

Neutropenia and Agranulocytosis

Mechanisms, marrow morphology, and infectious consequences

An integrated clinicopathologic teaching lecture

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Learning objectives

- Differentiate leukopenia, neutropenia, and agranulocytosis.
- Classify neutropenia by failure of marrow production versus peripheral loss.
- Relate bone-marrow patterns to the underlying mechanisms.
- Recognize infection patterns and the urgency of severe neutropenia.

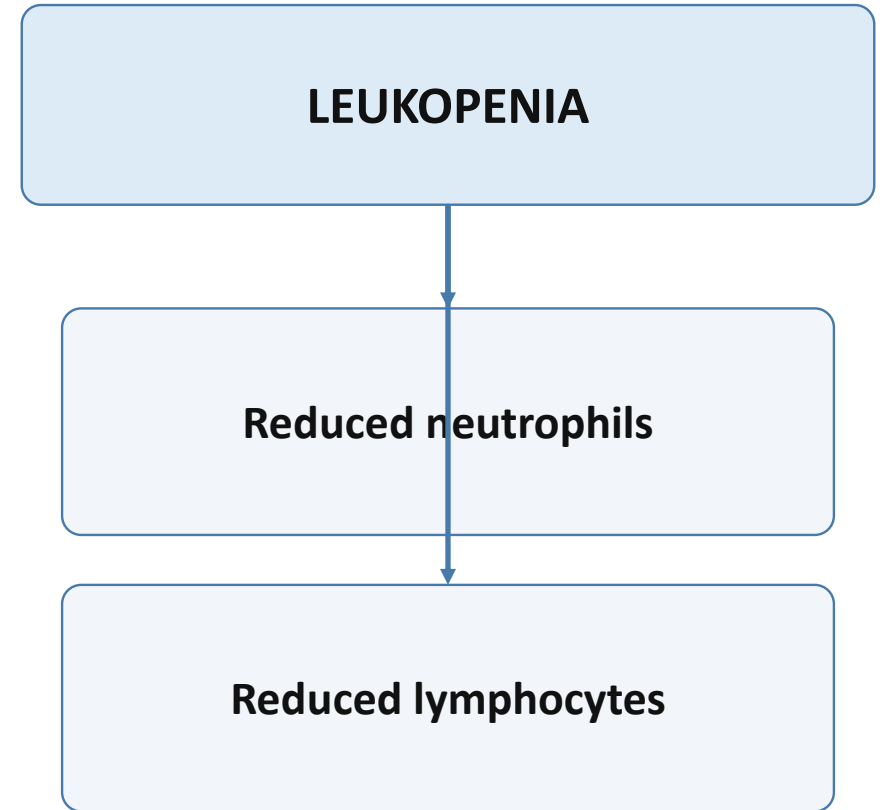
White-cell disorders: The immediate context

Proliferative disorders	Leukopenic disorders
Expansion of circulating or tissue leukocytes	Deficiency of circulating white cells
May be reactive or neoplastic	Most commonly reflects reduced neutrophils
Reactive increase often accompanies infection/inflammation	Reduced granulocytes impair the host response to infection

The lecture focuses on the leukopenic arm of white-cell pathology.

Leukopenia is not synonymous with neutropenia

- Leukopenia refers to a reduced total circulating white-cell count.
- Neutropenia designates a reduction in circulating neutrophils.
- Neutrophil loss is the most common explanation for leukopenia.
- Lymphopenia is a separate, less common explanation for leukopenia.

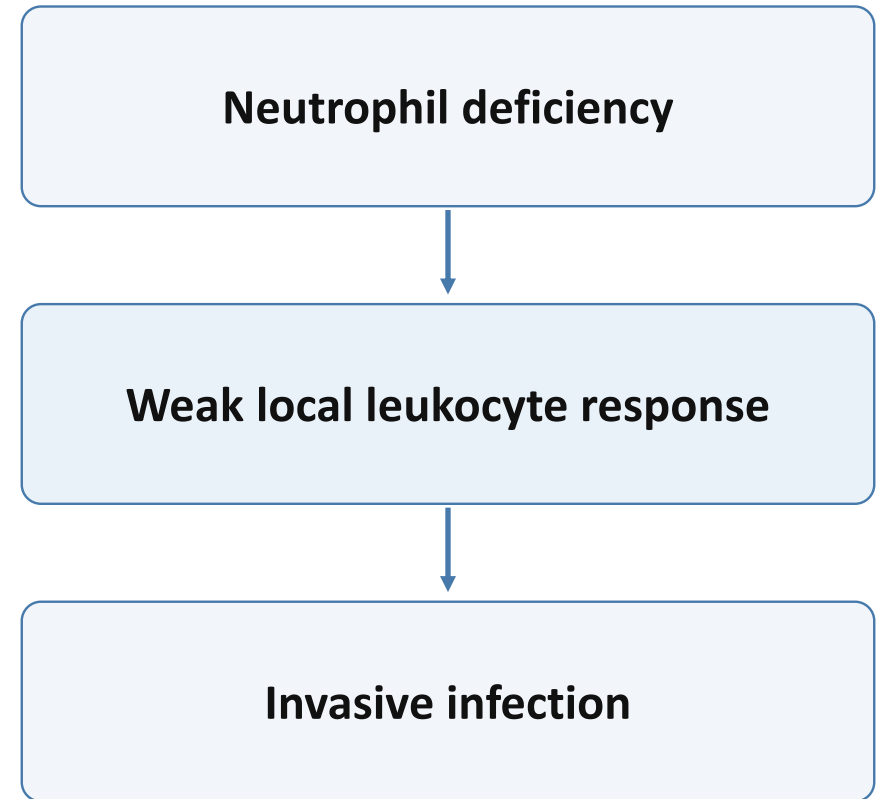


Lymphopenia provides a useful contrast

- Lymphopenia with immunodeficiency, advanced HIV infection, and several acquired disorders.
- Glucocorticoids, cytotoxic drugs, autoimmune disorders, and malnutrition can be associated with lymphopenia.
- Acute viral infection can redistribute T cells into lymph nodes and vascular compartments.
- The pathogenesis of neutropenia instead centers on granulopoiesis and peripheral neutrophil loss.

Neutrophils are essential antimicrobial effectors

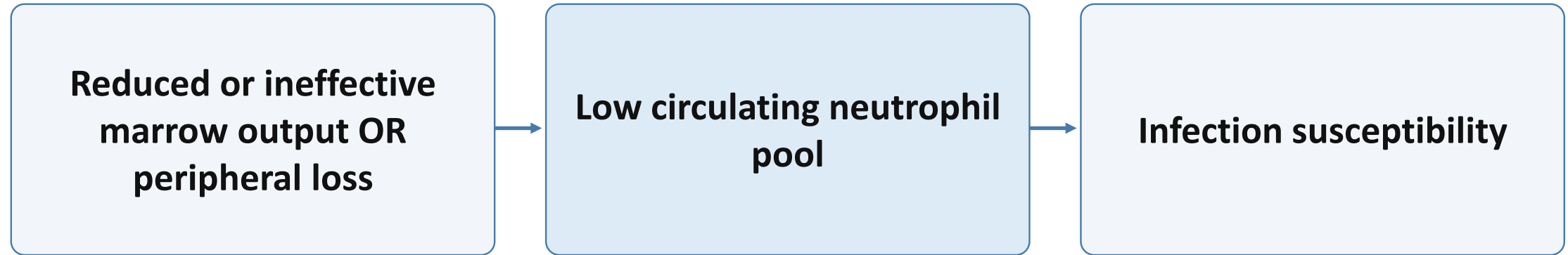
- A severe reduction in circulating neutrophils compromises defense against bacteria and fungi.
- Organisms can proliferate extensively when leukocyte recruitment is inadequate.
- The lesion may contain abundant microorganisms but little inflammatory-cell response.



Agranulocytosis represents profound neutrophil depletion

- Agranulocytosis denotes an extreme reduction in blood neutrophils.
- The resulting susceptibility to serious bacterial and fungal infections is central to its clinical importance.
- It is a severe neutropenic state, not a separate leukocyte lineage disorder.
- The term describes severity; The cause still requires investigation.

Two major pathogenetic pathways



Both inadequate granulopoiesis and peripheral destruction or sequestration can lead to the same severe clinical consequence.

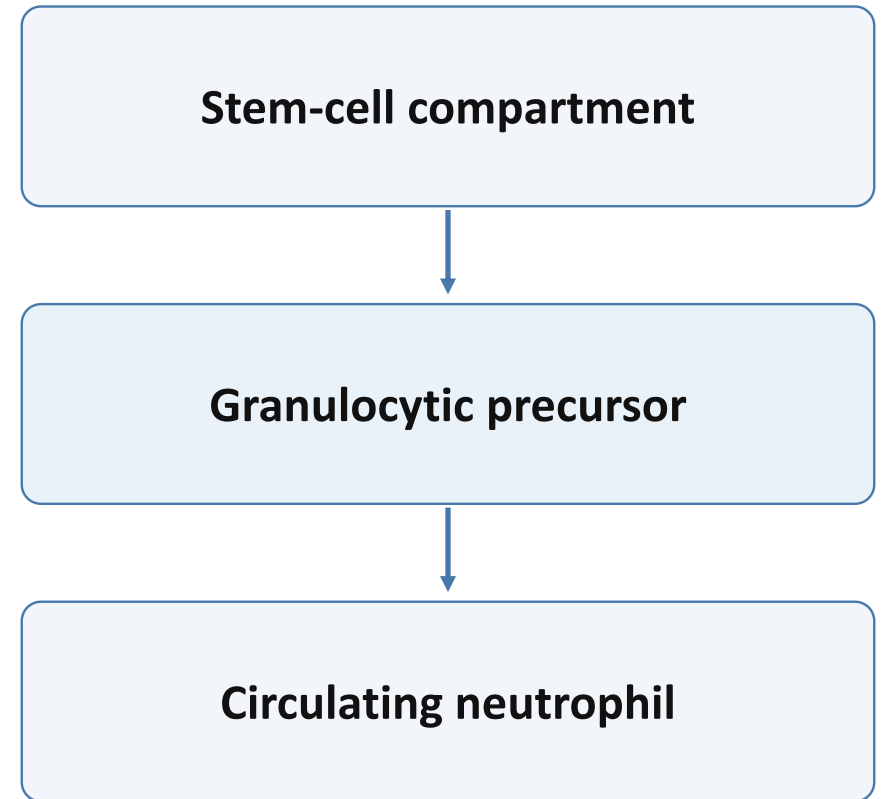
Production failure versus peripheral loss

Defective marrow output	Accelerated peripheral loss
Stem-cell or precursor suppression	Immune destruction of mature neutrophils
Ineffective granulopoiesis	Splenic sequestration/destruction
Congenital differentiation defects	Increased utilization during overwhelming infection
Marrow may be hypocellular OR hypercellular	Marrow often compensates by increasing granulopoiesis

The marrow response depends on which biologic step is disrupted.

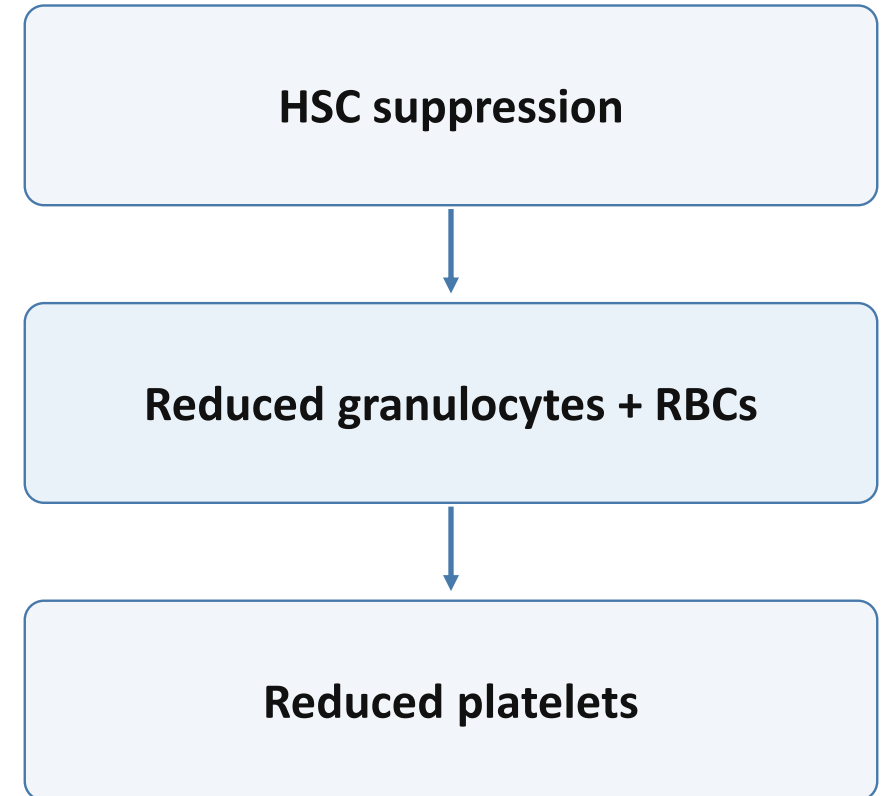
Normal granulopoiesis is a multistep process

- Hematopoietic stem cells generate committed granulocytic progenitors.
- Granulocytic precursors differentiate within marrow before mature neutrophils are released.
- Interruption can occur at the stem-cell, precursor, or maturation stage.
- The stage of interruption helps explain the associated cytopenias.



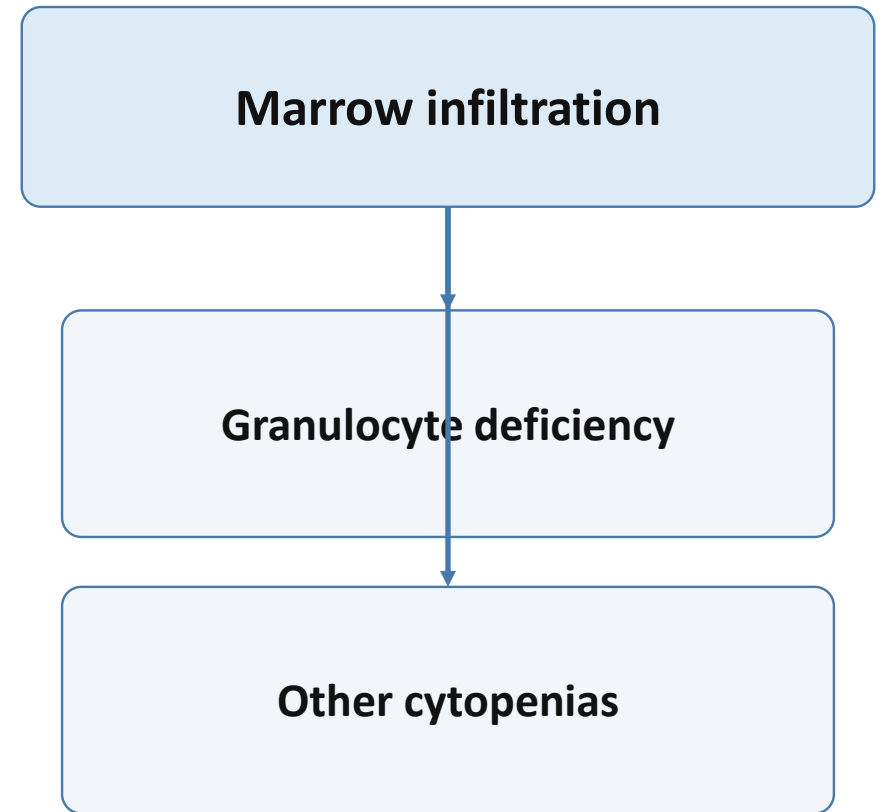
Stem-cell suppression reduces several blood lineages

- Aplastic anemia exemplifies suppression of hematopoietic stem cells.
- Neutropenia is accompanied by anemia and thrombocytopenia when stem-cell output is broadly impaired.
- The combined cytopenia pattern distinguishes generalized failure from an isolated neutrophil disorder.



Marrow infiltration also compromises hematopoiesis

- Tumors and granulomatous disease can occupy or disrupt the marrow compartment.
- Impaired hematopoietic output may affect granulocytes as well as red cells and platelets.
- A low neutrophil count with other cytopenias should raise suspicion of a shared marrow lesion.



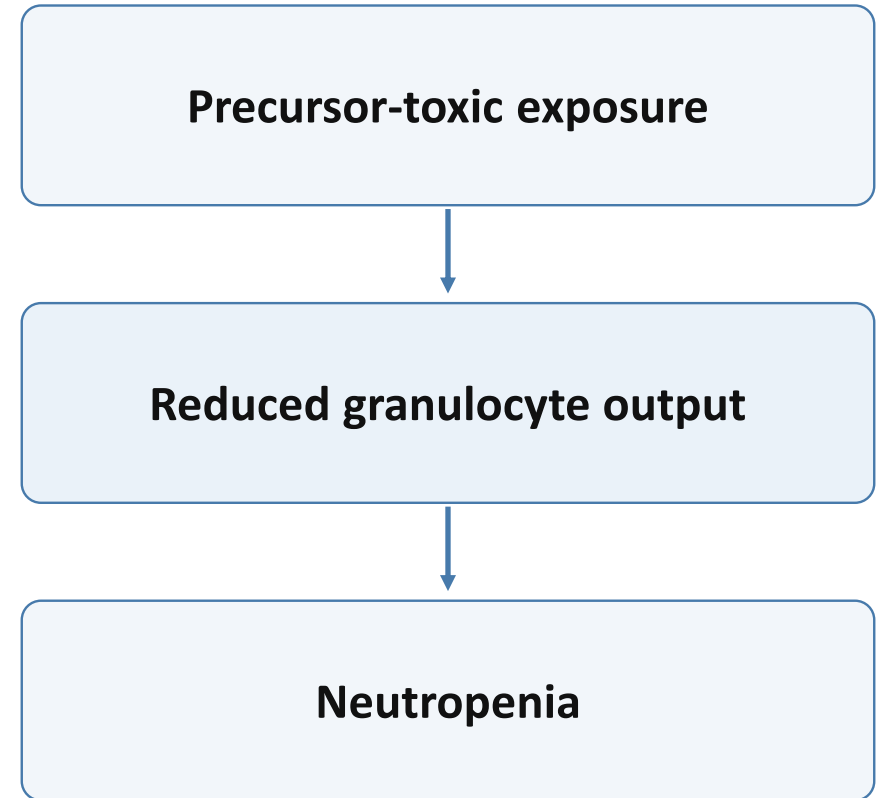
The cell-lineage pattern is a diagnostic clue

Blood-count pattern	Mechanistic implication
Neutropenia with anemia and thrombocytopenia	Consider broad marrow suppression or infiltrative disease
Predominantly neutropenia	Consider selective precursor toxicity, immune loss, or other granulocyte-specific pathways
Neutropenia with thrombocytopenia and splenomegaly	Consider splenic sequestration among the causes

These patterns guide reasoning but are not standalone diagnoses.

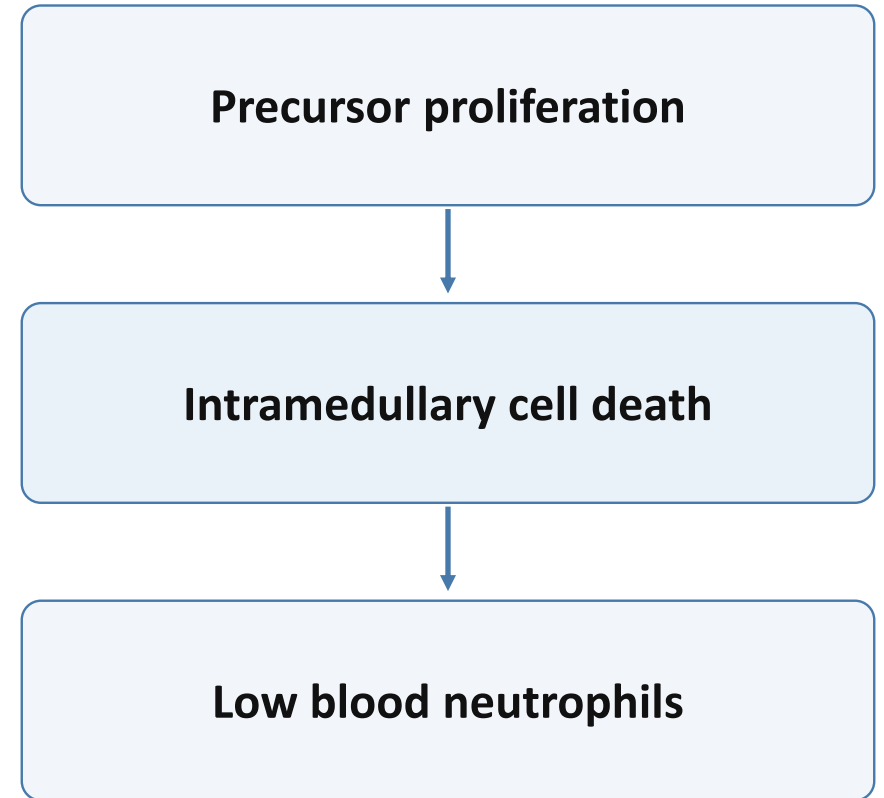
Committed granulocytic precursors can be targeted

- Some drugs preferentially suppress granulocyte precursors in marrow.
- Reduced maturation lowers neutrophil supply into the circulation.
- The pattern differs from generalized hematopoietic suppression, which affects multiple cell lines.
- A drug history becomes mechanistically relevant even when other counts are less affected.



Ineffective granulopoiesis: Production without output

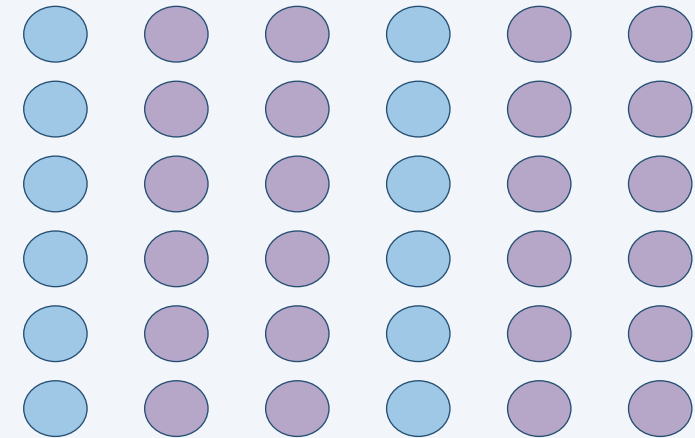
- Granulocytic precursors may be generated yet fail to survive and mature normally.
- Defective precursors die within the marrow compartment.
- The marrow can be hypercellular despite diminished circulating neutrophils.
- Cellularity alone therefore does not establish effective neutrophil production.



Megaloblastic anemia exemplifies ineffective output

- Megaloblastic anemia is a disease state associated with ineffective hematopoiesis.
- Defective hematopoietic precursors die in the marrow.
- Neutropenia can coexist with a cellular marrow rather than marrow aplasia.
- Interpret the neutrophil count together with the broader hematologic pattern.

Bone marrow • schematic



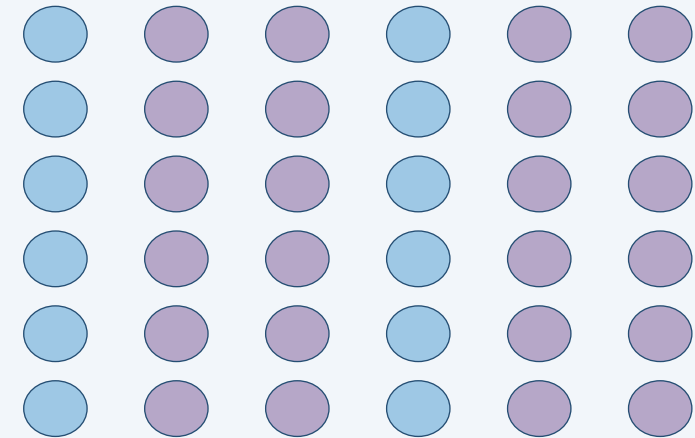
**Cellular marrow ≠ effective
granulopoiesis**

Cell-symbol diagram; Not histology

Myelodysplastic neoplasms also impair output

- Myelodysplastic neoplasms can produce neutropenia through ineffective granulopoiesis.
- The marrow may be hypercellular because precursor production persists.
- Ineffective maturation reduces the number of functional mature cells reaching blood.
- The key distinction is ineffective production, not accelerated peripheral removal.

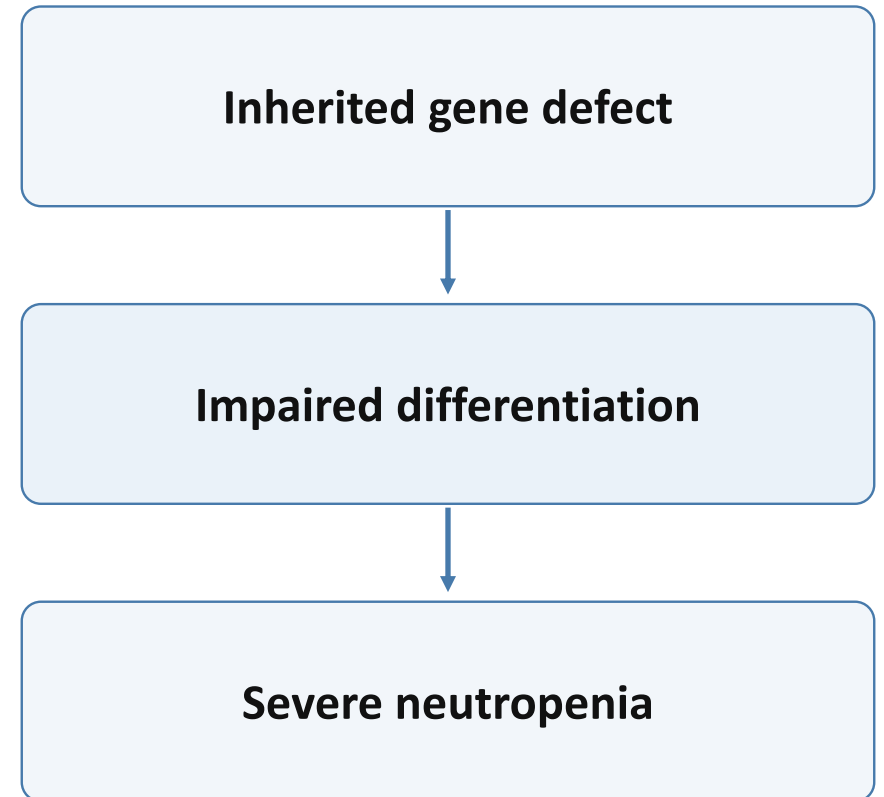
Bone marrow • schematic



Ineffective marrow production

Congenital neutropenia involves differentiation

- Rare inherited defects impair granulocytic differentiation.
- Severe congenital neutropenia (Kostmann syndrome) is one example.
- The essential defect acts during maturation of granulocytic cells.
- The clinical phenotype is reduced availability of mature circulating neutrophils.



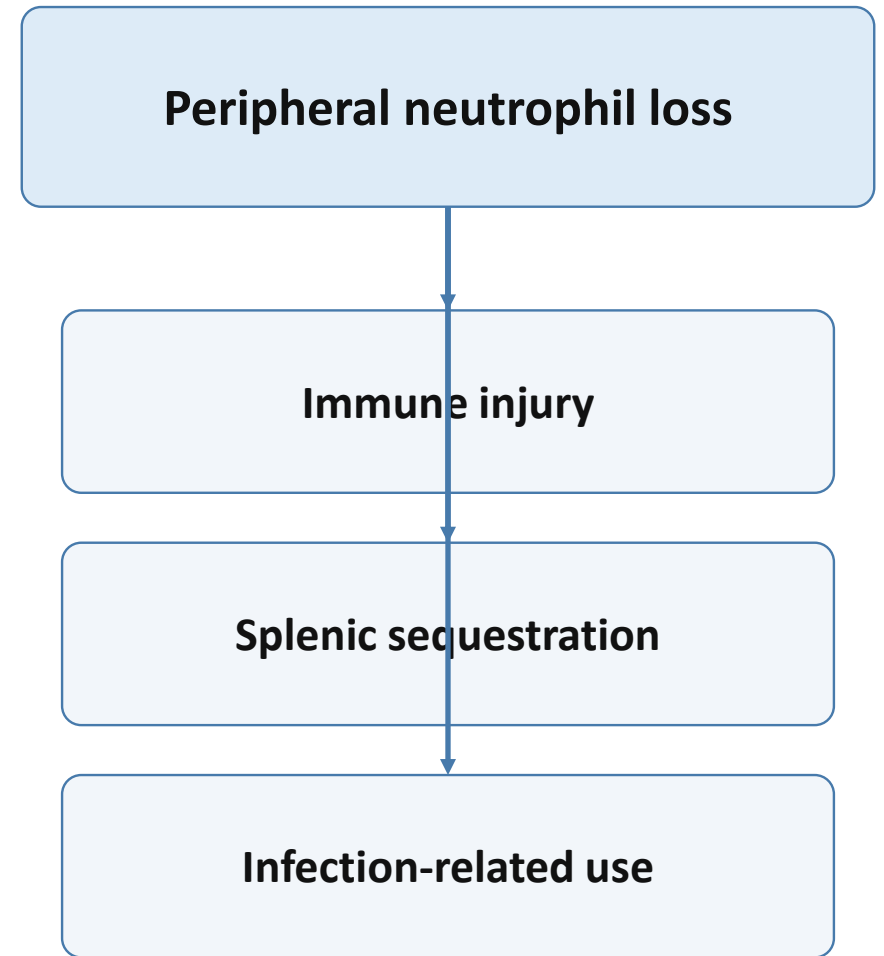
Production-side mechanisms are not equivalent

Mechanism	Example	Expected interpretation
Stem-cell suppression	Aplastic anemia	Broad hematopoietic deficit
Marrow replacement	Tumor / granulomatous disease	Multiple lineages may fall
Ineffective hematopoiesis	Megaloblastic anemia / MDS	Cellular marrow with poor effective output
Differentiation defect	Severe congenital neutropenia	Impaired granulocytic maturation

MDS = myelodysplastic neoplasm.

Peripheral neutrophil depletion has three routes

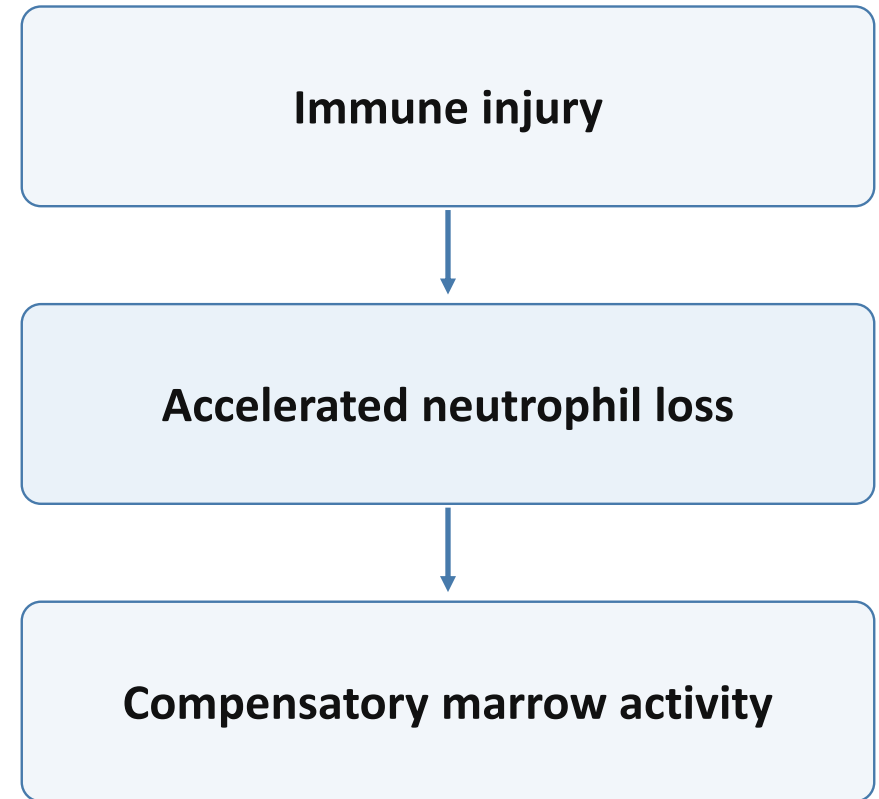
- Immune-mediated injury can destroy mature neutrophils.
- An enlarged spleen can increase sequestration and macrophage-mediated removal.
- Overwhelming infections can increase peripheral neutrophil utilization.
- In each route, peripheral demand or loss may outpace effective replacement.



Schematic

Immune-mediated neutrophil destruction

- Antineutrophil immune responses can increase peripheral neutrophil loss.
- The process may be idiopathic, associated with an autoimmune disorder, or drug-related.
- Marrow precursors may respond to peripheral loss by increasing granulopoiesis.
- The peripheral count and the marrow cellularity can therefore diverge.

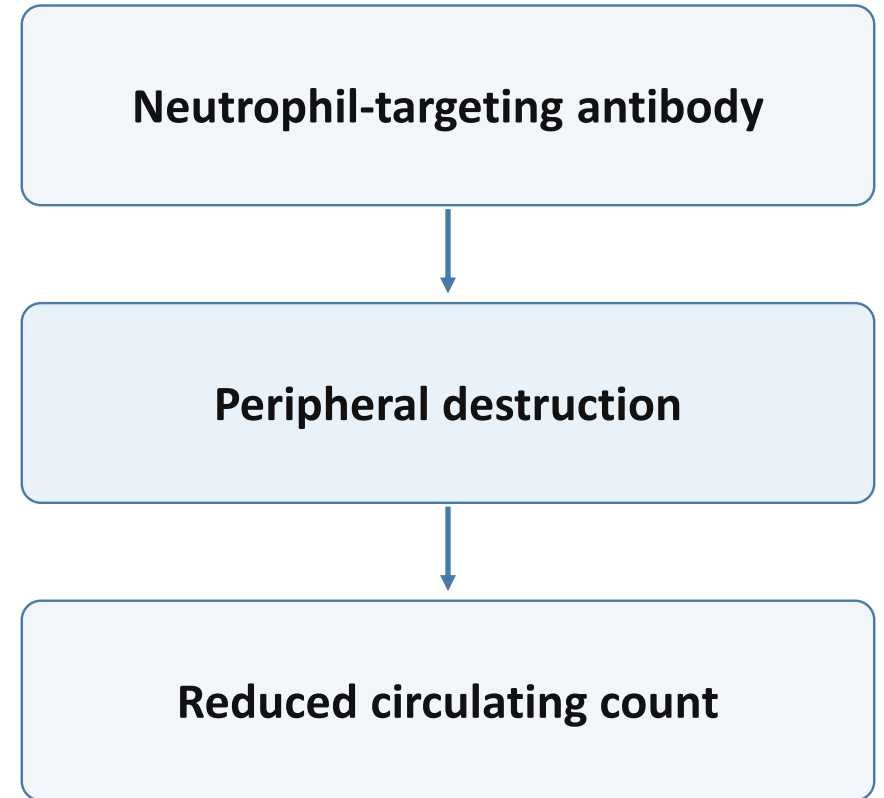


Autoimmune disease can cause neutropenia

- Systemic lupus erythematosus is an example of an immune disorder associated with neutrophil injury.
- The pathogenic category is peripheral immune destruction rather than intrinsic precursor maturation failure.
- Association with systemic autoimmunity helps place neutropenia in its clinical context.

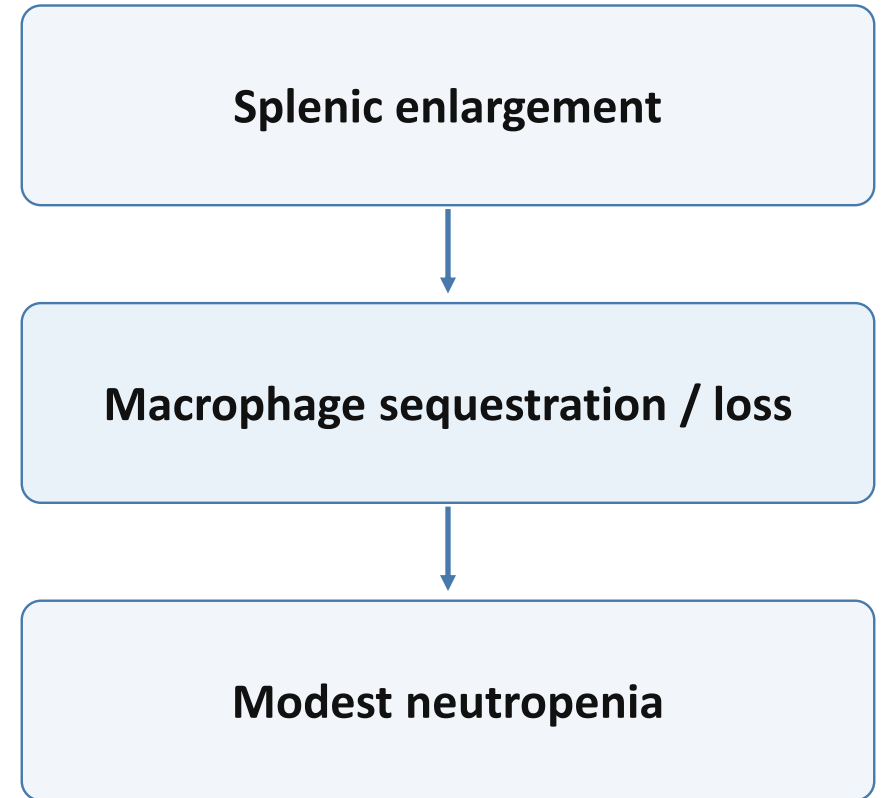
Acquired idiopathic neutropenia may be antibody mediated

- Some patients have antibodies directed against neutrophil-specific antigens.
- These autoantibodies accelerate destruction of circulating neutrophils.
- The presence of an immune mechanism does not imply malignant marrow replacement.
- An appropriate compensatory marrow response may be retained.



Splenomegaly increases neutrophil sequestration

- An enlarged spleen contains increased numbers and activity of macrophages.
- Sequestration and destruction of neutrophils can cause modest neutropenia.
- Thrombocytopenia is often associated; Anemia may also occur.
- The concurrence of splenomegaly and cytopenias supports a sequestration mechanism.



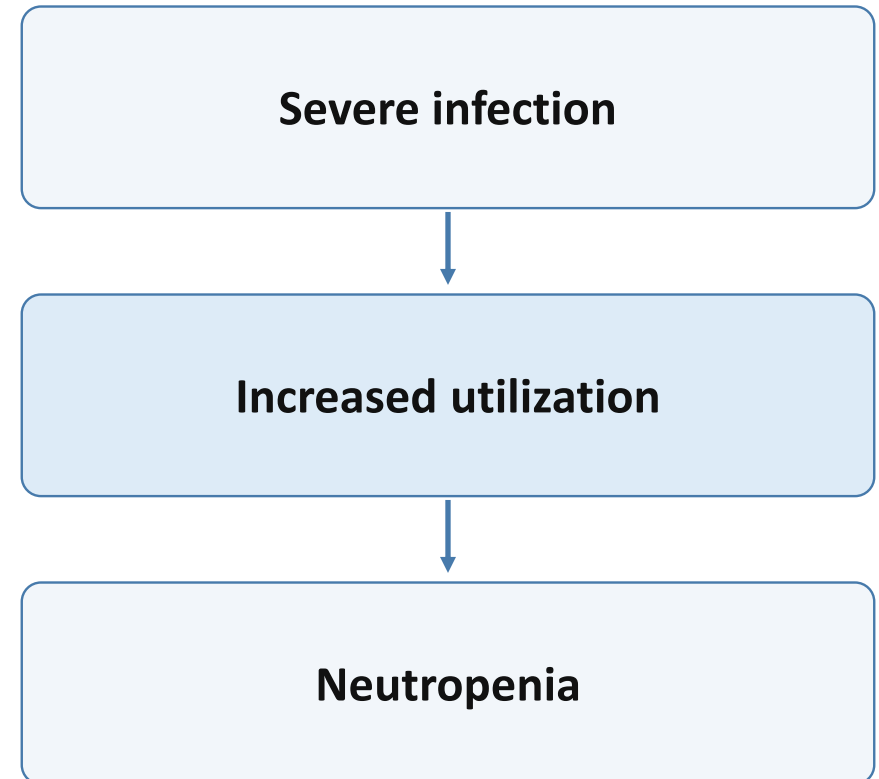
Splenic sequestration: Pattern recognition

Finding	Mechanistic interpretation
Enlarged spleen	Increased splenic cell pooling and macrophage activity
Modest neutropenia	Enhanced removal of circulating neutrophils
Thrombocytopenia, sometimes anemia	Multiple blood-cell lineages may be sequestered

The source describes this pattern, not a diagnostic numerical algorithm.

Overwhelming infection can consume neutrophils

- Severe bacterial, fungal, or rickettsial infection can increase peripheral utilization.
- Neutrophil consumption may become disproportionate to marrow replacement.
- Thus infection may be both a consequence and a cause of neutropenia.
- The direction of causation must be interpreted in clinical context.



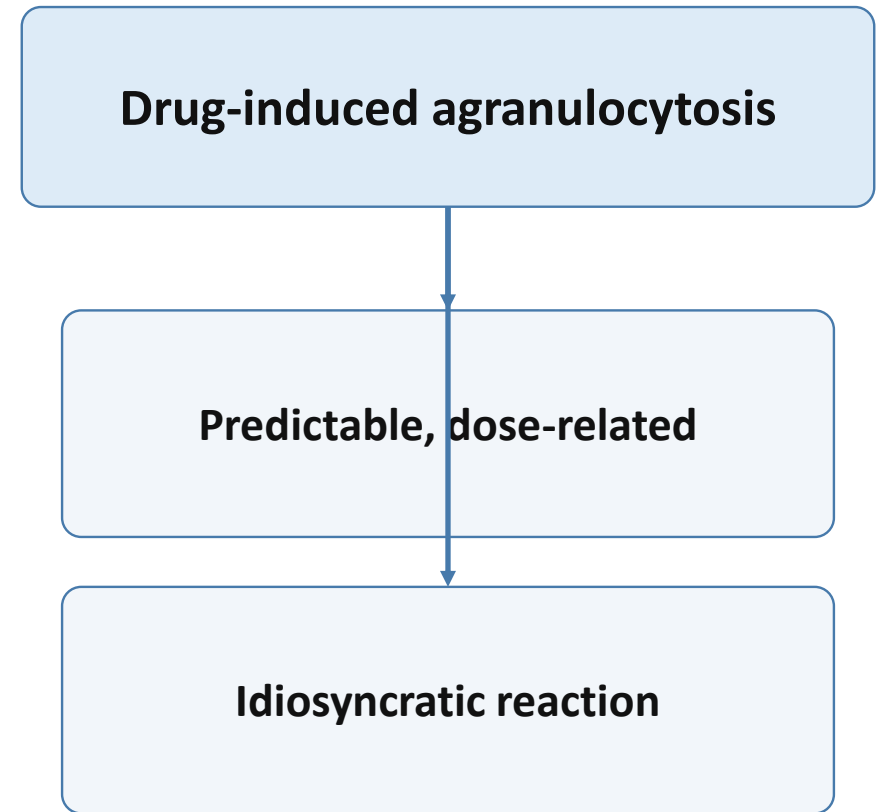
Conceptual sequence

Peripheral mechanisms compared

Immune	Splenic	Infection-associated
Antibody/immune injury	Macrophage pooling and destruction	Accelerated utilization
May be idiopathic, SLE-related, or drug-related	Typically accompanied by splenomegaly	Overwhelming bacterial, fungal, or rickettsial disease
Marrow compensation possible	Often modest neutropenia	Neutropenia can amplify subsequent infection

Drug toxicity is central to agranulocytosis

- Drug toxicity as the most common cause of agranulocytosis.
- Drugs can suppress marrow cell production or promote immune neutrophil destruction.
- Distinguishing predictable marrow toxicity from idiosyncratic reactions clarifies the mechanism.
- The medication exposure history is therefore essential to causal interpretation.



Cytotoxic drugs can cause predictable suppression

- Alkylating agents and antimetabolites are examples used in cancer treatment.
- Agranulocytosis may develop in a predictable, dose-related fashion.
- Their effects can suppress hematopoiesis beyond the granulocytic lineage.
- Red-cell and platelet production may also be compromised.

Myelosuppressive chemotherapy



Multilineage marrow suppression

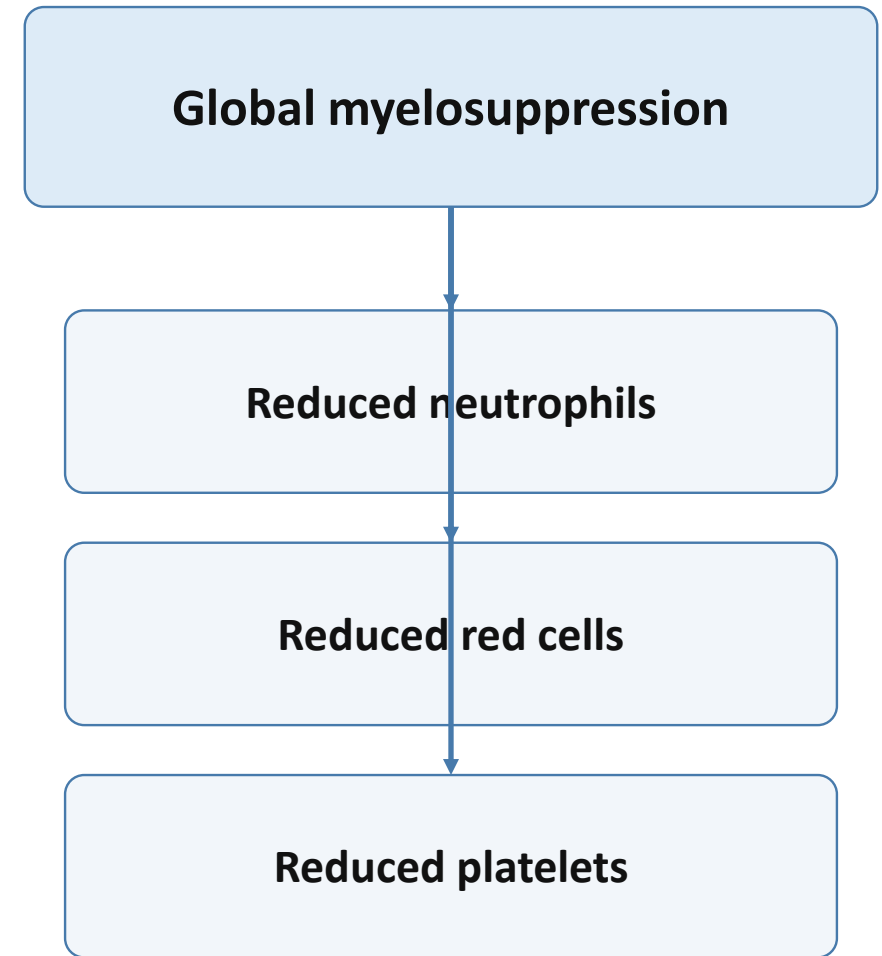


Neutropenia + other cytopenias

Schematic

Generalized drug toxicity affects three lineages

- Neutrophil production declines when granulocytic progenitors are injured.
- Concurrent effects on erythropoiesis and megakaryopoiesis explain anemia and thrombocytopenia.
- Multilineage involvement favors generalized hematopoietic suppression.
- The underlying mechanism should not be misclassified as isolated peripheral immune destruction.



Schematic

Idiosyncratic drug reactions are less predictable

- Agranulocytosis can occur as an idiosyncratic response to diverse medications.
- Certain antibiotics, anticonvulsants, anti-inflammatory agents, antipsychotics, and diuretics.
- A drug class does not determine a unique mechanism for every patient.
- The marrow-targeting and antibody-mediated pathways should be distinguished.

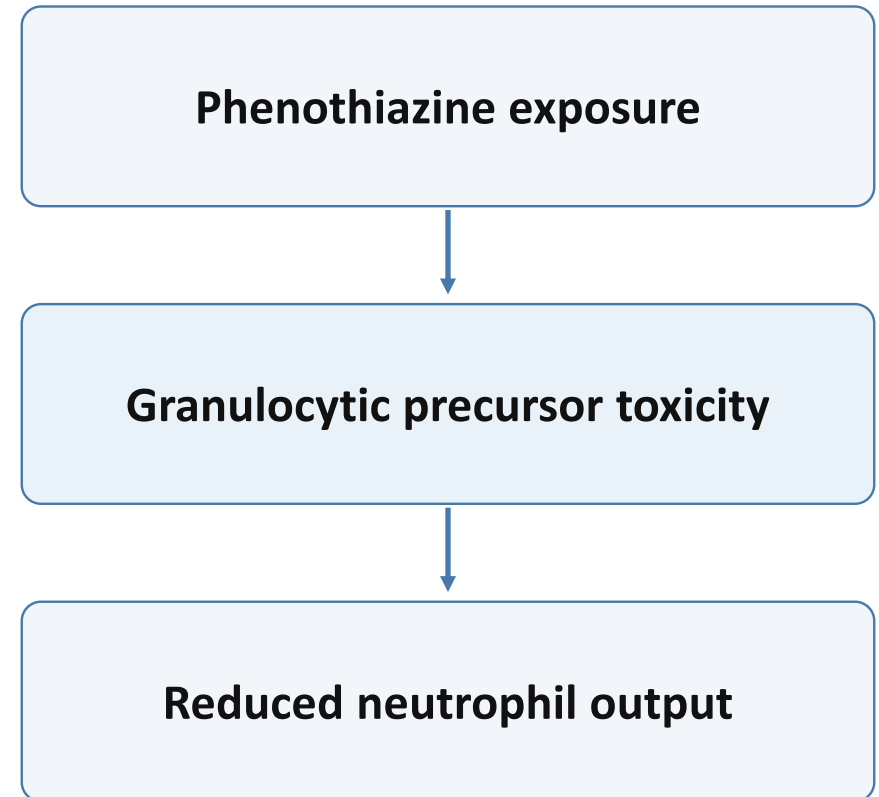
Drug-associated examples

Exposure group	Source-described association
Alkylating agents; Antimetabolites	Predictable, dose-related myelosuppression
Chlorpromazine / related phenothiazines	Toxic effect on granulocytic precursors
Sulfonamides	Probably antibody-mediated neutrophil destruction
Selected antibiotics, anticonvulsants, anti-inflammatory drugs, diuretics	Idiosyncratic agranulocytosis may occur

Categories and examples are not exhaustive; No relative-risk ranking is supplied.

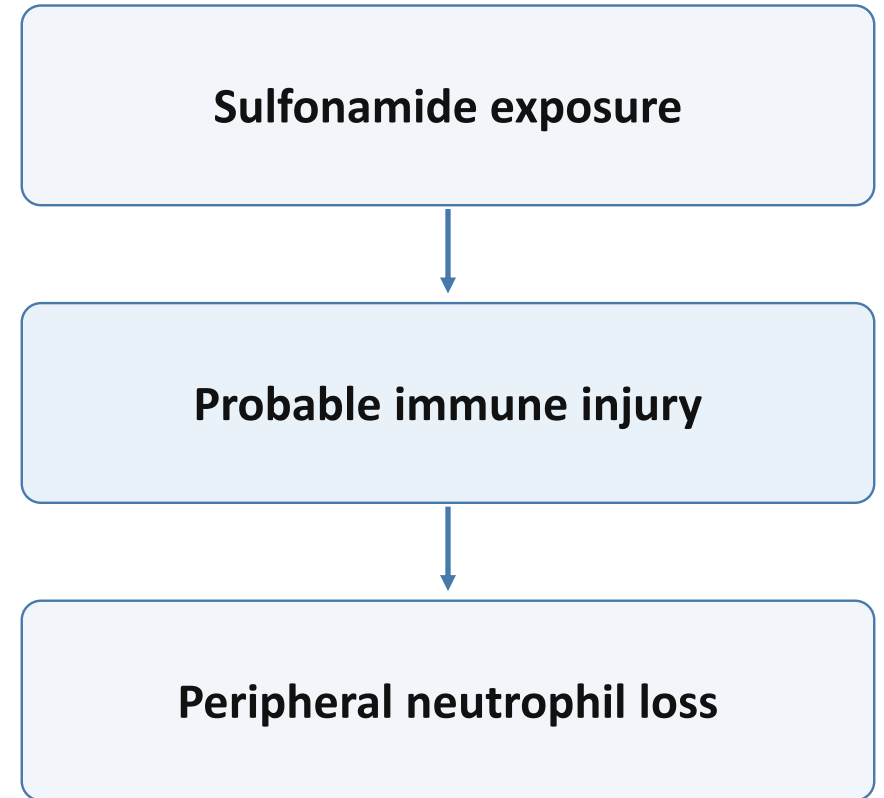
Phenothiazines can injure marrow precursors

- Chlorpromazine and related phenothiazines are antipsychotic drug examples.
- Their associated neutropenia is described as a toxic effect on granulocytic precursors.
- The mechanistic injury occurs before mature neutrophil release.
- Marrow suppression can explain the diminished blood neutrophil count.



Sulfonamide reactions suggest immune destruction

- An antibody-mediated mechanism for agranulocytosis following sulfonamides.
- The analogy is to drug-induced immunohemolytic anemia.
- The word “probably” matters: The source expresses mechanistic uncertainty.
- Peripheral immune injury differs biologically from direct marrow precursor toxicity.



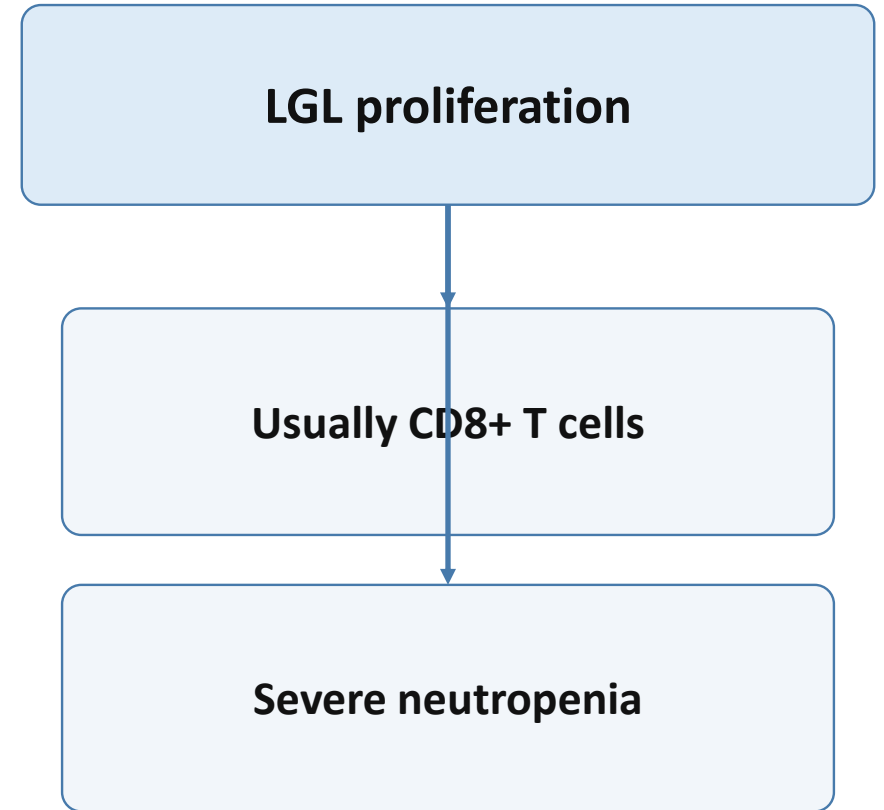
Two drug mechanisms predict different marrow states

Precursor toxicity	Peripheral immune destruction
Inhibits or destroys developing granulocytes	Targets circulating mature neutrophils
Reduced marrow output	Marrow may increase compensatory production
Hypocellularity when precursors are suppressed	Hypercellular marrow may be observed
Example: Phenothiazine mechanism	Example: Proposed sulfonamide mechanism

Patterns are mechanism-based expectations, not drug-specific biopsy rules.

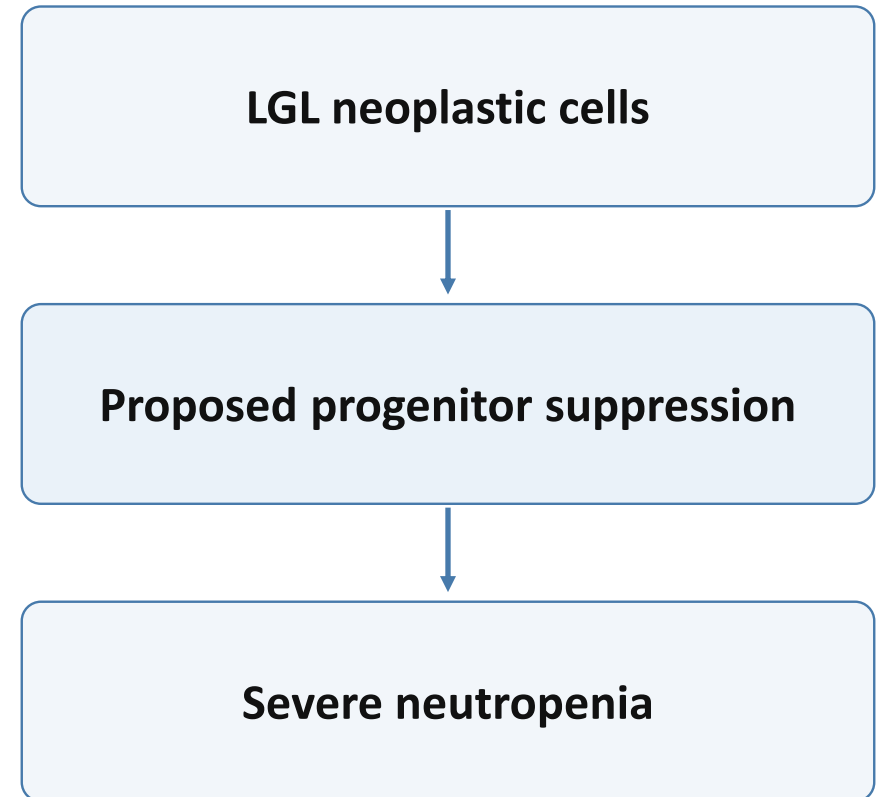
Large granular lymphocyte proliferations

- Severe neutropenia may accompany monoclonal proliferations of large granular lymphocytes.
- Robbins refers to this association as large granular lymphocyte (LGL) leukemia.
- The neoplastic population is usually a CD8-positive cytotoxic T-cell population.
- Recognition of the association broadens the differential beyond drugs and autoimmunity.

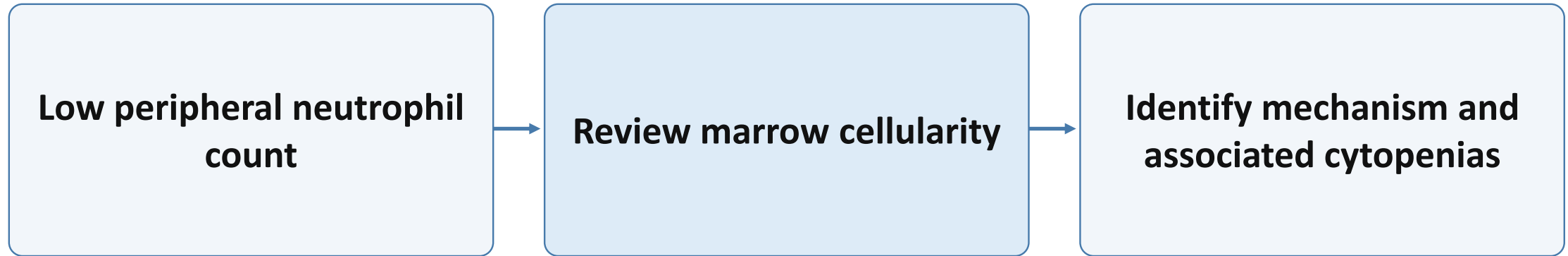


The LGL mechanism remains incompletely defined

- The mechanism of associated neutropenia is unclear.
- Suppression of granulocytic progenitors by neoplastic-cell products is considered most likely.
- Do not present this proposed pathway as a proven universal mechanism.
- Its inferred site of action is granulocytic production rather than simple splenic pooling.



Marrow cellularity is a mechanistic readout

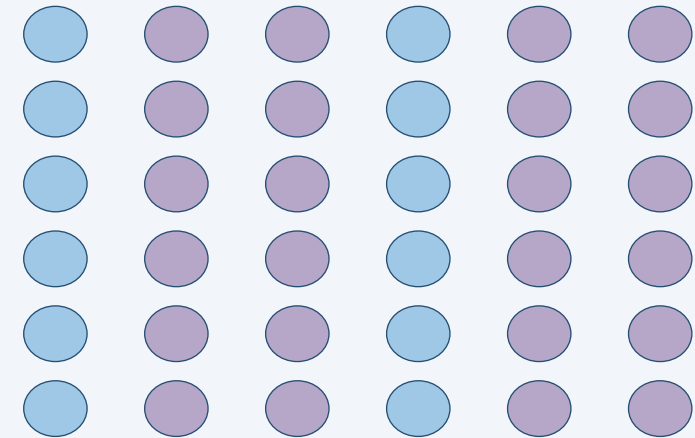


Hypercellularity can reflect compensation OR ineffective hematopoiesis;
Hypocellularity supports suppression of precursors.

Peripheral destruction usually stimulates marrow

- When mature neutrophils are removed in the periphery, granulocytic precursors can expand.
- The marrow is usually hypercellular in excessive peripheral destruction.
- The expanded marrow compartment is compensatory rather than evidence of adequate blood counts.
- Blood and marrow compartments must be interpreted separately.

Bone marrow • schematic



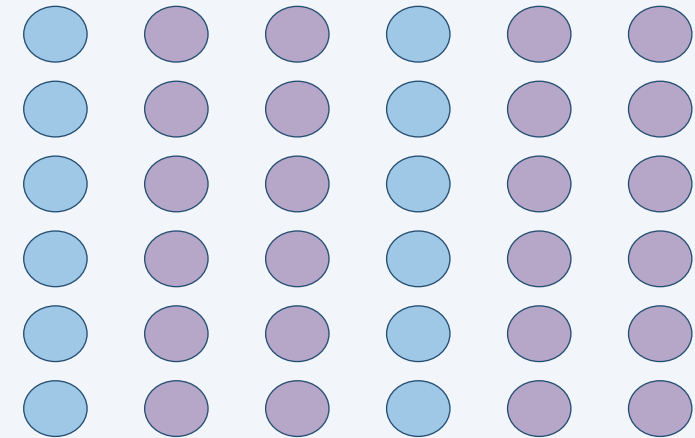
Compensatory granulocytic expansion

Cell-symbol diagram; Not histology

Ineffective granulopoiesis can also be hypercellular

- Megaloblastic anemia and myelodysplastic neoplasms commonly show marrow hypercellularity.
- Here the abundant precursors do not mature effectively into circulating neutrophils.
- Premature death of defective precursors accounts for impaired net output.
- The same marrow cellularity can therefore have a different underlying explanation.

Bone marrow • schematic

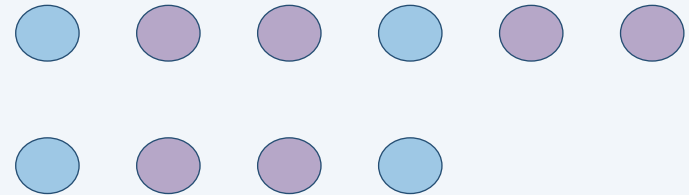


Many precursors; Poor effective output

Precursor-suppressing agents may cause hypocellularity

- Drug injury that suppresses or destroys granulocyte precursors reduces the developing-cell pool.
- Precursor-toxic agranulocytosis with marrow hypocellularity.
- This pattern contrasts with the hypercellular response to peripheral destruction.
- It also contrasts with the hypercellular but ineffective production of some marrow diseases.

Bone marrow • schematic



Suppressed developing granulocytes

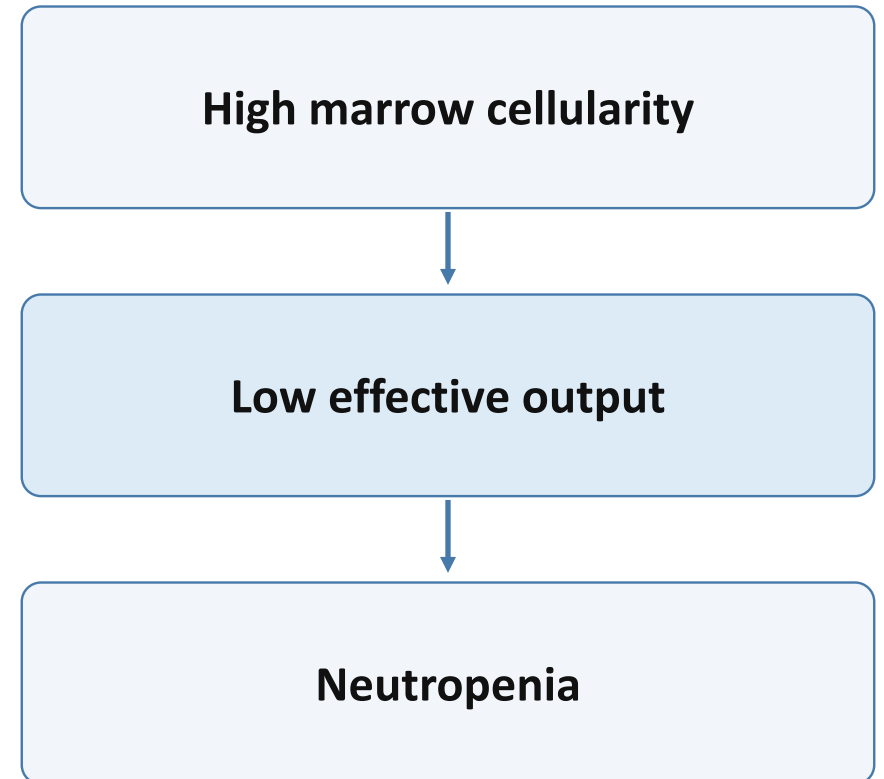
Three marrow patterns with one blood finding

Peripheral destruction	Ineffective granulopoiesis	Precursor suppression
Marrow often hypercellular	Marrow often hypercellular	Marrow may be hypocellular
Compensatory production	Precursors die or fail to mature	Precursor pool reduced
Neutrophils lost after release	Effective output diminished	Production capacity diminished

Interpret cellularity together with lineage composition and history.

Why marrow hypercellularity does not exclude neutropenia

- The peripheral count reflects successful release and survival of mature neutrophils.
- A cellular marrow may represent unsuccessful precursor maturation.
- It may alternatively reflect an appropriate response to peripheral destruction.
- Thus high marrow cellularity and low blood neutrophils are not contradictory.



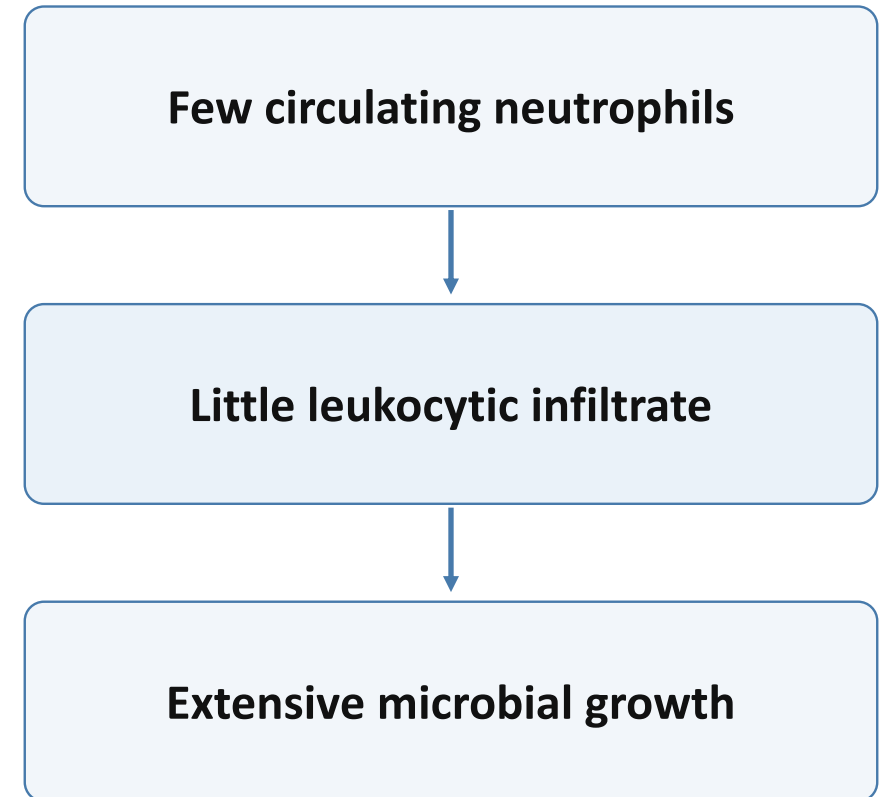
Conceptual sequence

Biopsy interpretation requires a clinicopathologic link

- Bone-marrow cellularity alone does not specify the diagnosis.
- Ask whether granulocytic cells are suppressed, ineffective, or compensating for peripheral loss.
- Assess whether red cells and platelets are also deficient.
- Integrate marrow observations with drug exposure, immune disease, infection, and splenomegaly.

Neutropenia changes the appearance of infection

- Infections can contain large burdens of bacteria or fungi.
- Sites of infection may show little leukocytic response despite extensive microbial growth.
- The paucity of inflammatory cells reflects impaired neutrophil availability.
- A muted local cellular response does not indicate a harmless lesion.



Necrotizing oral lesions are characteristic

- Agranulocytosis may produce necrotizing ulcerative lesions in the oral cavity.
- Frequent sites include gingiva, mouth floor, buccal mucosa, and pharynx.
- Ulcers are described as deep and undermined.
- Severe infection and impaired local inflammatory response contribute to the destructive morphology.

Sites

Gingiva

Floor of mouth

Buccal mucosa

Pharynx

The surface of oral ulcers may be necrotic

- Gray to green-black necrotic membranes covering characteristic ulcers.
- Bacteria or fungi can be recovered from these membranes.
- The combination of deep tissue damage and microbial overgrowth signals substantial local infection.
- No synthetic photomicrograph is substituted for authentic clinical-pathology evidence.

Other mucocutaneous sites may be affected

- Similar necrotizing ulcerative lesions occur less often outside the oral cavity.
- Documented sites include skin, vagina, and anus.
- Lesions can also occur along the gastrointestinal tract.
- Their distribution reflects vulnerability to infection when neutrophil-mediated defense is lost.

Sites

Skin

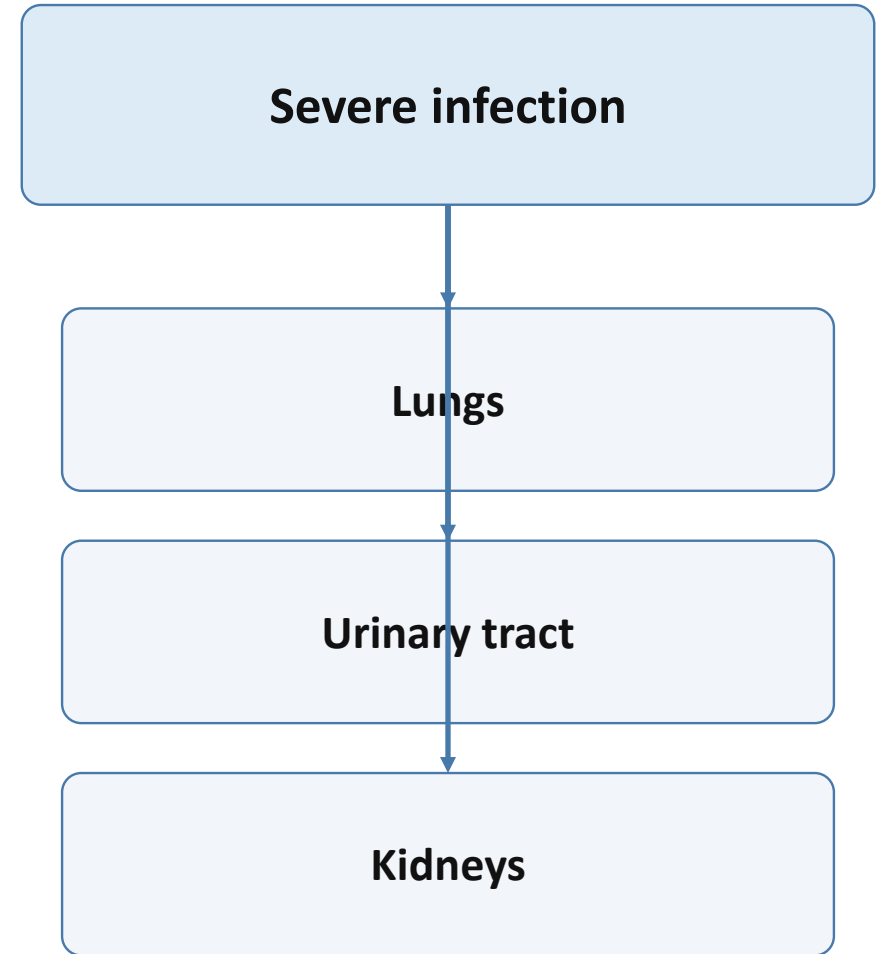
Anus

Vagina

Gastrointestinal tract

Deep infections extend beyond mucosal surfaces

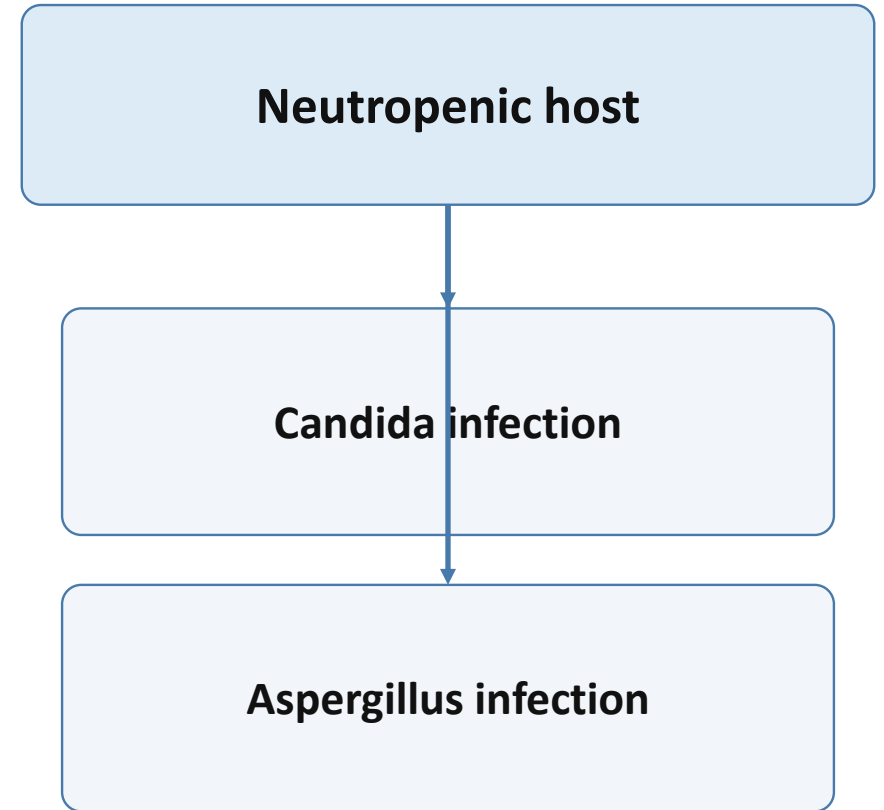
- Severe invasive bacterial or fungal infections can involve the lungs.
- The urinary tract and kidneys are additional reported sites.
- Invasiveness and rapid progression become major clinical concerns in profound neutropenia.
- Organism proliferation may be disproportionate to the visible leukocytic response.



Schematic

Candida and Aspergillus are key fungal threats

- Deep infections due to Candida species in neutropenic patients.
- Aspergillus is another important fungal threat in this setting.
- Both are examples of invasive fungal disease associated with profound neutrophil deficit.
- Organism identity and tissue invasion require genuine microbiologic or pathologic evidence.



Organ-site complications

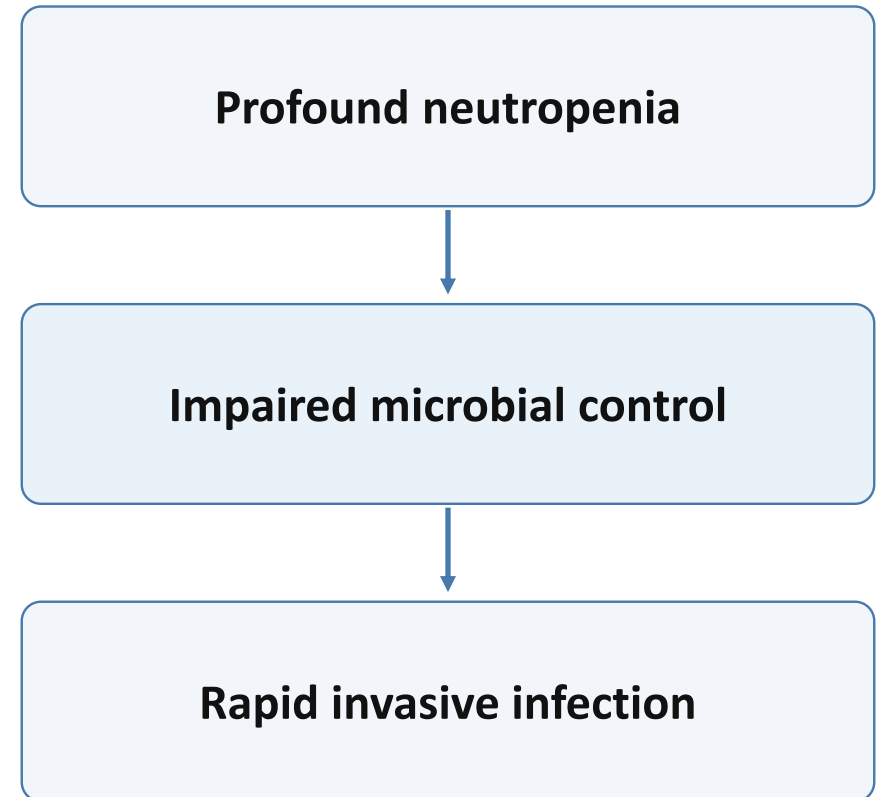
Site	Source-described implication
Oral mucosa	Deep undermined necrotizing ulcers
Skin / vagina / anus / GI tract	Less frequent ulcerative lesions
Lung	Potential life-threatening invasive infection
Urinary tract / kidney	Potential severe bacterial or fungal infection

The clinical syndrome is often infection driven

- Symptoms may include malaise, chills, and fever.
- Marked weakness and fatigability can follow.
- The severity depends strongly on the consequences of infection.
- Agranulocytosis can permit overwhelming, rapidly progressive infectious disease.

Infection may become fulminant in agranulocytosis

- The host may be unable to mount an adequate neutrophilic response.
- Bacterial or fungal growth can progress rapidly despite little local leukocyte infiltration.
- Overwhelming infections may be fatal within hours to days.
- Fever or new infectious symptoms in a severely neutropenic patient require immediate attention.



Risk rises sharply with severe count reduction

- Neutrophil counts below 500 per mm³ as especially associated with serious infection.
- The count is a marker of host-defense capacity, not a stand-alone diagnosis.
- The clinical trajectory and suspected infection site are essential alongside the count.
- Profound agranulocytosis denotes an even more severe neutrophil deficit.

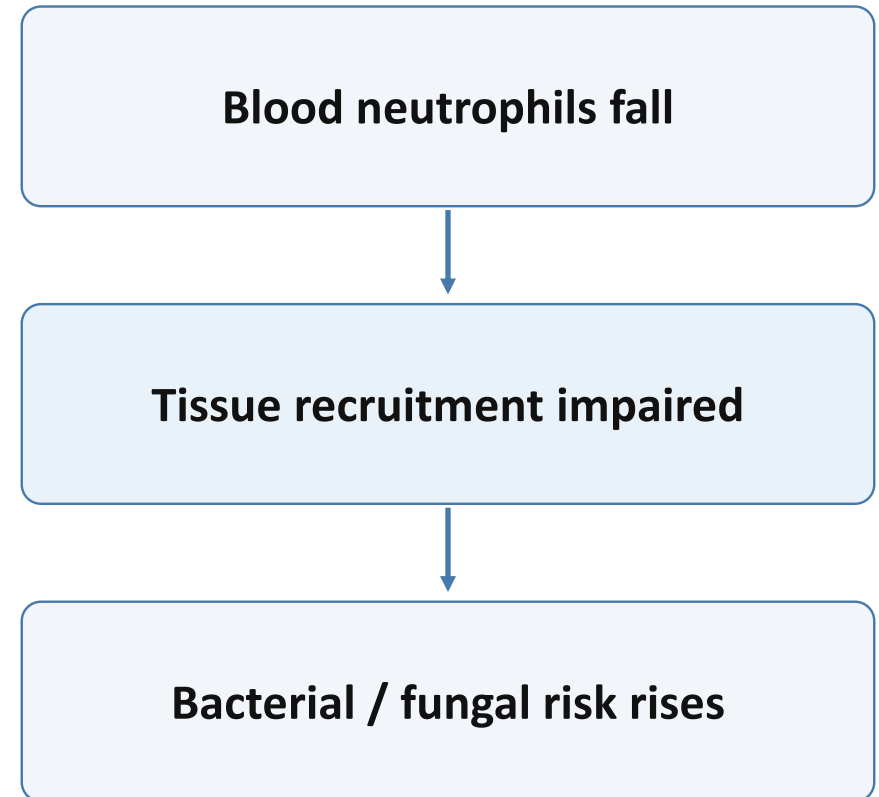
< 500/mm³

Serious infection becomes
particularly likely

Threshold cited

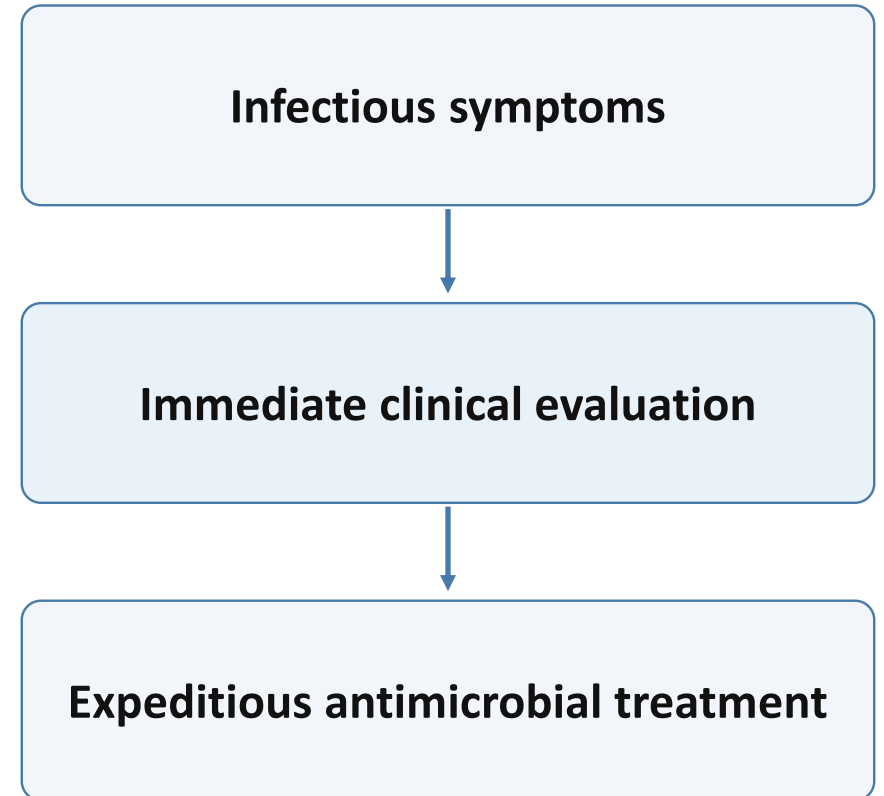
Why the peripheral blood count matters

- Blood neutrophils form an accessible marker of the host's antimicrobial defense.
- Loss of these cells compromises the cellular response at infected tissues.
- Very low counts correlate with potentially invasive, high-burden infection.
- Quantitative deficiency must be interpreted with the relevant clinical symptoms.



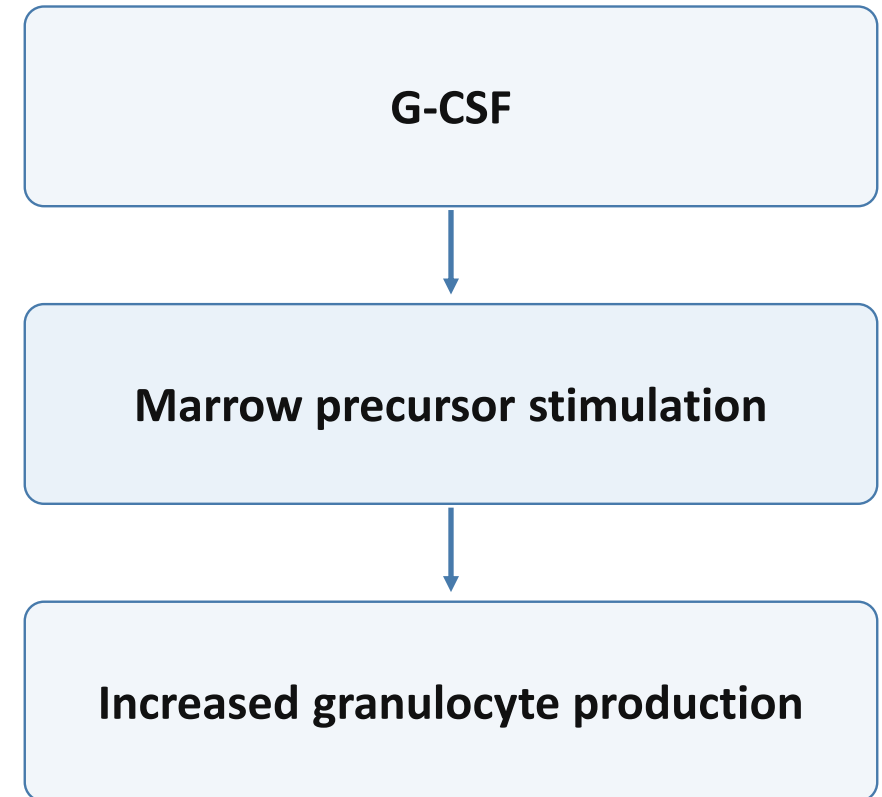
Prompt treatment is an emergency principle

- Expeditious broad-spectrum antibiotic therapy when infectious signs or symptoms occur.
- Treatment urgency follows the potential for fulminant infection.
- The immediate clinical priority is infection control while the neutropenia mechanism is assessed.
- This lecture addresses the principle, not a regimen or dosing protocol.



Granulocyte colony-stimulating factor may be used

- Granulocyte colony-stimulating factor (G-CSF) stimulates granulocyte production from marrow precursors.
- Robbins mentions its use in selected settings such as myelosuppressive chemotherapy.
- It acts on the production side of neutrophil homeostasis.
- The source does not prescribe a universal indication or dosage for every cause.



Management principles are mechanism-linked

Immediate issue	Source-supported action	Biologic rationale
Signs of infection	Expeditious broad-spectrum antibiotics	Prevent progression of invasive infection
Selected post-chemotherapy neutropenia	G-CSF may be given	Stimulate granulocyte output
Unexplained persistent neutropenia	Determine the underlying mechanism	Different causes imply different marrow states

Diagnostic evaluation is a clinicopathologic teaching inference; This is not a treatment guideline.

Case: Pancytopenia after chemotherapy

Following alkylating-agent treatment, a patient develops neutropenia with anemia and thrombocytopenia.

Which mechanism best explains the three-lineage pattern?

Generalized suppression of hematopoiesis.

Dose-related marrow toxicity affects granulocytic, erythroid, and platelet production.

Case: Cellular marrow despite neutropenia

A patient with a disorder of ineffective hematopoiesis has low blood neutrophils but increased marrow cellularity.

Is the marrow finding incompatible with neutropenia?

No. Hypercellularity may coexist with ineffective granulopoiesis.

Defective precursors do not deliver effective mature-neutrophil output.

Case: Autoimmunity and isolated neutrophil loss

A patient with systemic lupus erythematosus develops neutropenia without evidence of generalized marrow suppression.

Which pathogenetic route should be considered?

Peripheral immune-mediated neutrophil injury.

Destruction of mature neutrophils can provoke compensatory granulopoiesis.

Case: Splenomegaly with thrombocytopenia

An individual has splenomegaly, modest neutropenia, and thrombocytopenia.

Which mechanism connects these findings?

Splenic sequestration and macrophage-mediated destruction.

An enlarged spleen may remove multiple blood-cell lineages.

Case: Neutropenia during overwhelming infection

A patient with severe bacterial infection is found to have marked neutropenia.

Must neutropenia always precede the infection?

No. Overwhelming infection can increase peripheral neutrophil utilization.

Infection can both result from and contribute to severe neutropenia.

Case: Characteristic destructive oral disease

A profoundly neutropenic patient has deep undermined gingival ulcers covered by necrotic membrane.

Why might the lesion contain few inflammatory cells?

Neutrophil deficiency limits the leukocytic response.

Microbes may proliferate extensively despite a paucity of leukocytes.

Case: Febrile profound neutropenia

A patient with known severe neutropenia develops fever and chills.

What urgency is justified by the pathology?

Immediate clinical assessment and expeditious broad-spectrum antibiotics.

Infection may progress rapidly and become overwhelming.

Mechanism–marrow–clinical integration

Cause	Mechanism	Marrow clue	Clinical clue
Aplastic / infiltrative disease	Global marrow impairment	Reduced or disrupted hematopoiesis	Multiple cytopenias
Megaloblastic anemia / MDS	Ineffective precursors	Often hypercellular	Poor effective output
Immune loss	Peripheral destruction	Often hypercellular	Immune/drug association
Splenomegaly	Sequestration	Compensation possible	Splenic enlargement
Precursor-toxic drugs	Granulocytic suppression	May be hypocellular	Medication exposure

Pattern recognition should direct evaluation, not replace a diagnosis.

Major diagnostic distinctions

- Leukopenia may reflect neutropenia or, less often, lymphopenia.
- Neutropenia has two main mechanistic routes: Insufficient output and peripheral loss.
- Marrow hypercellularity occurs in both peripheral destruction and ineffective granulopoiesis.
- Drug-associated neutropenia includes predictable marrow toxicity and idiosyncratic mechanisms.

What the marrow tells us—and what it does not

- Hypercellularity indicates abundant hematopoietic cells, not necessarily successful granulocyte output.
- Hypocellularity can support progenitor suppression by toxic exposure.
- Peripheral immune destruction can coexist with a strong marrow response.
- The complete interpretation requires exposures, associated cytopenias, and clinical context.

What makes profound neutropenia dangerous

- Serious infection risk is elevated when neutrophils fall below $500/\text{mm}^3$.
- Necrotizing oral ulcers are a characteristic destructive manifestation.
- Candida and Aspergillus exemplify deep fungal threats.
- Microorganisms may be numerous while neutrophil infiltration remains scant.

Clinicopathologic synthesis

- Determine whether neutrophils are underproduced, ineffective, destroyed, sequestered, or consumed.
- Use marrow cellularity and other blood-lineage changes to refine the causal category.
- Recognize potentially fulminant bacterial and fungal infections promptly.
- Treat suspected infection urgently; G-CSF has selected production-stimulating applications.

Primary reference

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).

Chapter 13: Diseases of White Blood Cells, Lymph Nodes, Spleen, and Thymus.

Neutropenia, Agranulocytosis; printed pages 533–534.

Companion context: Disorders of White Cells; Leukopenia (page 533).