Leukopenia and Neutropenic Fever

Leukopenia and neutropenic fever are critical conditions in hospitalized patients, often signaling serious underlying diseases or complications. This pamphlet provides students with a detailed guide to evaluate, diagnose, and treat leukopenia and neutropenic fever, including emergencies, when to consult hematology/oncology, and clinical case scenarios.

Evaluation

• Definitions:

- **Leukopenia:** White blood cell (WBC) count <4,000/μL.
- **Neutropenia:** Absolute neutrophil count (ANC) <1,500/μL; severe if <500/μL, profound if <100/μL.
- **Neutropenic Fever:** Temperature ≥38.3°C (single reading) or ≥38°C sustained for 1 hour, with ANC <500/μL (or expected to fall below 500/μL within 48 hours).

• History:

- Symptoms:
  - Fever, chills, fatigue, sore throat, mouth sores, cough, diarrhea, skin infections, or recent chemotherapy.
- Risk Factors:
  - Chemotherapy, radiation, infections (HIV, HCV), medications (e.g., clozapine, methotrexate), alcohol use, malignancy, or autoimmune diseases (SLE).
- Systemic Symptoms:
  - Weight loss, night sweats (malignancy), bone pain (leukemia), or rash (drug reaction, infection).

• Physical Exam:

- General:
  - Fever, tachycardia, hypotension (sepsis).
- Infections:
  - Oral ulcers, perirectal tenderness, skin abscesses, pneumonia (crackles), catheter site erythema.

- Organomegaly:
  - Splenomegaly (hypersplenism, lymphoma), lymphadenopathy (malignancy, infections).
- Other:
  - Pallor (anemia), petechiae (thrombocytopenia), jaundice (liver involvement).

• Initial Labs:

- CBC with Differential:
  - WBC, ANC, check for anemia or thrombocytopenia (pancytopenia suggests marrow failure).
- Peripheral Smear:
  - Assess for blasts (leukemia), dysplastic cells (MDS), or infection-related changes (toxic granulation).
- Inflammatory Markers:
  - CRP, procalcitonin (sepsis).

Causes

• Decreased Production:

- Bone Marrow Suppression:
  - Chemotherapy: Cyclophosphamide, cisplatin (dose-dependent, nadir 7-14 days), pancytopenia.
  - Radiation: Pelvic/spinal radiation → Hypocellular marrow, often with pancytopenia.
  - Alcohol: Direct toxicity to marrow, often with macrocytosis and thrombocytopenia.
- Infections:
  - Viral: HIV (marrow suppression, CD4 depletion), HCV (cirrhosis, hypersplenism), EBV/CMV (marrow suppression), parvovirus B19 (pure red cell aplasia, neutropenia in sickle cell).
  - Bacterial: Sepsis (endotoxin-mediated suppression), TB (marrow infiltration, granulomas).
  - Fungal: Histoplasmosis, disseminated candidiasis (marrow involvement, immunocompromised).
- Marrow Infiltration:
  - Leukemia: AML/ALL (blasts replace marrow), pancytopenia, blasts on smear.

    - Lymphoma: Bone marrow involvement (e.g., DLBCL, Hodgkin's), lymphadenopathy, B symptoms.
- Metastatic Cancer: Breast, prostate, lung (marrow fibrosis), teardrop cells on smear.
- Nutritional Deficiencies: B12/Folate Deficiency:
- Megaloblastic anemia, pancytopenia, hypersegmented neutrophils.
- Copper Deficiency: Rare, post-gastric surgery, neurologic symptoms, neutropenia.
- Aplastic Anemia: Idiopathic, post-viral (e.g., parvovirus, hepatitis), drugs (chloramphenicol), hypocellular marrow, pancytopenia.
- Myelodysplastic Syndrome (MDS): Dysplastic cells, often progresses to AML, pancytopenia.

• Increased Destruction/Sequestration:

- Hypersplenism:
    - Cirrhosis: Portal hypertension, splenomegaly, often with thrombocytopenia.
- Myelofibrosis: Splenomegaly, teardrop cells, marrow fibrosis.
- Infections: Malaria, leishmaniasis → Splenic sequestration, parasitemia on smear.
- Autoimmune: Systemic Lupus Erythematosus (SLE):
    - Anti-neutrophil antibodies, often with anemia/thrombocytopenia.
- Felty's Syndrome:
    - Rheumatoid arthritis, splenomegaly, neutropenia.
- Drug-Induced:
    - Clozapine: Agranulocytosis (1% risk), onset 6-12 weeks, requires monitoring.
- Methotrexate: Marrow suppression, dose-dependent, often with macrocytosis.
- Sulfonamides: Immune-mediated destruction, rash, fever.

• Other Causes:

- Cyclic Neutropenia:
    - Genetic (ELANE mutation), 21-day cycles, recurrent infections.
- Hemophagocytic Lymphohistiocytosis (HLH):
    - Cytokine storm, fever, splenomegaly, ferritin >10,000 µg/L, hemophagocytosis on bone marrow.
- Vitamin C Deficiency:
    - Scurvy, poor nutrition, bleeding gums, mild leukopenia.

- Hypothermia:
  - Severe (<32°C) → Impaired marrow function, often in trauma.

Diagnostic Studies and Testing

• Step 1: Calculate ANC:

o ANC = WBC × [(Neutrophils % + Bands %) / 100]; e.g., WBC 2,000/µL, neutrophils 20%, bands 5% → ANC = 2,000 × (25/100) = 500/µL.

• Step 2: Peripheral Smear:

o **Blasts:** Leukemia (urgent).
o **Dysplastic Cells:** MDS.
o **Toxic Granulation/Döhle Bodies:** Sepsis.
o **Hypersegmented Neutrophils:** B12/folate deficiency.

• Step 3: Additional Labs:

- Infections:
  - **Blood Cultures:** At least 2 sets (aerobic/anaerobic), before antibiotics.
  - **HIV/HCV:** Viral load, CD4 count.
  - **EBV/CMV:** PCR (immunocompromised), IgM/IgG (acute infection).
  - **Fungal:** Beta-D-glucan, galactomannan (aspergillosis), cultures.
- Marrow Failure:
  - **Aplastic Anemia:** Bone marrow biopsy (hypocellular), pancytopenia.
  - **Leukemia:** Blasts on smear, bone marrow biopsy (hypercellular, >20% blasts).
  - **B12/Folate:** Low B12/folate, high MMA/homocysteine.
- Autoimmune:
  - **ANA, Anti-dsDNA:** SLE (if positive, check anti-neutrophil antibodies).
  - **Rheumatoid Factor:** Felty's syndrome (RA + neutropenia + splenomegaly).
- HLH:
  - Ferritin (>10,000 µg/L), triglycerides, fibrinogen, soluble IL-2 receptor (CD25), bone marrow (hemophagocytosis).
- Other:
  - **LFTs:** Cirrhosis (low albumin, high bilirubin), hypersplenism.
  - **SPEP/UPEP:** Multiple myeloma (monoclonal spike).
  - **Clozapine-Induced:** Weekly CBC (first 6 months), stop if ANC <1,000/µL.

• Step 4: Imaging/Tests:

- **CT Chest/Abdomen/Pelvis:** Occult infection (pneumonia, abscess), malignancy (lymphoma, metastatic cancer).
- **Bone Marrow Biopsy:** Leukemia, lymphoma, aplastic anemia, MDS, HLH.
- **Ultrasound:** Splenomegaly (cirrhosis, myelofibrosis).

Treatment

• General Principles:

- Treat underlying cause (e.g., stop offending drug, treat infection).
- **Neutropenic Fever:** Start empiric antibiotics within 1 hour of presentation.

• Neutropenic Fever:

- Empiric Antibiotics:
  - High-Risk (ANC <100/µL, prolonged neutropenia >7 days, hemodynamic instability):
    - Piperacillin-tazobactam 4.5 g IV q6h OR cefepime 2 g IV q8h.
    - Add vancomycin 15 mg/kg IV q12h if MRSA suspected (e.g., catheter infection, skin findings).
  - Low-Risk (ANC 100-500/µL, brief neutropenia, no comorbidities):
    - Ciprofloxacin 500 mg PO BID + amoxicillin-clavulanate 875/125 mg PO BID (outpatient).
- Antifungals:
  - **Add if fever persists >4-7 days:** Voriconazole 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h.
- Antivirals:
  - Acyclovir 5 mg/kg IV q8h (if HSV suspected, e.g., oral ulcers).
- Growth Factors:
  - G-CSF (filgrastim) 5 mcg/kg/day SC (chemotherapy-induced, ANC <500/µL), until ANC >1,000/µL.

• Specific Treatments:

- Aplastic Anemia:
  - Immunosuppression: ATG (40 mg/kg/day IV x 4 days) + cyclosporine (5 mg/kg/day PO).
  - Bone marrow transplant: (if <40 years, HLA-matched donor).

- Leukemia (AML):
  - Induction chemotherapy: Cytarabine 100 mg/m² IV daily x 7 days + daunorubicin 60 mg/m² IV x 3 days.
  - Supportive: G-CSF, antibiotics (febrile neutropenia).
- Infections:
  - HIV: Antiretroviral therapy (e.g., tenofovir + emtricitabine + dolutegravir).
- Sepsis: Broad-spectrum antibiotics (e.g., meropenem 1 g IV q8h if resistant organisms), fluids (NS 30 mL/kg IV).
- Fungal: Amphotericin B 0.5-1 mg/kg IV daily (disseminated histoplasmosis).
- Drug-Induced:
  - Clozapine: Stop immediately if ANC <1,000/µL; G-CSF (filgrastim) if severe.
  - Methotrexate: Folinic acid (leucovorin) rescue 15 mg IV q6h (if toxicity).
- B12/Folate Deficiency:
  - Cyanocobalamin: 1,000 mcg IM daily x 7 days, then weekly x 4 weeks, then monthly.
  - Folic acid: 1-5 mg PO daily.
- Autoimmune:
  - SLE: Prednisone 1 mg/kg/day PO; cyclophosphamide 1-2 mg/kg/day IV (severe cases).
  - Felty's Syndrome: G-CSF (filgrastim), rituximab 375 mg/m² IV weekly x 4.
- HLH: Etoposide 150 mg/m² IV twice weekly + dexamethasone 10 mg/m²/day PO/IV x 8 weeks (HLH-94 protocol).
- Cirrhosis/Hypersplenism:Treat portal hypertension:
  - Propranolol 20 mg PO BID (titrate to HR 55-60 bpm).
  - Splenectomy: (if severe, refractory).

• Key Tips:

- Avoid invasive procedures (e.g., rectal exam, IM injections) in neutropenic patients.
- **Monitor for infection:** Daily CBC, cultures if fever spikes, imaging if fever persists.

Emergencies

- **Neutropenic Fever with Sepsis:**
  - Signs:
    - Hypotension (SBP <90 mmHg), tachycardia (HR >100 bpm), lactate >2 mmol/L.
  - Action:
    - Broad-spectrum antibiotics (e.g., meropenem 1 g IV q8h), fluids (NS 30 mL/kg IV), ICU consult.
- **Agranulocytosis (ANC <100/µL):**
  - Causes:
    - Clozapine, chemotherapy, severe infections.
  - Action:
    - Stop offending drug, G-CSF (filgrastim), broad-spectrum antibiotics, heme/onc consult.
- **Leukemia with Blasts:**
  - Signs:
    - Blasts >20% on smear, pancytopenia, bone pain, B symptoms.
  - Action:
    - Urgent heme/onc consult, bone marrow biopsy, chemotherapy (e.g., cytarabine + daunorubicin).
- **HLH:**
  - Signs:
    - Ferritin >10,000 µg/L, fever, splenomegaly, cytopenias.
  - Action:
    - Urgent heme/onc consult, start etoposide + dexamethasone, ICU if multi- organ failure.

When to Consult Hematology/Oncology

- Blasts on peripheral smear (>5%) or bone marrow involvement (leukemia, lymphoma).
- Suspected HLH (ferritin >10,000 µg/L, hemophagocytosis).
- Aplastic anemia (pancytopenia, hypocellular marrow).
- MDS (dysplastic cells, cytopenias).

- Neutropenic fever not responding to antibiotics after 4-7 days (suspect fungal infection).
- Chemotherapy-induced neutropenia requiring G-CSF or complex management.

Diagnostic Approach Table

Category	Key Labs	Diagnosis	Notes
Decreased Production	Bone marrow biopsy, B12/ folate	Aplastic anemia: Hypocellular marrow Leukemia: Blasts >20%	Check for HIV/HCV; blasts require urgent consult.
Increased Destruction	ANA, RF, ferritin	SLE: Positive ANA HLH: Ferritin >10,000 µg/L	HLH: Check for hemophagocytosis in HLH.
Neutropenic Fever	Blood cultures, CT, fungal markers	Sepsis: Positive Fungal: Positive galactomannan	Start antibiotics within 1 hour; add antifungals if fever persists.

Treatment Guidelines Table

Condition	Treatment	Agent/Dose	Notes
Neutropenic Fever	Empiric antibiotics	Piperacillin-tazobactam 4.5 g IV q6h	Add vancomycin if MRSA suspected; antifungals if fever persists.
Aplastic Anemia	Immunosuppression, transplant	ATG 40 mg/kg/day IV x 4 days	Bone marrow transplant if <40 years.
HLH	Etoposide, dexamethasone	Etoposide 150 mg/ m^2 IV twice weekly	ICU if multi-organ failure; urgent heme/onc consult.
Leukemia (AML)	Induction chemotherapy	Cytarabine 100 mg/ m^2 IV daily x 7 days	Supportive care with G-CSF, antibiotics.

Complications

- **Acute:**
  - Sepsis:
    - Multi-organ failure, mortality (20-40% in neutropenic fever with sepsis).
  - Invasive Fungal Infections:
    - Aspergillosis, candidiasis (10-20% mortality in prolonged neutropenia).
- **Chronic:**
  - Progression:
    - MDS → AML (10-30% risk), leukemia-related infections.

- Bone Marrow Failure:
    - Recurrent infections, bleeding (aplastic anemia).

- **Underlying Disease:**

- Chemotherapy:
    - Mucositis, prolonged neutropenia.
- HIV:
    - Opportunistic infections (e.g., PCP, MAC).

Key Pearls

- **Calculate ANC:** ANC <500/µL = high infection risk; <100/µL = profound risk.
- **Neutropenic Fever:** Start antibiotics within 1 hour; piperacillin-tazobactam or cefepime for high-risk patients.
- **Peripheral Smear:** Blasts (leukemia), dysplastic cells (MDS), toxic granulation (sepsis)— urgent findings require heme/onc consult.
- **Emergencies:** Sepsis, agranulocytosis, leukemia with blasts, HLH—require immediate action.
- **G-CSF:** Use in chemotherapy-induced neutropenia; avoid in leukemia (may stimulate blasts).
- **Monitor for infection:** Daily CBC, cultures if fever spikes, CT if fever persists >4 days.

References

- **UpToDate:** “Approach to Leukopenia in Adults” (2025).
- **IDSA:** “Clinical Practice Guideline for Neutropenic Fever” (2024).
- **NEJM:** “Hemophagocytic Lymphohistiocytosis: Diagnosis and Treatment” (2023).
- **Blood:** “Myelodysplastic Syndromes: Diagnosis and Management” (2024).

Case Scenarios

Case 1: A 32-Year-Old Male with Fever Post-Chemotherapy

- Presentation: A 32-year-old male with AML, 10 days post-induction chemotherapy (cytarabine + daunorubicin), presents with fever (38.5°C), chills, and fatigue. Exam shows oral mucositis, no focal findings. BP 110/70 mmHg, HR 100 bpm.

- Labs: WBC 800/μL, ANC 100/μL, Hgb 9 g/dL, platelets 20,000/μL. Blood cultures pending.
- Diagnosis: Neutropenic Fever (high-risk) → ANC <500/μL, recent chemotherapy, prolonged neutropenia expected.
- Management: Start cefepime 2 g IV q8h immediately. Add vancomycin 15 mg/kg IV q12h (mucositis = MRSA risk). G-CSF (filgrastim) 5 mcg/kg/day SC. Blood cultures grow Pseudomonas aeruginosa—continue cefepime, monitor for clinical improvement. CT chest if fever persists >4 days (suspect fungal infection).

Case 2: A 55-Year-Old Female with Fatigue and Pancytopenia

- Presentation: A 55-year-old female presents with fatigue, bruising, and recurrent infections for 3 months. No recent medications or infections. Exam shows pallor, petechiae, no splenomegaly.
- Labs: WBC 2,000/μL, ANC 400/μL, Hgb 8 g/dL, platelets 30,000/μL. Peripheral smear: No blasts. Bone marrow biopsy: Hypocellular marrow.
- Diagnosis: Aplastic Anemia → Pancytopenia, hypocellular marrow, no underlying cause identified.
- Management: Urgent heme/onc consult. Start ATG 40 mg/kg/day IV x 4 days + cyclosporine 5 mg/kg/day PO. Transfuse PRBCs (Hgb <7 g/dL) and platelets (<10,000/μL). Monitor for infections (prophylactic levofloxacin 500 mg PO daily). Consider bone marrow transplant if eligible.

Case 3: A 40-Year-Old Male with Fever and Rash

- Presentation: A 40-year-old male presents with fever (39°C), rash, and fatigue for 5 days. History of rheumatoid arthritis on methotrexate. Exam shows splenomegaly, generalized rash, no lymphadenopathy.
- Labs: WBC 1,500/μL, ANC 300/μL, Hgb 10 g/dL, platelets 90,000/μL. Ferritin 15,000 μg/L, triglycerides 400 mg/dL, fibrinogen 120 mg/dL. Bone marrow: Hemophagocytosis.
- Diagnosis: Hemophagocytic Lymphohistiocytosis (HLH) → Ferritin >10,000 μg/L, cytopenias, hemophagocytosis, likely triggered by methotrexate or infection.
- Management: Urgent heme/onc consult. Start etoposide 150 mg/m^2 IV twice weekly + dexamethasone 10 mg/m^2/day IV. Stop methotrexate. Broad-spectrum antibiotics (cefepime 2 g IV q8h) for fever. Monitor in ICU for multi-organ failure. Test for infections (EBV, CMV PCR).