

Immunodeficiencies Associated With Systemic Diseases

Inherited multisystem syndromes and secondary immune deficiency

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Learning goals

- Identify the systemic features and immune defects of Wiskott–Aldrich syndrome.
- Connect ATM-dependent DNA damage responses to the phenotype of ataxia-telangiectasia.
- Distinguish inherited multisystem immunodeficiency from acquired immune suppression.
- Relate the major acquired causes to their dominant mechanisms.

Two routes to immune dysfunction

Inherited systemic disorder

A germline defect affects immunity and other organs

Acquired systemic condition

Disease, treatment, or organ loss interferes with immunity

Both routes can produce infection susceptibility, but their initiating lesions differ.

Why “systemic” matters

- In the inherited syndromes, immune deficiency coexists with conspicuous nonimmune findings.
- The combination of infection susceptibility and a multisystem phenotype guides recognition.
- In acquired deficiency, the systemic disease or exposure often precedes immune dysfunction.
- An abnormal antibody profile does not fully describe tissue and cellular immunity.

Immune compartments implicated

T lymphocytes

Progressive depletion or impaired T-cell function may reduce cellular immunity.

B-cell responses

Antigen-specific responses and isotype-switched antibody production may be impaired.

Marrow leukopoiesis

Cancer or cytotoxic treatments may reduce leukocyte production.

Splenic clearance

Loss of the spleen decreases phagocytosis of blood-borne microbes.

Inherited versus secondary deficiency

Inherited syndromes

Initiating cause: A gene defect.

Wiskott–Aldrich and ataxia-telangiectasia are the two systemic examples in the source.

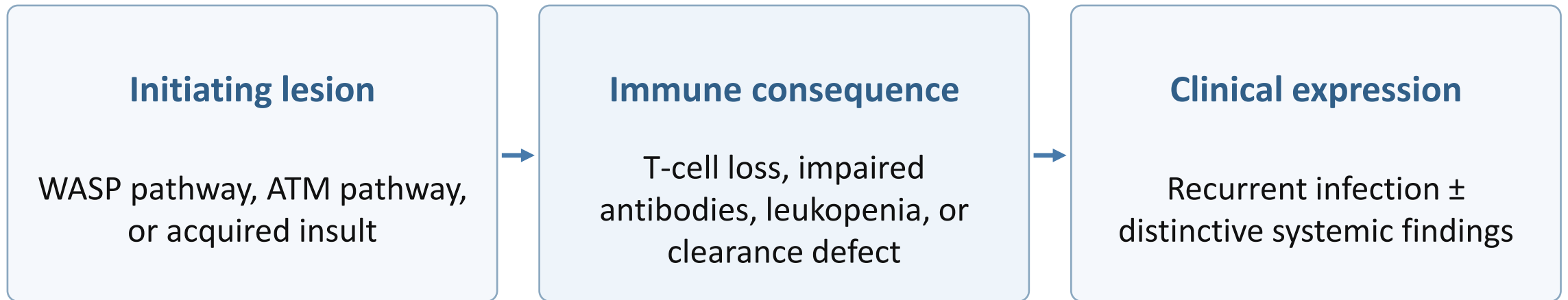
Immune and extraimmune findings coexist.

Secondary deficiency

Initiating context: Systemic illness, treatment, nutritional deficit, chronic infection, or splenic removal.

The mechanisms include decreased production, function, or clearance.

Read the phenotype from the mechanism



The same endpoint—susceptibility to infection—can arise through different mechanisms.

What the textbook does—and does not—specify

- Robbins gives two inherited multisystem examples: Wiskott–Aldrich and ataxia-telangiectasia.
- It groups a broad set of secondary causes and summarizes selected mechanisms.
- The supplied section does not give complete diagnostic algorithms or quantitative test thresholds.
- AIDS receives its own subsequent section; Here, it is retained as a cause of secondary deficiency.

Wiskott–Aldrich: Clinical triad

Thrombocytopenia

A platelet abnormality is part of the defining syndrome.

Eczema

Cutaneous disease is a prominent extraimmune manifestation.

Recurrent infections

Marked vulnerability reflects associated immune dysfunction.

The WAS triad signals one inherited syndrome

Thrombocytopenia

Hematologic

Eczema

Cutaneous

Susceptibility to infection

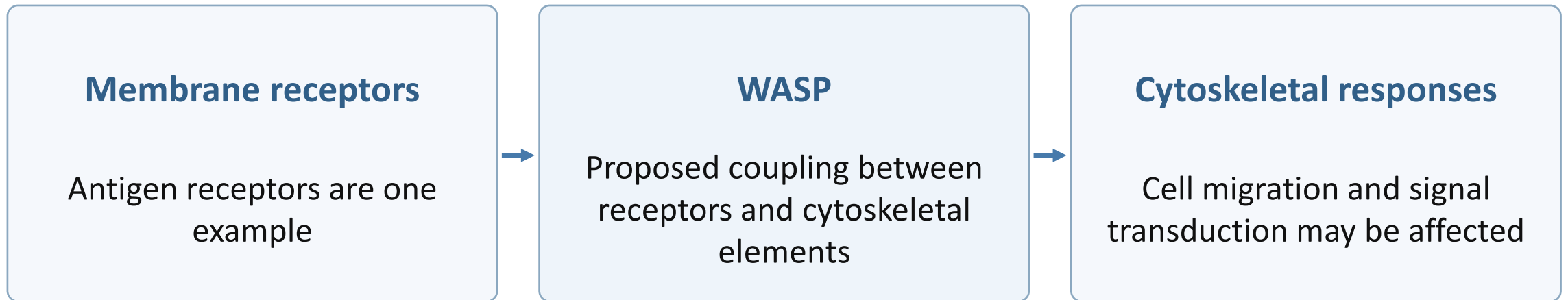
Immune

Three coexisting findings—not one isolated immunoglobulin abnormality.

Inheritance and molecular location

- Wiskott–Aldrich syndrome is X-linked.
- The causal gene lies at chromosome Xp11.23.
- It encodes Wiskott–Aldrich syndrome protein (WASP).
- The named protein links a genetic defect to immune-cell cytoskeletal function.

WASP: Receptor-to-cytoskeleton linkage

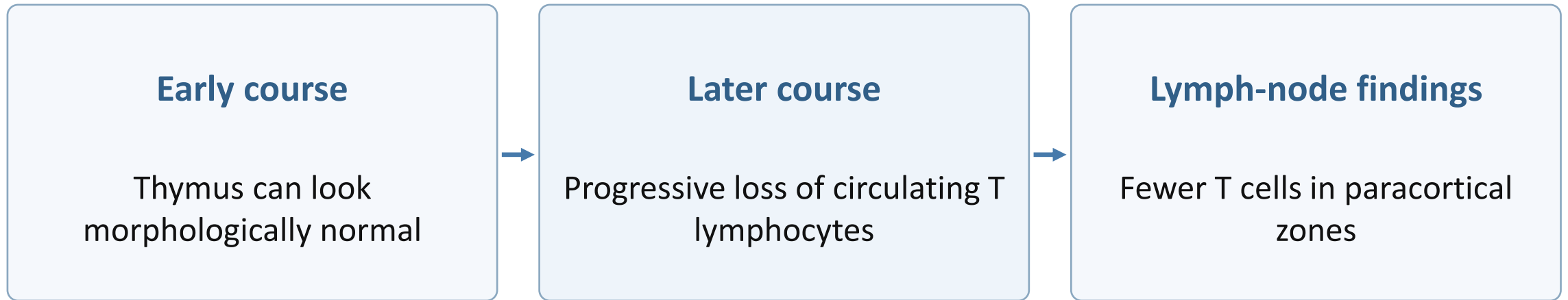


Mechanism is phrased as proposed rather than established for each cellular response.

Mechanistic caution: What is established?

- The disease is associated with mutations in the gene encoding WASP.
- WASP belongs to a protein family believed to link surface receptors to cytoskeletal elements.
- The source proposes roles in migration and signal transduction.
- Do not read the schematic as a fully demonstrated, single-pathway account of all clinical findings.

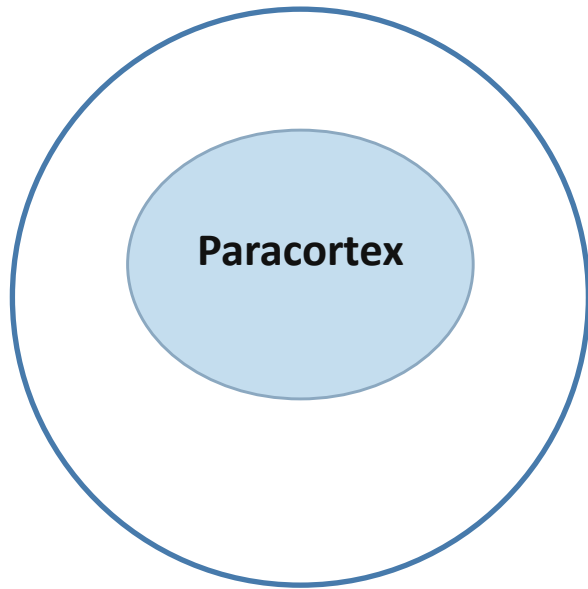
T-cell compartment changes over time



Normal early thymic morphology does not exclude evolving peripheral dysfunction.

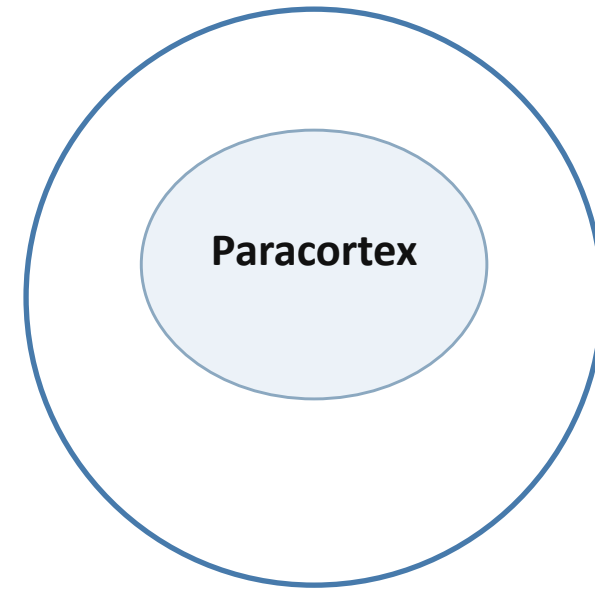
WAS: Progressive depletion of paracortical T cells

Earlier in disease



T-cell zone present

Later in disease



Reduced paracortical T cells

Conceptual lymph-node sections — not H&E microscopy

Functional cellular immunity is variable

- Progressive peripheral T-cell loss is a characteristic finding.
- The accompanying impairment of cellular immunity varies among patients.
- The T-cell compartment cannot be inferred solely from initial thymic morphology.
- Lymph-node paracortical depletion is a tissue correlate of the systemic T-cell abnormality.

Antibody responses: Antigen matters

Polysaccharide antigens

Patients fail to make antibodies to these antigens.

Protein antigens

Antibody responses are poor rather than wholly absent.

Serum IgG

Usually normal in concentration despite defective antigen-specific responses.

Normal IgG does not ensure effective responses

Serum measurement

IgG concentration can be normal

Functional measurement

Specific responses to antigens are abnormal

Clinical inference

A normal single class level does not exclude immune deficiency

Concentration and functional responsiveness answer different questions.

Characteristic immunoglobulin profile

IgM

Typically decreased in serum.

IgG

Usually within the normal range.

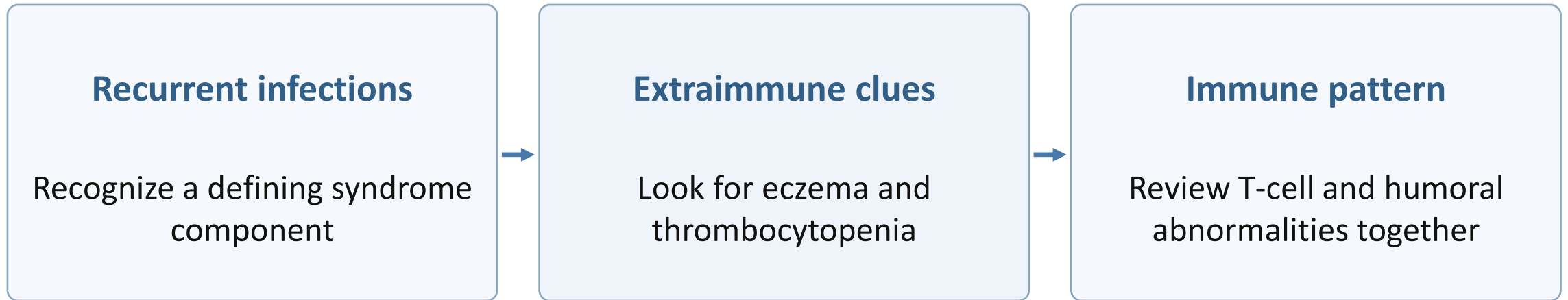
IgA / IgE

Often elevated, despite impaired responses to other antigens.

The WAS immune phenotype is mixed

- Cellular compartment: Progressive T-lymphocyte depletion.
- Humoral compartment: Abnormal antigen-specific antibody production.
- Serum immunoglobulins: A nonuniform pattern across classes.
- Combined functional defects help explain susceptibility to repeated infections.

Clinical interpretation of recurrent infection

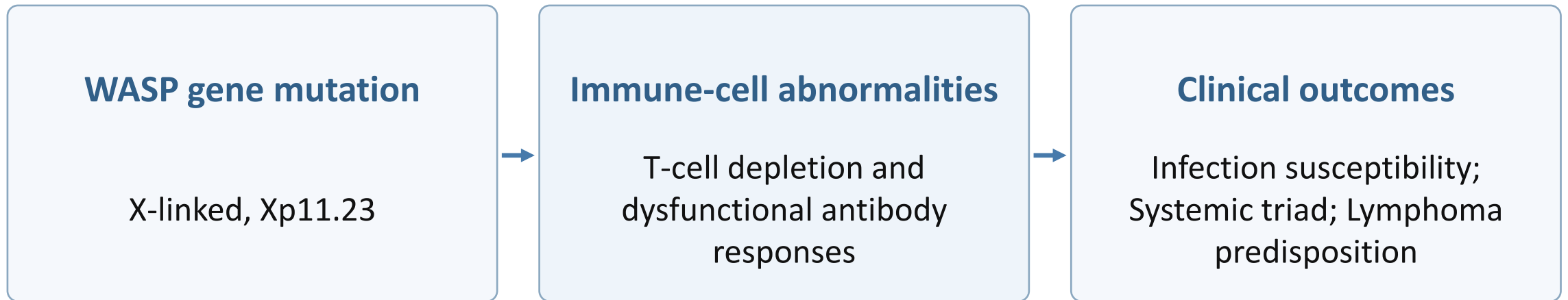


The cluster is more distinctive than infection alone.

WAS: Lymphoma susceptibility

- Increased susceptibility to B-cell lymphomas.
- Infection vulnerability and malignancy risk coexist in this inherited condition.
- Lymphoma association is distinct from the characteristic presenting triad.
- The supplied section does not quantify the risk or specify lymphoma subtypes.

WAS: Molecular lesion to major manifestations



Concept map—does not imply every manifestation has a single established intermediate.

WAS: Therapeutic statement

- The supplied text names hematopoietic stem-cell (HSC) transplantation as treatment.
- This is a statement from the specified textbook section.
- No transplant indications, outcomes, or alternative treatment regimen is detailed here.
- Clinical management recommendations require sources beyond this excerpt.

Case application: Wiskott–Aldrich

A young male patient has recurrent infections, eczematous skin disease, and thrombocytopenia. Immunologic testing shows low serum IgM; IgG is not reduced.

Clinical reasoning

- Which inherited syndrome unites the findings?
- Why does normal total IgG not dismiss dysfunction?

Reasoning through the WAS case

Syndrome match

The constellation of eczema, thrombocytopenia, and infection supports Wiskott–Aldrich.

Humoral finding

IgG can be normal while antibody response to polysaccharide and protein antigens is defective.

Cellular context

Progressive T-cell loss and variable cellular immune impairment may coexist.

Ataxia-telangiectasia: Multisystem phenotype

Neurologic

Abnormal gait (ataxia) and other neurologic deficits.

Vascular

Telangiectases are characteristic vascular malformations.

Immune

Variable B-cell and T-cell abnormalities with recurrent infection.

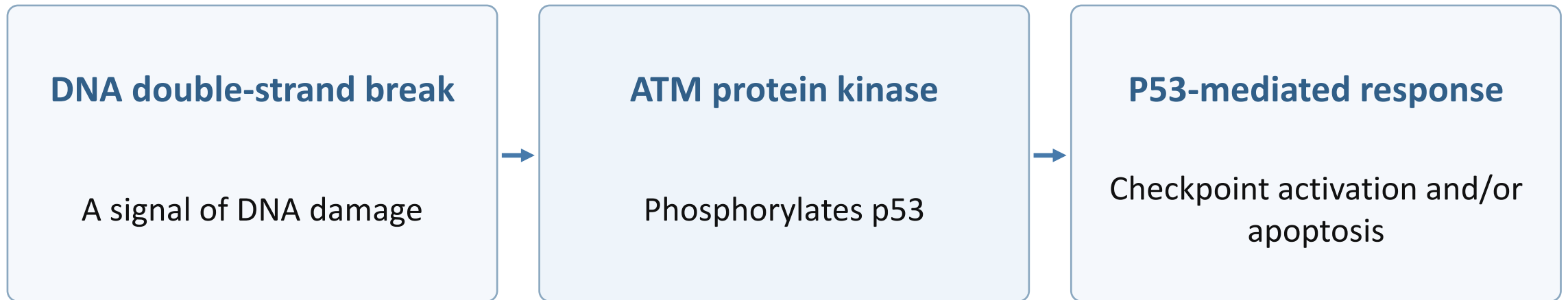
Neoplastic

Increased incidence of tumors, including lymphoma.

Inheritance and gene product

- Ataxia-telangiectasia is autosomal recessive.
- The causal gene is located on chromosome 11.
- It encodes ATM: Ataxia telangiectasia mutated protein kinase.
- ATM participates in the response to DNA double-strand breaks.

ATM is activated in response to DNA damage

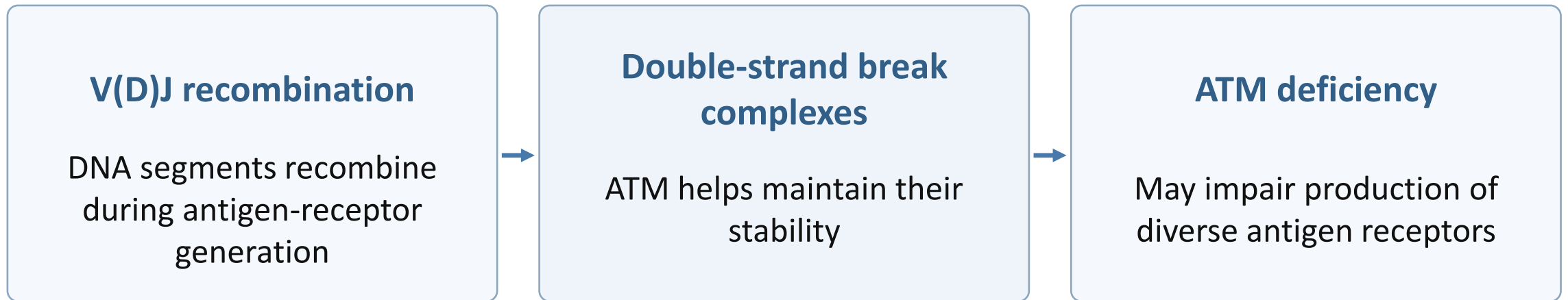


The p53 response follows DNA damage; Outcome depends on the cell context.

Cell-cycle checkpoints protect damaged cells

- ATM-dependent phosphorylation activates p53 after double-strand breaks.
- P53 can initiate checkpoint responses in cells containing damaged DNA.
- P53 can also activate apoptosis under appropriate circumstances.
- Deficient ATM disrupts this DNA-damage response axis.

Antigen-receptor recombination also uses DNA breaks



This is a potential route from DNA repair defect to impaired lymphocyte function.

ATM deficiency: Two immunologic routes

Antigen-receptor generation

Abnormal DNA break processing may compromise V(D)J recombination.

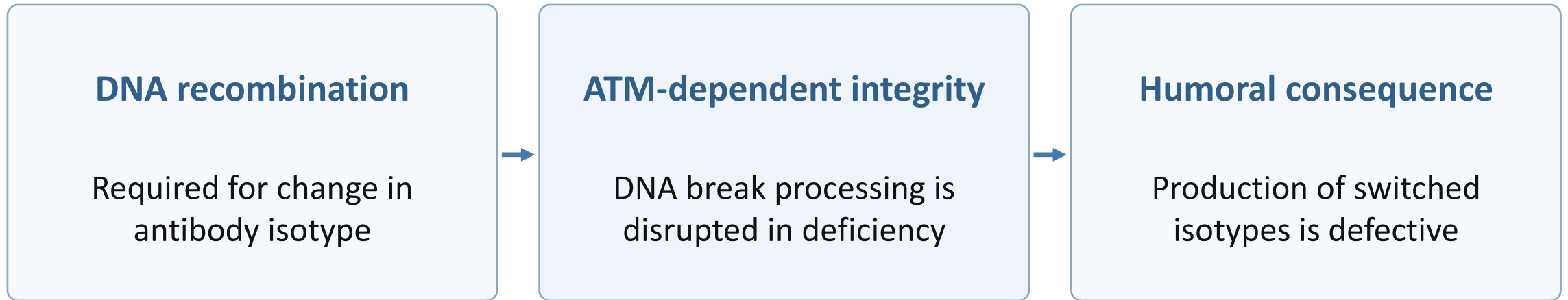
Antibody class switching

Defective DNA recombination may impair isotype switching.

DNA-damage surveillance

Abnormal checkpoint/apoptotic signaling accompanies repair defects.

Immunoglobulin isotype switching in A–T



The strongest stated abnormalities involve IgA and IgG2.

A–T: Principal humoral abnormalities

- Defective production of isotype-switched antibodies is prominent.
- IgA and the IgG2 subclass.
- The severity of B-cell dysfunction differs among affected individuals.
- This pattern is distinct from the characteristic serum immunoglobulin changes in Wiskott–Aldrich syndrome.

A–T: T-cell abnormalities

- T-cell defects may occur, but are usually less prominent than the humoral defects.
- The source associates T-cell defects with thymic hypoplasia.
- B-cell and T-cell involvement may vary in severity.
- An isolated antibody assessment may not describe the full defect.

Distinct tissue features in the two syndromes

Wiskott–Aldrich

Thymus may be morphologically normal initially

Ataxia-telangiectasia

T-cell defects are associated with thymic hypoplasia

A normal thymus early in WAS is not equivalent to thymic hypoplasia reported in A–T.

A–T: Infection phenotype

- Patients are vulnerable to bacterial infections in the upper respiratory tract.
- Lower respiratory tract bacterial infections also occur.
- The text describes combined immune abnormalities with variable severity.
- The infection pattern must be interpreted alongside neurologic and vascular findings.

A–T: Consequences beyond infection

Autoimmunity

Multiple autoimmune phenomena occur.

Neoplasia

Cancers become increasingly frequent with advancing age.

Lymphoma

A markedly increased incidence.

ATM deficiency: Immune and neoplastic associations

ATM deficiency

Abnormal response to double-strand DNA damage

Immune effects

Potential recombination and isotype-switching defects

Cancer association

Increased occurrence of malignancy, especially lymphoma

Shared molecular context helps integrate immune deficiency and malignancy.

A–T: Certainty of molecular statements

- ATM-mediated phosphorylation of p53 is described directly.
- ATM also contributes to stability of DNA-break complexes during V(D)J recombination.
- Effects on antigen-receptor generation are presented as possible.
- Disordered class switching is linked to defective DNA repair as a proposed mechanism.

Case application: Ataxia-telangiectasia

A child has abnormal gait, telangiectases, and recurrent bacterial respiratory infections. Studies indicate poor production of IgA and IgG2.

Clinical reasoning

- Which syndrome best integrates the abnormalities?
- Which DNA-damage-response protein is affected?

Reasoning through the A–T case

Syndrome

Ataxia and telangiectases distinguish the phenotype from a generic immunodeficiency.

Immunology

Impaired isotype-switched antibody production matches the IgA / IgG2 pattern.

Pathogenesis

ATM dysfunction links DNA-damage signaling with immune recombination problems.

Wiskott–Aldrich versus ataxia-telangiectasia

Feature	Wiskott–Aldrich	Ataxia-telangiectasia
Inheritance	X-linked	Autosomal recessive
Core gene product	WASP	ATM protein kinase
Extraintestinal clues	Eczema; Thrombocytopenia	Ataxia; Telangiectases
Typical immune pattern	T-cell decline; Poor antibody responses	IgA / IgG2 switching defects
Neoplasia	B-cell lymphoma risk	Lymphoma; Other cancers

Two molecular bottlenecks

WASP

Membrane-receptor/cytoskeletal linkage and cell responses.

ATM

Double-strand-break response, DNA recombination, and class switching.

Shared outcome

Immune defects plus increased lymphoma susceptibility, via distinct mechanisms.

Secondary immunodeficiencies are more common

- Secondary (acquired) immunodeficiency arises in the setting of systemic conditions or exposures.
- These collectively outnumber primary genetic immunodeficiency disorders.
- Possible initiating events include underlying disease, therapeutic intervention, or organ removal.
- The resulting deficit may involve immune-cell production, immunoglobulin synthesis, cell survival, or microbial clearance.

Systemic settings associated with acquired deficiency

Systemic illnesses	Cancer, diabetes/other metabolic disorders, chronic infection, aging.
Nutritional status	Protein-calorie malnutrition.
Therapeutic exposure	Cancer chemotherapy or irradiation; Immunosuppressive medications.
Anatomic loss	Removal of the spleen.

Acquired deficiency: Four dominant mechanisms

Reduced production

Marrow infiltration;
Chemotherapy;
Radiation

Impaired function

Malnutrition-linked
lymphocyte
dysfunction

Cell loss

Drug- or infection-
associated depletion

Reduced clearance

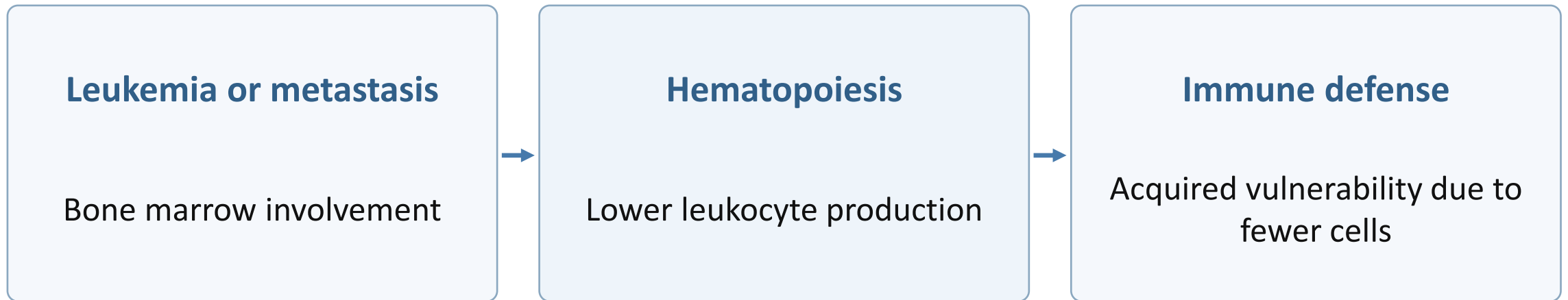
Splenic removal

Different initiating conditions may converge on similar susceptibility to infection.

Cancer can compromise the bone marrow

- Leukemias may involve the marrow, interfering with normal leukocyte production.
- Metastatic cancer can likewise occupy marrow and reduce production.
- Reduced immune-cell output is a recognized route to secondary deficiency.
- This mechanism is different from an inherited lymphocyte-signaling defect.

Marrow involvement: Effect on host defense

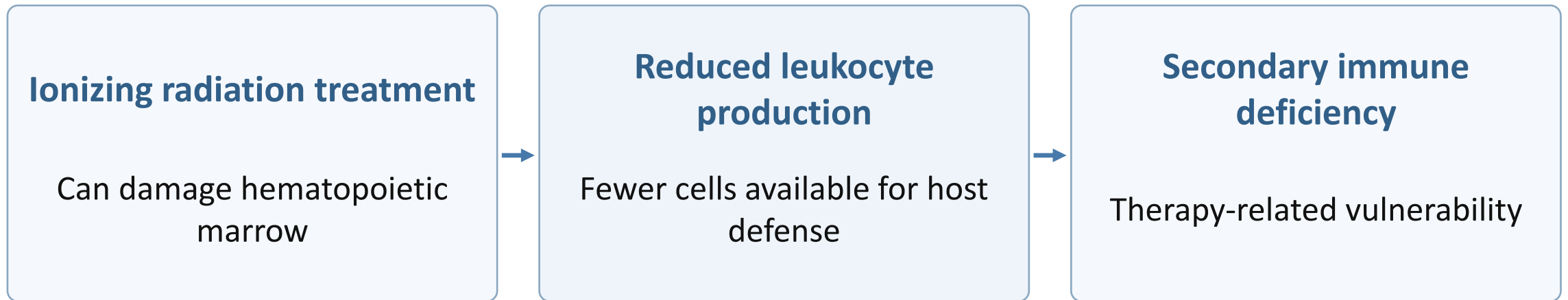


A production deficit is an acquired quantitative mechanism.

Chemotherapy: An iatrogenic mechanism

- Cancer-directed chemotherapy is a listed cause of secondary immunodeficiency.
- One key mechanism is reduced leukocyte production.
- Treatment exposure may generate immune dysfunction in addition to the underlying malignancy.
- The textbook excerpt does not supply drug-specific risk or recovery timelines.

Radiation therapy and leukocyte production



Radiation and chemotherapy appear together Table 6.13.

Protein-calorie malnutrition

Systemic context

Insufficient nutrition is a listed acquired cause.

Mechanism

Metabolic derangements inhibit lymphocyte maturation and function.

Antibody production

The narrative also describes inadequate immunoglobulin synthesis.

Interpretation

Nutritional state may impair more than one arm of immune defense.

Malnutrition can disrupt multiple immune functions

Protein-calorie malnutrition

Metabolic derangement

Lymphocyte compartment

Maturation and function
inhibited

Humoral response

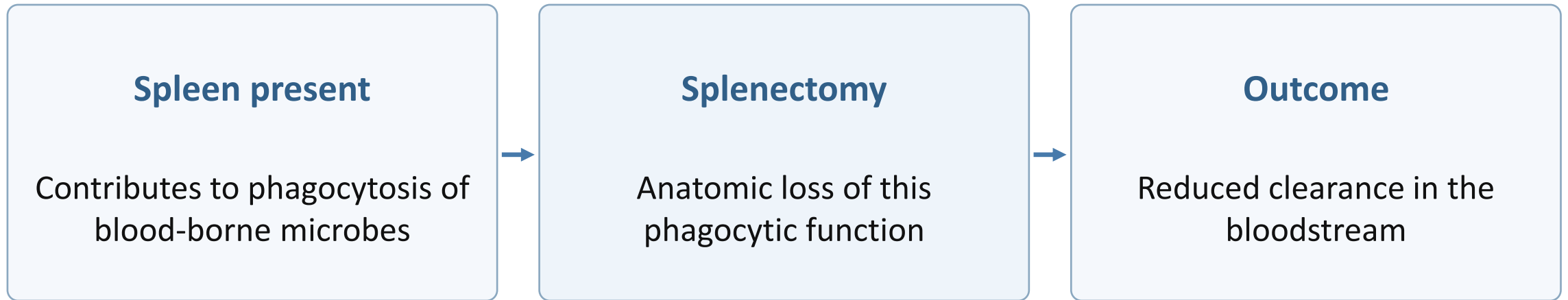
Immunoglobulin synthesis may
be inadequate

Effects on lymphocytes and Ig production are both source-described.

Loss of the spleen: A clearance defect

- Splenic removal is specifically listed in Table 6.13.
- The table identifies decreased phagocytosis of blood-borne microbes as the mechanism.
- Unlike chemotherapy-related deficiency, the primary defect described is not reduced marrow output.
- This illustrates an acquired defect of a host-defense organ.

Spleen removal changes microbial handling



This is not a depiction of a specific pathogen or infection risk estimate.

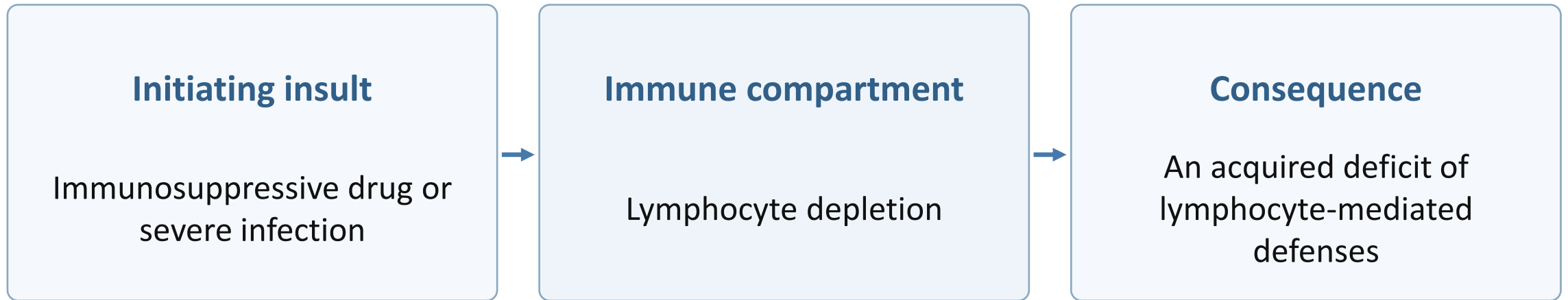
HIV: Lymphocyte depletion as a prototype

- HIV infection is one cause Table 6.13.
- Its listed immune mechanism is depletion of CD4-positive helper T cells.
- The following AIDS section describes profound immunosuppression and opportunistic disease.
- HIV pathogenesis and clinical AIDS are developed in separate Robbins teaching units.

Additional acquired contexts named by Robbins

Diabetes / metabolic disease	Associated with secondary immune deficiency; No specific mechanism detailed here.
Aging	Recognized as a context, without an age-specific mechanism in this excerpt.
Chronic infection	Can be associated with lymphocyte depletion during severe infection.
Immunosuppressive drugs	Given for graft rejection prevention or autoimmune disorders; Depletion may occur.

Drugs and severe infection can deplete lymphocytes



The effect is broadly described; No specific drug class or pathogen is inferred.

Robbins Table 6.13: Cause–mechanism map

Cause	Listed mechanism
HIV infection	CD4 helper-T-cell depletion
Chemotherapy / irradiation	Reduced leukocyte production
Cancer involving marrow	Reduced leukocyte production
Protein-calorie malnutrition	Inhibited lymphocyte maturation and function
Splenectomy	Reduced phagocytosis of blood-borne microbes

Mechanism-first clinical discrimination

Production defect

Ask whether cytotoxic therapy or tumor infiltration affects marrow.

Functional defect

Consider malnutrition and abnormal lymphocyte performance.

Cell-depletion defect

Consider drugs or severe infection; HIV specifically targets CD4 helper T cells.

Clearance defect

Ask whether the spleen is absent.

Case: Immunodeficiency after cancer therapy

A person receiving cancer chemotherapy develops evidence of reduced leukocyte production and increased susceptibility to infections.

Clinical reasoning

- Is the initiating cause inherited or acquired?
- Which mechanism does the Robbins table identify?

Case interpretation: Cancer therapy

Classification

Secondary (treatment-associated) immunodeficiency.

Mechanism

Chemotherapy can suppress leukocyte production.

Distinction

This differs from WASP- or ATM-associated genetic immune syndromes.

Case: A clearance rather than production problem

A person without a spleen is being assessed for predisposition to infection. There is no statement that marrow leukocyte production has fallen.

Clinical reasoning

- What host-defense function is explicitly impaired by splenectomy?
- Why is a marrow-production model insufficient?

Case interpretation: Splenectomy

Primary deficit

Less phagocytosis of blood-borne microbes.

Mechanistic category

Loss of an organ-dependent microbial clearance function.

Contrast

Chemotherapy and marrow cancer are linked to reduced leukocyte production.

Genetic lesions and acquired insults converge

Inherited systemic examples

WASP-associated defect: Linked to cell signaling/cytoskeletal function.

ATM-associated defect: DNA-damage response and immune recombination.

Both have nonimmune syndromic clues.

Acquired causes

Reduced leukocyte output, inadequate immunoglobulin synthesis, lymphocyte depletion, or impaired phagocytosis.

A preceding illness, therapy, or organ loss may identify the route.

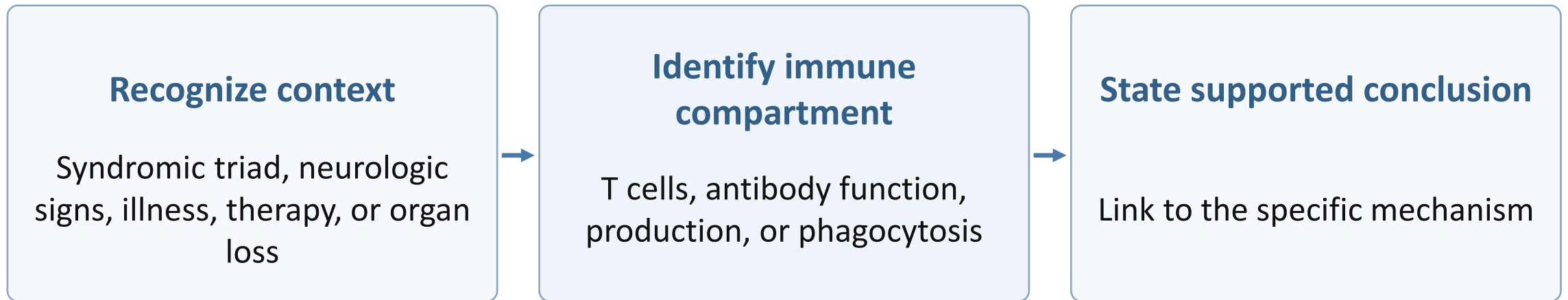
Match the clue to the dominant mechanism

Clinical or contextual clue	Source-supported interpretation
Eczema + thrombocytopenia	Consider Wiskott–Aldrich
Ataxia + telangiectases	Consider ataxia-telangiectasia
Cancer occupying marrow	Reduced leukocyte production
Protein-calorie malnutrition	Lymphocyte maturation/function impaired
History of splenectomy	Reduced phagocytosis of blood-borne microbes

Interpretations to avoid

- Do not treat a normal total IgG level as proof of normal antigen-specific immunity in WAS.
- Do not assume that all A–T immune defects are strictly humoral: T-cell abnormalities may occur.
- Do not equate every acquired deficiency with low leukocyte production; Splenectomy is a clearance defect.
- Do not expand the brief HIV table entry into a full AIDS lecture within this topic.

Clinical reasoning: Phenotype → mechanism



Avoid overextending the source into unverified tests or management algorithms.

Synthesis: Four distinctions worth retaining

- WAS: X-linked WASP defect; Thrombocytopenia, eczema, infections; T-cell loss and abnormal antibody responses.
- A–T: Recessive ATM defect; Ataxia, telangiectases, impaired switched antibodies, lymphoma risk.
- Secondary disorders are common and are usually recognized in a relevant systemic or treatment context.
- The dominant immune mechanism differs substantially across acquired causes.

Reference and source boundary

Primary text	Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
Direct section	Chapter 6, “Immunodeficiencies Associated With Systemic Diseases,” p. 218.
Grouped subsection	“Secondary Immunodeficiencies,” pp. 218–219, including Table 6.13.
Evidence limitation	Source Markdown available; original PDF pages and photographic figures were not supplied.