systems: HLA class I (A, B, C) and HPA system (e.g., HPA1–4) which are specific to platelets.
- ABO antigens are not expressed on platelets themselves but may be passively adsorbed from donor endothelium.
- Pathogen-reduction techniques (e.g., amotosalen/UVA) are variably implemented; they also inactivate residual T cells.

Management and treatment

- **Individual patient approach:** hemorrhagic phenotype and kinetics of platelet decline must always be taken into account thresholds serve as guidance but decisions must be individualized.
- **Thresholds for prophylaxis:**
 - $10 \times 10^9/L$ if no additional risk factors (e.g., aplastic anemia, congenital thrombocytopenia).
 - $10\text{--}20 \times 10^9/L$ if fever $\geq 38.5^\circ C$, infection, hypertension, grade ≥ 2 mucositis, lesion with bleeding potential, rapid decline in platelet count within 72 h, or severe thrombocytopathies, minor surgical procedures.
 - $25\text{--}30 \times 10^9/L$ for patients on therapeutic anticoagulation or before gastroscopy (with or without biopsy).
 - $50 \times 10^9/L$ in disseminated intravascular coagulation, during anticoagulation, in AML M3, or prior to invasive procedures (adjust if peripheral destruction).
 - $80 \times 10^9/L$ before epidural anesthesia.
 - $100 \times 10^9/L$ before neurosurgery.
- **Therapeutic transfusion irrespective of count:**
 - Active or life-threatening bleeding with impaired platelet function.
 - Bleeding due to immune thrombocytopenia (ITP) or thrombotic microangiopathy (TMA).
 - Note: In ITP or TMA without bleeding, prophylactic platelet transfusion is not indicated.

○ Compatibility

- ABO-compatible units are preferable but not mandatory if anti-A or anti-B titers are low in both donor unit and recipient.
- For patients with alloimmunization (HLA or HPA), use phenotyped or compatible PCs.

○ Monitoring efficacy

- The response to platelet transfusion should be assessed by the Corrected Count Increment (CCI):

$$CCI = \frac{\text{post transfusion plt count} - \text{pre transfusion plt count} \left(\frac{\times 10^9}{L} \right) \times \text{body surface area (m}^2\text{)}}{\text{transfused plt count} (\times 10^{11})}$$

- An ineffective transfusion is defined after a second ABO-compatible PC stored < 72 h, if:
 - CCI < 7.5 at 1 h, or
 - CCI < 5.0 at 20 h.

○ Management of refractoriness

- If alloimmunization (HLA or HPA) is present: use phenotyped or compatible PCs.
- Consider fractionated transfusions within 24 h in bleeding patients.
- Avoid prophylactic transfusions in refractory states.

○ Other contributing factors to refractoriness

- Fever, with or without infection.
- DIC, microangiopathic hemolytic anemia, or splenomegaly.
- Complications of HSC transplantation (eg, veno-occlusive disease, CMV, GVHD, TMA).
- Drug interference (eg, amphotericin B, vancomycin).

Special circumstances

○ Irradiated PC

- From 7 days before HSC collection, including CAR T; also discussed for lymphapheresis.
- Before and after autologous HSC transplantation or CAR T therapy (≥ 6 months after; up to day 365 if TBI).
- Post allograft from day 0 to day 365 (longer if ongoing immunosuppression or chronic GvHD).
- Up to 1 year after treatment with purine or pyrimidine analogues (fludarabine, bendamustine, pentostatin, cladribine).

- Profound T-cell deficiency other than HIV (eg, ATG, anti-CD52, congenital deficiency).
 - Intra-family directed donations (requires exemption).
 - HLA-matched products.
- **Deplasmatised (washed) PC**
 - IgA deficiency with anti-IgA antibodies.
 - History of severe or repeated allergic transfusion reactions (eg, shock, angioedema).
- **HLA/HPA compatibility**
 - In cases of refractoriness with anti-HLA and/or anti-HPA alloimmunization.
- **Pathogen-reduced PC**
 - May be used where available; reduces risk of transmission of pathogens and inactivates residual T lymphocytes.

- **Dosing**
 - Adult unit = 200–300 mL.
 - 10–15 mL/kg for DIC, factor V/protein S/plasminogen deficiency with active or potential bleeding.
 - 10–30 mL/kg after plasma exchange or in non-severe bleeding.
- **Additional considerations**
 - In thrombotic microangiopathies: plasma has a recognized therapeutic effect at high volumes (40–60 mL/kg, ≈1–1.5 plasma volumes). This volume supplies ADAMTS13 in TTP and complement proteins in HUS, which is why plasma administration is preferably by plasma exchange.
 - No threshold in hemorrhagic shock; follow local major hemorrhage protocols.
 - In DIC with prolonged PT activity: plasma may be indicated.
 - If fibrinogen <1 g/L after plasma exchange: use cryoprecipitate or fibrinogen concentrate rather than plasma.
- **Compatibility**
 - ABO compatibility should be respected; if group is unknown, AB plasma is preferred.
 - Guide for ABO compatibility of FFPs:

Recipient blood group	1st choice	2nd choice	3rd choice	4th choice
Unknown	AB	-	-	-
O	O	A	B	AB
A	A	AB	-	-
B	B	AB	-	-
AB	AB	-	-	-

Table 16.3: ABO compatibility of FFPs

Plasma supplies all plasma proteins, in particular coagulation factors and complement fractions. Plasma is the only product capable of supplying factor V, protein S, plasminogen, and ADAMTS13, as well as certain complement fractions. These factors are not available in stable purified form among plasma-derived medicinal products.

16.3 Plasma transfusion

Fresh frozen plasma (FFP) is transfused to replace clotting factors in specific conditions. It provides all plasma proteins, including factor V, protein S, plasminogen, ADAMTS13, and complement fractions, which are not available as stable purified products.

Management and treatment

- **Indications**
 - Disseminated intravascular coagulation (DIC).
 - Thrombotic thrombocytopenic purpura (TTP).
 - Factor V deficiency.
 - Bleeding in patients with liver insufficiency.
 - Loss or dilution of coagulation factors during massive transfusion or plasmapheresis.
 - Acute attacks of hereditary angioedema, particularly with laryngeal involvement, but only when C1 inhibitor or icatibant is not immediately available.
 - Severe VKA overdose if:
 - Prothrombin complex concentrate (PCC) is not available, or
 - Only heparin-containing PCCs are available in a patient with history of HIT.

- **Special circumstances**
 - Use HEV-negative plasma if available.
 - Consider in hepatopathy, organ transplant, allograft/autograft, or during pregnancy

16.4 Granulocyte transfusion

Granulocyte concentrates (apheresis or buffy-coat derived) are rarely used and should be considered only in selected cases of severe, uncontrolled infection. Their use requires close coordination with the blood bank, as products must be collected and transfused rapidly after donor preparation.

Management and treatment

- **Indications**
 - Febrile aplasia with a severe bacterial or fungal infection not controlled by antimicrobial therapy (eg, cellulitis of the pelvis or face, or other documented septic conditions), when recovery from aplasia cannot be awaited.
 - Anticipated exit from aplasia within the next few days.
 - Not indicated in palliative care.
 - Other rare indications: chronic granulomatous disease or other functional neutrophil defects with uncontrolled sepsis.
- **Dosage**
 - Adult unit: 200–650 mL
- **Compatibility**
 - ABO compatibility rules apply, depending on component preparation (e.g., CGrA modification).
- **Product characteristics**
 - Granulocyte transfusion may use:
 - Apheresis granulocyte concentrates (preferred), collected after donor stimulation (e.g., corticosteroids) to increase granulocyte yield.
 - Buffy-coat–derived granulocytes if apheresis products are unavailable.
 - Transfusion should occur as soon as donor serological results are available.
 - May be carried out before results of viral genomic screening (HIV-1, HCV) if clinically urgent, but only with informed consent of the patient or family.

16.5 Complications of transfusion

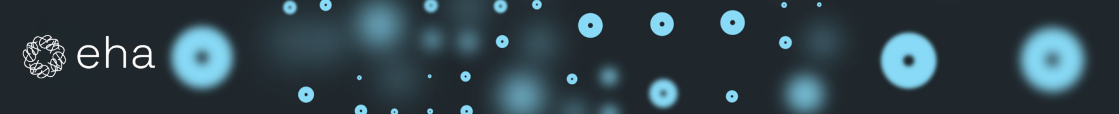
Transfusion is a medical act, and the prescribing physician is responsible for its indication and follow-up. A physician must be available in the event of complications. Whenever possible, transfusions should be administered during the day rather than at night. Patients should be educated about the early warning signs of transfusion reactions.

The spectrum of transfusion reactions is broad, and severity is difficult to predict since most begin with nonspecific symptoms. The patient's pre-existing condition and comorbidities may further complicate interpretation. Careful monitoring during and after transfusion is essential.

Acute complications (<24 h)

Acute transfusion reactions can occur with any blood component. They typically develop during or shortly after transfusion and may present with nonspecific signs such as fever, chills, or hypotension. Other potential complications to keep in mind include febrile neutropenia and gas embolism. The table below summarizes the major acute complications, their clinical presentation, para-clinical features, and recommended treatment.

Serious Reactions	Clinical	Para-clinical	Treatment
Transfusion associated cardiac overload (TACO) (all) Risk factors: History of cardiovascular disease, hypertensive surge (> 30 mmHg during the first RBC transfusion)	Acute respiratory distress, rather high blood pressure, possible associated signs of CDI	Bilateral infiltrate on chest X-ray with hilar redistribution, NTproBNP increased, if pleural puncture = transudate	Transfuse 1 unit at a time and slow the transfusion rate within 3 hours in high-risk patients (cardiac history, hypertensive crisis during the 1st unit). Furosemide can be applied
Anaphylaxis (all)	Often rapid response (few minutes) hypotension, even anaphylactic shock, urticaria/angioedema, bronchospasm, digestive disorders, rare fever	Serum tryptase and histamine	Immediate and definitive transfusion stop Adrenaline IM or IV + antihistamine therapy Discuss MV and bronchodilators IgA antibody test and IgA quantitative assay Next PSL: deplasmatized



Serious Reactions	Clinical	Para-clinical	Treatment
TRALI (all) ~Rare in male only plasma policy	Acute respiratory distress rather hypotensive, fever possible: ARDS	Bilateral infiltrate on chest X-ray, leukopenia, anti-PNN/HLA positive in donor, if pleural puncture = exudate	Immediate and definitive transfusion stop Transfer to intensive care, supportive care
Acute hemolytic shock (RBC and plasma)	Fever, chills, hypotension or even vasodilatory shock, acute low back pain, oliguria/anuria (rarely due to non-immunological causes such as heat shock)	Coombs + (low NPV), increased LDH and conjugated bilirubin, collapsed haptoglobin hemoglobinuria (urine dipstick+ for blood), often ARF and DIC Causes include ABO incompatibility, irregular immune antibodies of Rh, Kell, Duffy, Kidd, MNS, antibodies to high-frequency antigens, or anti-Wra (Diego system).	Immediate and definitive stop of transfusion. Redo IAT IV saline hydration Next transfusions with crossmatched PRBCs if IAT+.
Transfusion-transmitted bacterial infections (all)	Fever, chills, low blood pressure, even septic shock A predominantly digestive picture with profuse diarrhea, abdominal pain and vomiting is possible.	Bacteremia, hyperleukocytosis, possible DIC	Immediate and definitive stop of transfusion Blood culture patient and bag then broad spectrum antibiotics
Hypocalcemia (in case of massive transfusion)*	Paresthesia, malaise, rigidity, rhythm disorders hypothermia	Hypocalcemia	Calcium supplementation

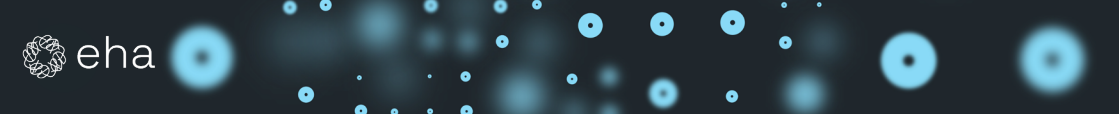
Serious Reactions	Clinical	Para-clinical	Treatment
Hyperkalemia (in case of massive transfusion in young patients or peri-operative setting)	Muscle weakness, rhythm disorders, cardiac arrest	Hyperkalemia	Calcium gluconate, glucose – insulin, furosemide
Post-transfusion purpura (all) Up to 10 days after transfusion	Mucocutaneous hemorrhagic syndrome lasting several hours, occurs mainly in female recipients	Acute profound thrombocytopenia	Testing for anti- HLA/ HPA antibodies Discuss IVIg 1g/kg per day If bleeding: transfusion of HPA-compatible platelets
Non-malignant: monitor carefully			
Urticaria (especially with plasma-containing products)	Isolated urticaria	-	Antihistamines (repeat once if necessary), corticosteroids If repeated with severe reactions: Washed products
Febrile Non-Hemolytic Transfusion Reaction (FNHTR)	Fever, myalgia; Common in non-leukoreduced blood products	-	Slow flow paracetamol

Table 16.4: Major acute transfusion reactions (<24 h)

* In hemorrhagic shock, also address early trauma-related coagulopathy ('lethal triad' of coagulopathy, hypothermia, and acidosis). Platelets should be systematically supplied (e.g., 1 PC for 4–6 RBC/FFP units or as per local massive transfusion protocol).

General management

- Common signs: fever, chills, sometimes pruritus.
- Warning signs to evaluate:
 - dyspnea/desaturation
 - hemoglobinuria
 - altered consciousness
 - hypertension or hypotension
 - acute low back pain



- bleeding syndrome
- oliguria
- For all suspected reactions:
 - Pause transfusion.
 - Maintain IV access with NaCl 0.9%.
 - Verify patient identity and perform clinical assessment.
 - Provide oxygen support as indicated.
 - Monitor the patient closely; repeat bedside testing if needed.
 - Contact the blood bank; send samples for CBC, urea/creatinine, Coombs, D-dimers, NT-proBNP, chest X-ray, blood gases, IgA/anti-IgA, tryptase, histamine, Ca²⁺, phosphorus (according to presentation).
 - Return the implicated component to the blood bank with an adverse event form.
 - Re-evaluate the need for further transfusion.

Delayed complications (>24 h)

- **Infectious risks (all components)**
Despite stringent testing, residual risks of viral transmission remain (HIV, HCV, HBV, HTLV-1, CMV, WNV, parvovirus B19), as well as parasitic transmission (*Plasmodium* spp., *Trypanosoma cruzi*).
- **Transfusion-associated graft-versus-host disease (RBC, PC)**
Occurs within 4–30 days. Manifestations may be cutaneous, digestive, hepatic, or medullary (due to HLA class II expression). Seen in patients with cellular immunodeficiency or partial HLA matching (eg, family donation). Diagnosis is difficult, differential diagnoses are broad, and mortality is >90%. Management is mainly immunosuppressive, hence the importance of prevention through irradiation.
- **Delayed hemolysis (all components)**
Hemolytic anemia, often asymptomatic and extravascular, up to 4 weeks post-transfusion. Clinical status and renal function must be monitored. Routine follow-up with IAT ± CBC at 1–3 months post-transfusion is recommended.

References

○ Carson JL, et al. JAMA. 2023;330:1892–1902.

○ Maier CL, et al. Transfus Med Rev. 2023;37:150751.

○ Apolseth TO, et al; Biomedical Excellence for Safer Transfusion Collaborative. Transfusion. 2024;64:1116–1131.

○ Roberts LN, et al. J Thromb Haemost. 2022;20:39–47.

○ Stanworth SJ, et al; Transfusion Task Force of the British Society for Haematology. Br J Haematol. 2022;198:654–667.

○ Estcourt LJ, et al. Br J Haematol. 2017;176:365–394.

○ Wood EM, McQuilten ZK. Hematology Am Soc Hematol Educ Program. 2020;2020:167–174.

○ Wang Y, Rao Q, Li X. Expert Rev Hematol. 2022;15:711–726.

○ Delaney M, et al; Biomedical Excellence for Safer Transfusion Collaborative. Lancet. 2016;388:2825–2836.

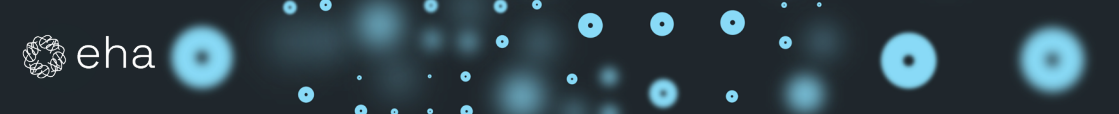
○ Foukaneli T, et al; BCSH Committee. Br J Haematol. 2020;191:704–724.

○ Transfusion Medicine and Hemostasis: Clinical and Laboratory Aspects. 3rd ed. Amsterdam: Elsevier; 2018.

○ Cardigan R, et al. Vox Sang. 2020;115:606–616.

○ Practical Transfusion Medicine. 6th ed. Hoboken, NJ: Wiley-Blackwell; 2022.

○ Levi M, et al. Br J Haematol. 2009;145:24–33.



17. Vaso-occlusive crisis in sickle cell disease

Key facts

- Suspect vaso-occlusive crisis in any patient with sickle cell disease presenting with pain.
- Provide prompt pain relief: start with simple analgesics, escalate to opiate analgesia, and use patient-controlled opioid analgesia if needed.
- Prevent and treat potential triggers.
- Monitor closely for signs of acute chest syndrome.

Important definitions:

- **Vaso-occlusive crises (VOCs):** may occur anywhere in the body. Bone or soft-tissue involvement often presents with severe pain.
- **Acute chest syndrome (ACS):** Multifactorial condition involving hypoventilation due to costal infarction, pulmonary infection, in situ vaso-occlusion, and fatty or cruric embolism. ACS accounts for 20% of deaths for approximately 20% of deaths in sickle cell disease (SCD).
- **Delayed hemolytic transfusion reaction (DHTR):** usually occurs within 2 to 4 weeks after red cell transfusion. A direct antiglobulin test is positive and a new alloantibody is detected in about 50% of cases. Leads to hemolysis of both autologous and transfused red blood cells. Seen most often in occasionally transfused patients with a history of alloantibody formation. The distinction between DHTR and hyperhemolysis is not fully consensual.
- **Splenic or hepatic sequestration:** most common in children and young adults with SCD. Caused by VOC in the splenic or hepatic microvasculature, manifesting as acute splenomegaly or hepatomegaly with a fall in baseline hemoglobin.

Background information

- SCD is the most prevalent genetic disease in Europe, caused by a mutation in the β chain resulting in structural abnormalities of hemoglobin.
- Major sickle cell syndromes: SS, S β^0 thalassemia, SC, and S β^+ thalassemia hemoglobinopathies.

17.1 Management of vaso-occlusive crisis

Management of VOCs in SCD includes prompt recognition of clinical features, appropriate diagnostic evaluation, interpretation of laboratory findings, and rapid initiation of treatment to relieve pain and prevent complications.

Clinical presentation

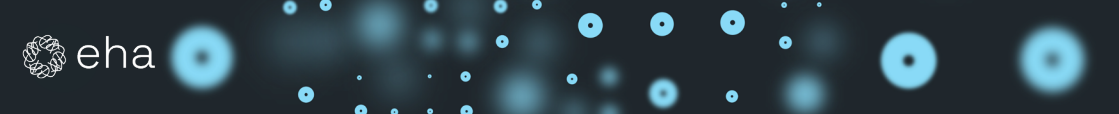
- Pain is the primary symptom, often affecting the long bones and the spine.
- Assess for factors that may precipitate crisis: dehydration, infection, hypoxia, corticosteroid therapy, air travel, stress, lack of rest, menstrual periods, and temperature changes.
- Fever may be present, but does not always exceed 38.5 °C.
- Monitor for signs of acute chest syndrome, which complicates about 20% of crises. Acute chest syndrome presents as acute hypoxemia with chest pain and a new pulmonary infiltrate on imaging.
- Always document the timing of the last transfusion and the baseline hemoglobin level. This is essential for differential diagnosis of DHTR and to avoid overtransfusion and hyperviscosity.

17.2 Diagnostic evaluation and laboratory findings

Diagnostic evaluation and laboratory testing are essential to confirm VOCs, identify complications, and guide management decisions.

Diagnostic evaluation

- **Mandatory tests:** CBC, reticulocyte count, LDH, electrolytes, liver function tests, and CRP. Assess hemoglobin fraction by hemoglobin electrophoresis (%HbS).
- **Optional tests (selected cases):** Arterial blood gas analysis and chest x-ray if respiratory signs are present, blood cultures if fever is present.



Laboratory findings in vaso-occlusive crisis

- Hyperleukocytosis with high neutrophil count.
- Elevated CRP, LDH, and transaminases.
- Hemoglobin usually remains stable (a crisis is not always associated with a drop of hemoglobin).

17.3 Clinical management

Clinical management focuses on effective pain control, correction of precipitating factors, and prevention of further complications.

Pain management

- Morphine titration: 0.1 mg/kg initially, followed by 2 mg every 10 minutes until the visual analog scale (VAS) score is <4/10. There are different protocols available, and local practice should be followed.
- Patient-controlled analgesia (PCA) morphine: 2 mg every 15 minutes, maximum 24 mg over 4 hours. Avoid continuous infusion to reduce risk of hypoventilation (monitor respiratory rate closely).
- PCA is contraindicated in patients with chronic renal failure. If pain recurs, re-titrate morphine.
- Use regular paracetamol; consider NSAIDs.

Prevention of triggering factors

- Ensure adequate hydration with isotonic solution (2L/24h), adjusted for cardiac status.
- Administer oxygen and encourage incentive spirometry to prevent atelectasis. Sustained maximal inspiration exercise is an acceptable alternative.
- Prescribe empiric antibiotics for fever, with pneumococcal coverage (e.g., amoxicillin 1 g three times daily) due to functional asplenia.
- Encourage rest and keep the patient warm.
- Consider thromboprophylaxis in hospitalized patients.
- Prescribe daily folic acid to support increased red cell turnover.

Considerations at discharge

- Ensure folic acid supplementation (5 mg daily).
- Do not prescribe opioids for home use (to avoid delayed presentation of future crises and risk of misuse).
- Expert advice is required if more than 3 VOC occurred during one year for major SCD patients

17.4 Special circumstances

Red blood cell transfusion should always be discussed with an expert. Occasional transfusion in an emergency is a major risk factor for DHTR. Check efficiency with hemoglobin level and HbA percentage (increase of 7–12% of HbA after 1 unit).

Indication for emergency transfusion exchange:

- Severe ACS (extensive bilateral opacities, respiratory distress, unfavorable course within 48–72 h)
- Stroke
- Abdominal or thoracic surgery, or surgery with prolonged general anesthesia
- Persistent priapism > 3 hours
- Crisis lasting > 8 days

References

○ Platt O, et al. N Engl J Med. 1991;325(1):11-16.
○ Gonzalez ER, et al. Arch Intern Med. 1991;151(7):1373-1378.
○ Bartolucci P, et al. Blood. 2009;114(18):3742-3747.
○ Bartolucci P, et al. Curr Opin Hematol. 2012;19(3):149-155.
○ Maitre B, et al. Chest. 2000;117(5):1386-1392.

18. Superior vena cava syndrome

Key facts

- Superior vena cava syndrome is a clinical urgency that needs immediate evaluation.
- In undiagnosed cases, adequate histological sampling must be rapidly performed before systemic therapy (e.g., glucocorticoids, radiotherapy).

Important definitions:

- **Superior vena cava** syndrome (SVCS) is a clinical manifestation that results from obstruction of the superior vena cava by external compression (e.g., tumor, lymphadenopathy) or internal blockage (e.g., thrombosis, intravascular device).
- Most common causes are malignancies, mainly lung cancer and non-Hodgkin lymphoma. Other malignancies such as thymoma may also be implicated. Concomitant thrombosis is frequent, and device-associated thrombosis is becoming an increasingly common cause.

18.1 Clinical presentation

Symptom severity depends on the degree of obstruction and the rapidity of onset.

- Facial, neck, thoracic, or upper-extremity edema
- Collateral thoracic venous circulation
- Jugular venous distension
- Chest pain, dyspnea (worse in supine position)
- Cough
- Facial plethora or cyanosis
- Headache, altered consciousness (intracranial hypertension)

18.2 Diagnostic work-up

Always:

- Chest X-ray: mediastinal widening, pleural effusion
- CT angiography (if stable supine): cause and extent of obstruction
- Histological sampling: Perform urgently before systemic therapy, as treatment may alter pathology and interfere with diagnosis. Acceptable methods include excisional, incisional, or core biopsy of peripheral lymph nodes, transbronchial biopsy, or mediastinoscopy. Fine-needle aspiration can be useful for diagnosing solid organ tumors, but is usually insufficient for lymphoproliferative disease.

Optional/special cases:

- Venography
- Doppler ultrasound of internal thoracic vein
- MRI venography
- PET scan for extension studies in lymphoma or metabolically active solid tumors

18.3 Clinical management

The first priorities in superior vena cava syndrome are supportive: maintain the patient in an upright position and provide oxygen if needed. Rapid assessment is essential to decide whether treatment can be delayed until adequate histological sampling is obtained, or whether immediate intervention is required.

Management then depends on the underlying cause and clinical severity. In steroid-responsive malignancies, glucocorticoids may be initiated while awaiting biopsy results. In cases with severe acute symptoms, intravascular stenting or urgent radiotherapy can provide rapid relief. If thrombosis is present, anticoagulation is indicated once hemostatic parameters are stable. Placement of central venous catheters in the superior vena cava should be avoided until resolution is documented.

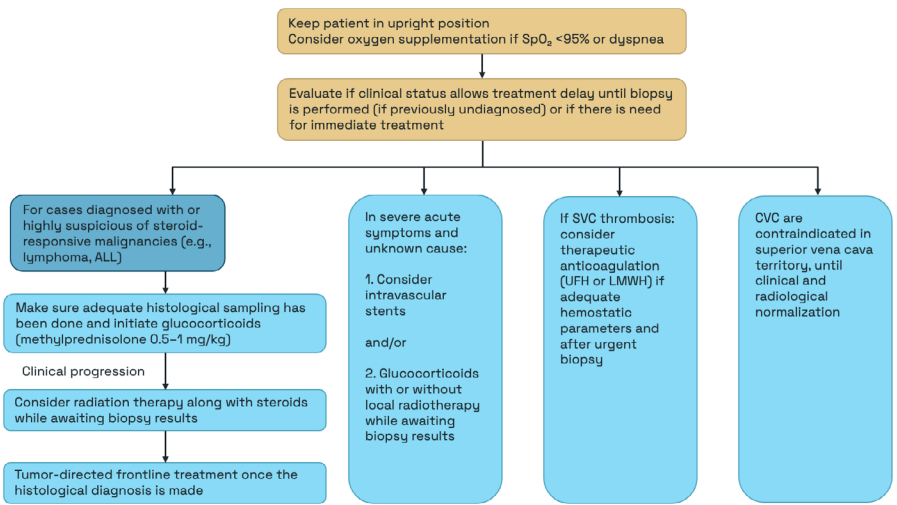


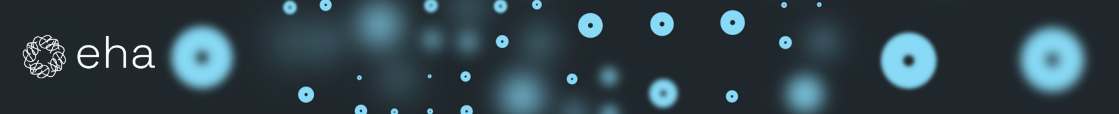
Figure 18.1: Clinical management of SVCS

18.4 Special circumstances

In cases caused by intravascular thrombosis associated with catheters or pacemakers, anticoagulation is the main treatment. Catheter removal should be considered.

References

- Zimmerman S, Davis M. Emerg Med Clin North Am. 2018;36:577–584
- Yu JB, et al. J Thorac Oncol. 2008;3:811–814.



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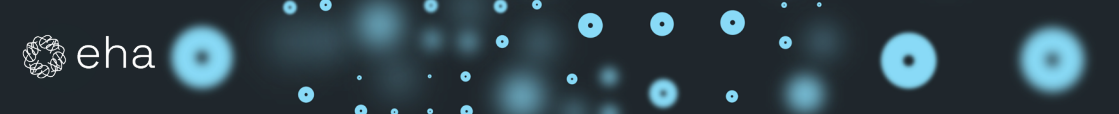
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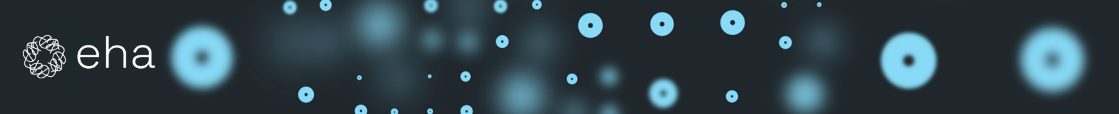
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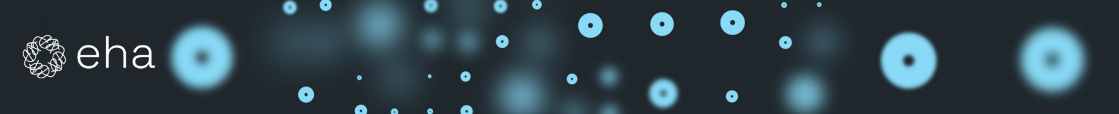
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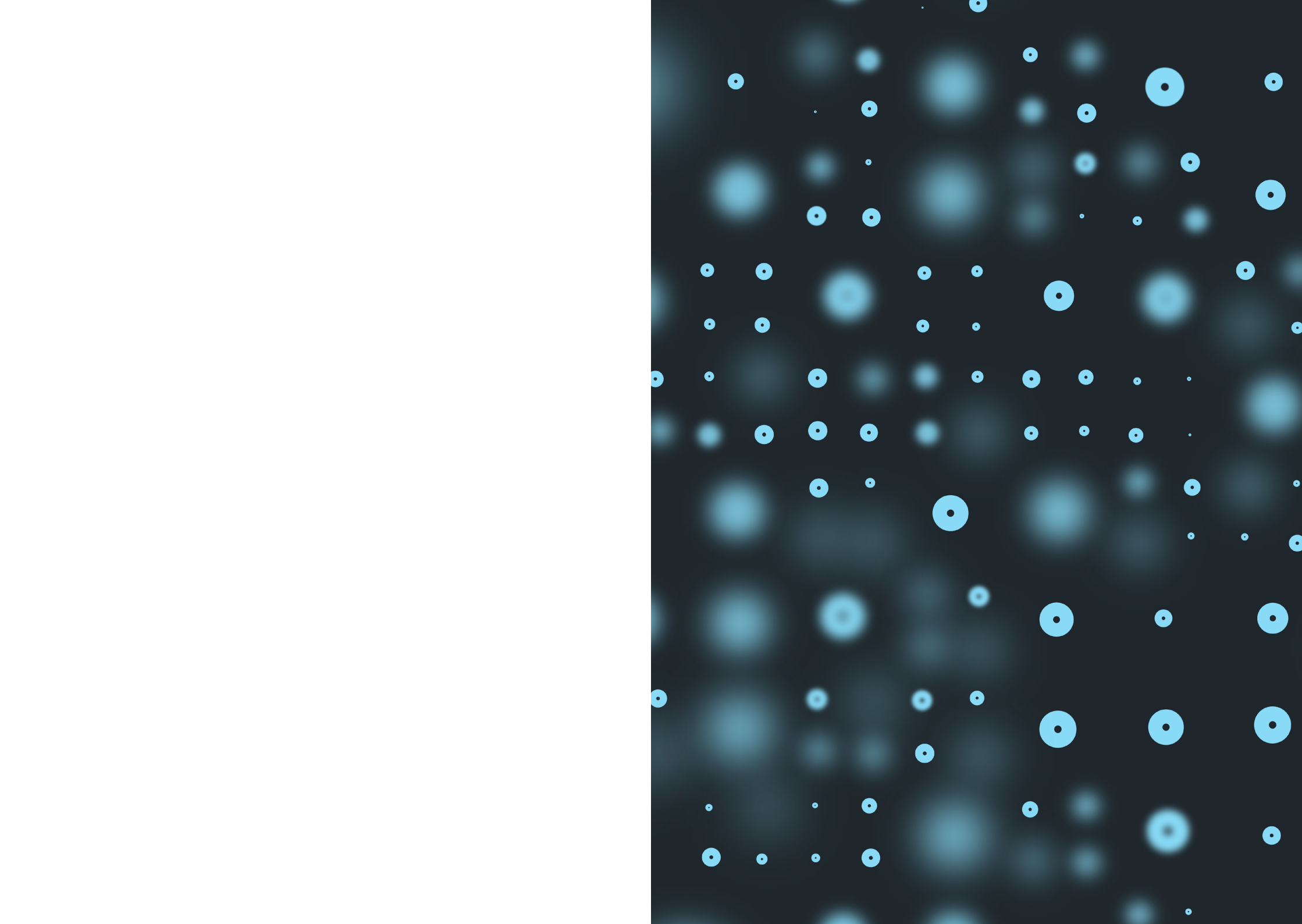
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