

Infections in People With Immunodeficiencies

Pathogenesis • immune-defect patterns • clinicopathologic correlations

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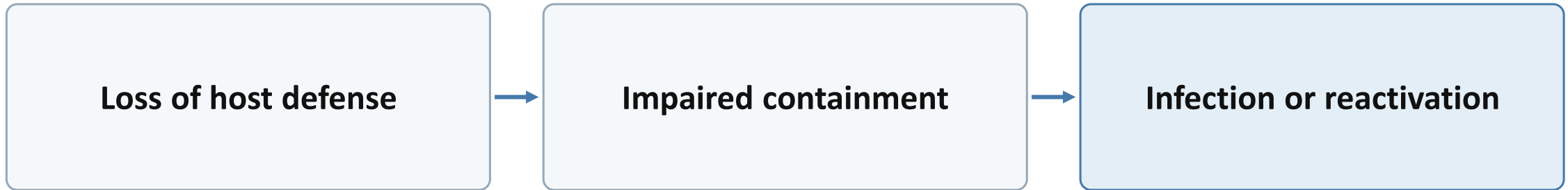
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Learning outcomes

- Explain how loss of a defined defense changes infection susceptibility.
- Link inherited defects to characteristic microbial vulnerabilities.
- Analyze acquired immune deficits, reactivation, and nonimmune susceptibility.
- Interpret clinical presentations using immune mechanism rather than organism lists.

Why immunodeficiency changes infection risk



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- Impaired innate or adaptive immunity permits infections that effective host defenses usually control.
 - Defects may be inherited or acquired; The affected component determines the vulnerability.
 - Infection may represent a new exposure or reactivation of a previously contained organism.

Defense is distributed across distinct layers

Barrier integrity

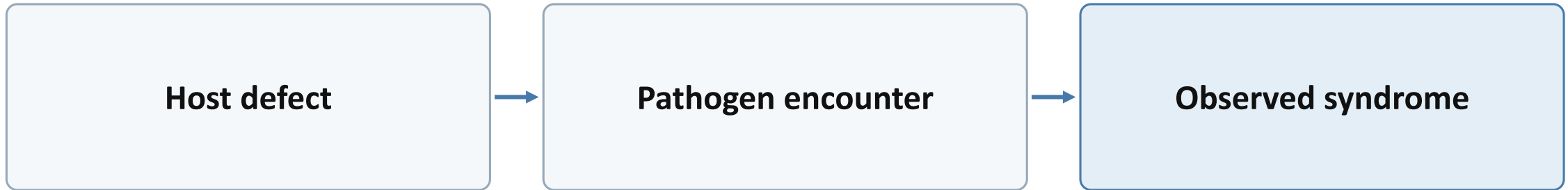
Phagocyte killing

Complement activity

T-cell / B-cell responses

- Physical barriers reduce microbial access to tissues.
- Phagocytes and complement provide rapid innate protection.
- B-cell antibodies aid neutralization and opsonization; T cells coordinate cellular defense.

An immune deficit predicts—but does not dictate—the pathogen



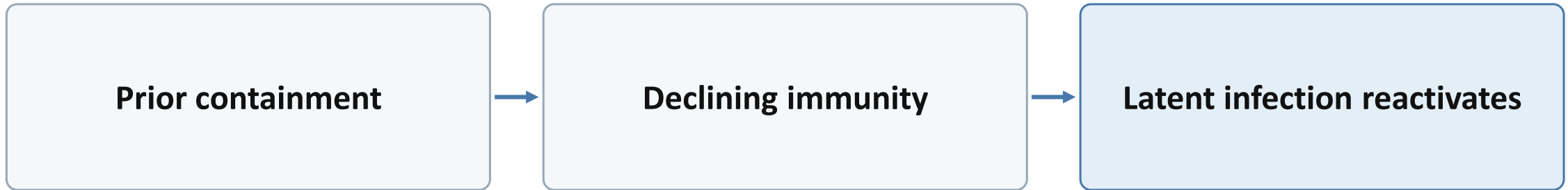
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- The clinical pattern reflects both the defect and the microbial exposure.
 - Innate defects favor infections requiring phagocytic or complement-mediated clearance.
 - Adaptive defects may compromise antibodies, cellular immunity, or both.
 - Nonimmune injuries can produce similar susceptibility without a primary immune defect.

Primary versus secondary immunodeficiency

Primary / inborn	Secondary / acquired
Genetic defect in immune pathway	Disease, infection, treatment or malnutrition
Frequently recognized in early life	May arise at any age
Examples: CGD, SCID, BTK deficiency	Examples: HIV, leukemia, chemotherapy

- Primary defects arise from inherited abnormalities of immune development or function.

New infection versus reactivation



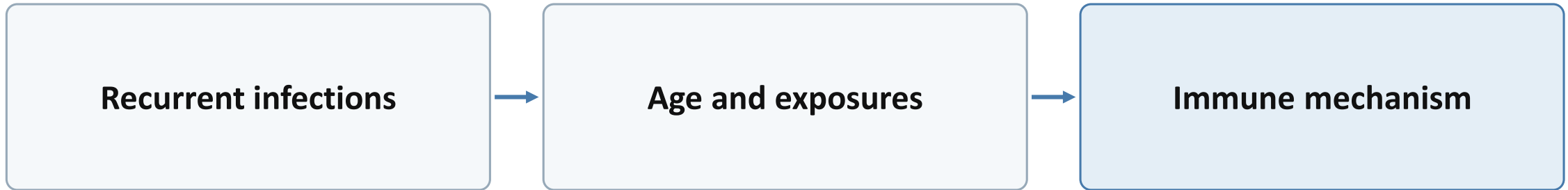
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- New infection follows acquisition of an organism that breaches inadequate defenses.
 - Reactivation follows loss of control over organisms persisting after an earlier exposure.
 - Herpesviruses and *Mycobacterium tuberculosis* are textbook examples of reactivation.

Pattern recognition begins with the impaired function

Predominant vulnerability	Immune component to consider
Pyogenic bacterial infections	Phagocytes, complement or antibodies
Viral and fungal infections	T-cell / combined immunity
Recurrent Neisseria	Terminal complement

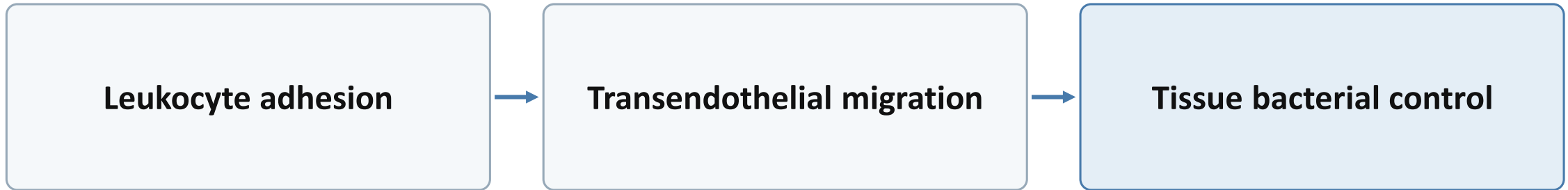
- Recurrent pyogenic infections suggest insufficient phagocyte, complement or antibody function.

Age at recognition can help localize a defect



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- Many inherited immune deficiencies become evident during infancy or childhood.
 - Some humoral defects appear after maternally acquired immunoglobulin declines.
 - Acquired causes should be sought when susceptibility develops in an appropriate clinical context.

Leukocyte migration is essential for tissue protection



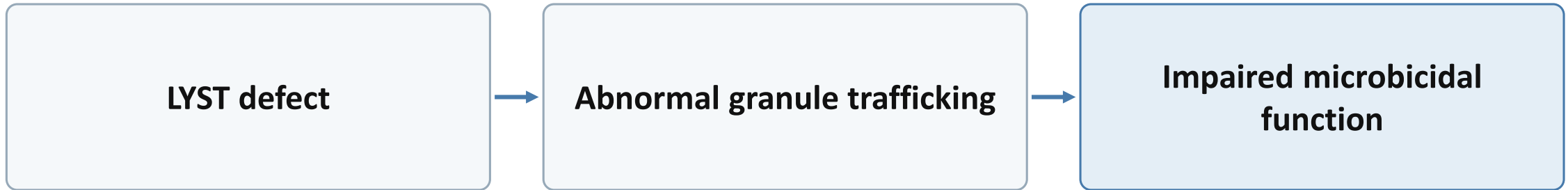
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- Neutrophils must adhere to endothelium and migrate into infected tissue.
 - Leukocyte adhesion deficiency disrupts this recruitment step.
 - The result is susceptibility to recurrent, sometimes life-threatening bacterial infections.

Leukocyte adhesion deficiencies: Two distinct defects

LAD type 1	LAD type 2
β 2 integrin chain defect	Fucosyltransferase-related defect
Defective stable adhesion	Defective selectin ligand production
Bacterial infection susceptibility	Bacterial infection susceptibility

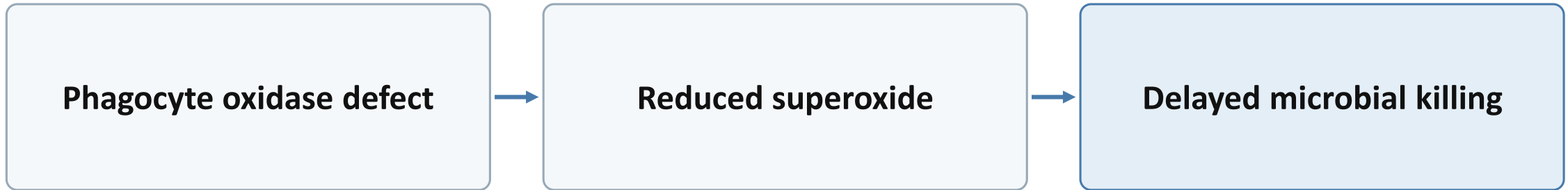
- Type 1 involves the β 2 chain shared by LFA-1 and Mac-1 integrins.

Chédiak–Higashi: Impaired vesicle trafficking



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- Defective LYST-associated lysosomal trafficking disrupts phagolysosome function.
 - Neutropenia, abnormal degranulation and delayed microbial killing contribute to infection.
 - Giant leukocyte granules coexist with albinism, neurologic and bleeding manifestations.

Chronic granulomatous disease: An oxidative burst defect



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- Inherited phagocyte oxidase defects prevent effective superoxide generation.
 - Neutrophils ingest organisms but have impaired oxygen-dependent killing.
 - Recurrent bacterial infection and macrophage-rich granulomatous inflammation follow.

CGD inheritance reflects oxidase subunits

Genetic example	Affected oxidase component
X-linked CGD	gp91phox, membrane component
Autosomal recessive CGD	p47phox, cytoplasmic
Autosomal recessive CGD	p67phox, cytoplasmic

- The common X-linked form affects the membrane component gp91phox.

Why granulomas form in CGD



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- Failure of initial neutrophil killing permits persistent infection.
 - Macrophages accumulate and become activated in a later attempt at containment.
 - The resulting granulomas express chronic inflammation, not adequate bacterial eradication.

Patterned innate sensing: TLR signaling

Innate sensing defect	Illustrative consequence
TLR3	Herpes simplex encephalitis
MyD88	Severe bacterial infection / pneumonia

- TLR3 senses viral RNA; Defects are associated with recurrent herpes simplex encephalitis.

Interleukin-12–interferon- γ axis



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- IL-12 promotes Th1 responses; IFN- γ activates antimicrobial defenses.
 - Inherited defects in IL-12 or IFN- γ receptors impair protection against intracellular microbes.
 - Environmental mycobacteria of low virulence can then cause disease.

Type I interferons restrict viral infection



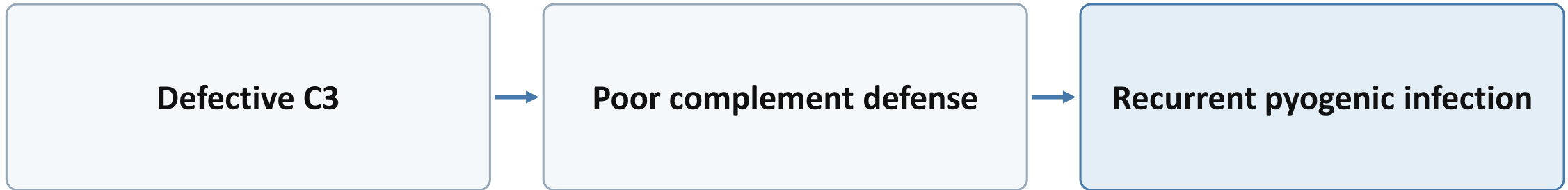
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- Type I interferons participate in antiviral host defense.
 - Mutations affecting their function, or acquired antibodies against them, can increase viral susceptibility.
 - The source identifies severe COVID-19 among associated clinical infections.

Complement contributes three forms of defense



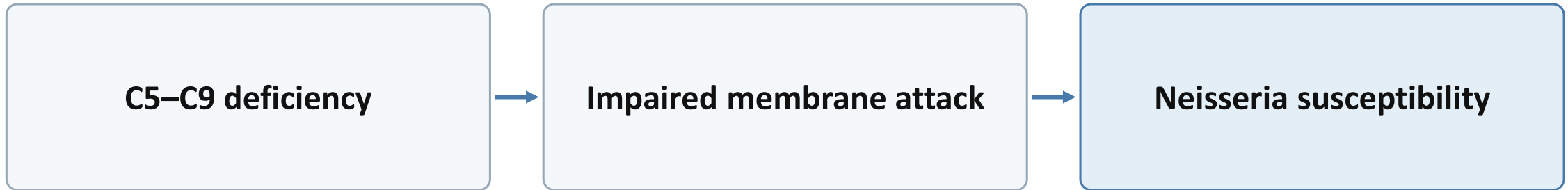
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- Early pathway proteins initiate complement activation.
 - C3 participates in shared central complement functions, including opsonization.
 - C5–C9 assemble the membrane attack complex that lyses susceptible organisms.

C3 deficiency compromises multiple complement functions



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- C3 acts downstream of both classical and alternative pathways.
 - Deficiency permits serious, recurrent pyogenic infections.
 - Immune complex–associated glomerulonephritis may also occur.

Terminal complement deficiency favors *Neisseria*



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- Deficiency of any terminal component C5 through C9 impairs membrane attack complex formation.
 - Recurrent meningococcal or gonococcal infection is characteristic.
 - The organism pattern points toward a lytic complement defect.

Different complement deficiencies give different clues

Affected segment	Reported infection association
Early classical (C2/C4)	Variable bacterial / viral infections
Alternative (properdin / factor D)	Recurrent pyogenic infections
Central C3	Serious recurrent pyogenic infections
Terminal C5–C9	Recurrent Neisseria

- C2 or C4 deficiency may cause infection or immune dysregulation; Some carriers remain asymptomatic.

A complement clue must be interpreted cautiously

- A single episode of bacterial infection does not establish complement deficiency.
- Several C2/C4-deficient individuals have no infectious phenotype.
- The recurring organism, severity and clinical context matter more than any isolated association.

Adaptive immune defects overlap in practice

B-cell / antibody arm

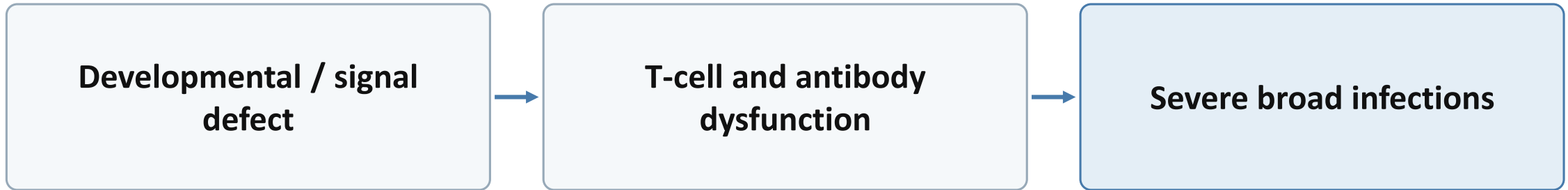
T-cell cellular arm

T-cell help for B cells

Combined immune deficiency

- B lymphocytes mediate antibody production; T lymphocytes mediate cellular responses and provide B-cell help.
- Severe T-cell deficits commonly diminish antibody responses as well.
- Thus clinically 'T-cell' and 'combined' immunodeficiencies are not always separable by presentation.

SCID is a failure of both adaptive arms



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- Severe combined immunodeficiency (SCID) includes several genetically distinct disorders.
 - The common phenotype is profound compromise of cellular and humoral immunity.
 - Infants are vulnerable to multiple unrelated pathogen groups.

SCID: Early clinical pattern

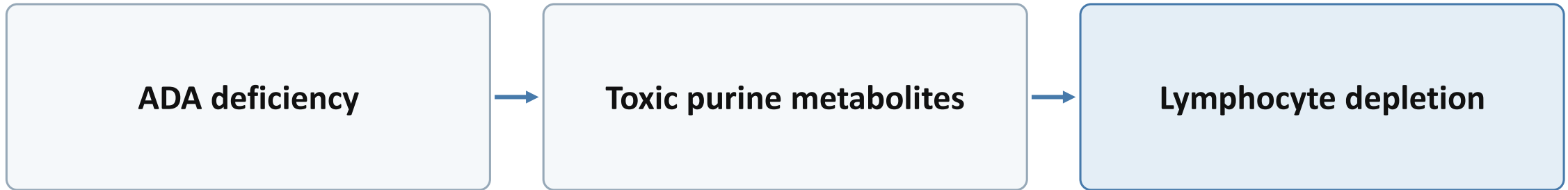
- Oral candidiasis (thrush) is a prominent early manifestation.
- Extensive diaper rash, recurrent infection and failure to thrive may coexist.
- A morbilliform neonatal rash can reflect maternal T-cell engraftment with graft-versus-host injury.

X-linked SCID: Cytokine receptor signaling fails



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- Mutations affect the common γ -chain (γ_c) shared by several cytokine receptors.
 - Loss of IL-7 receptor signaling markedly impairs T-cell development.
 - IL-15 signaling deficiency also frequently reduces NK-cell development; B cells can persist but function poorly.

ADA deficiency: Metabolic toxicity to lymphocytes



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- Autosomal recessive adenosine deaminase deficiency is an important form of SCID.
 - Accumulation of deoxyadenosine derivatives, including deoxy-ATP, is proposed to injure developing lymphocytes.
 - T-cell numbers may be reduced more profoundly than B-cell numbers.

SCID may arise from receptor assembly or downstream signaling

Defect	Key functional consequence
RAG / receptor recombination	Failure of TCR and Ig gene rearrangement
JAK3	Loss of common γ -chain receptor signaling
TCR pathway components	Impaired T-cell activation / maturation

- RAG-related defects prevent antigen-receptor gene rearrangements needed for T- and B-cell development.

SCID-associated infections span multiple organism groups

Organism group	Examples described in SCID
Fungal / opportunistic	Candida; Pneumocystis
Viral	CMV; varicella
Bacterial	Pseudomonas and other bacteria

- The Robbins examples include *Candida albicans* and *Pneumocystis jirovecii*.

SCID morphology: Hypoplastic lymphoid organs

Small, lymphocyte-poor thymus

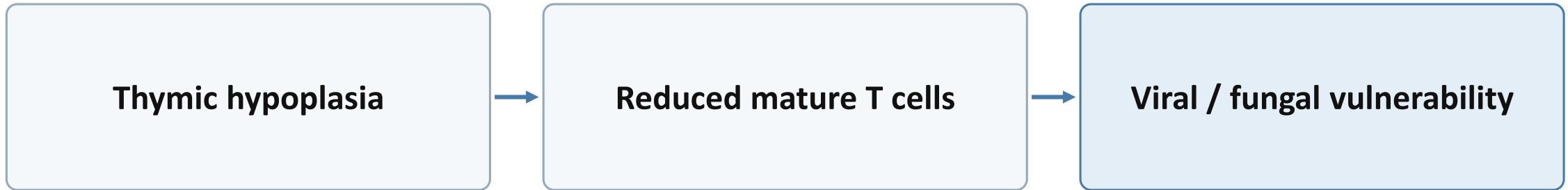
T-zone depletion

Variable B-zone depletion

Loss of normal lymphoid architecture

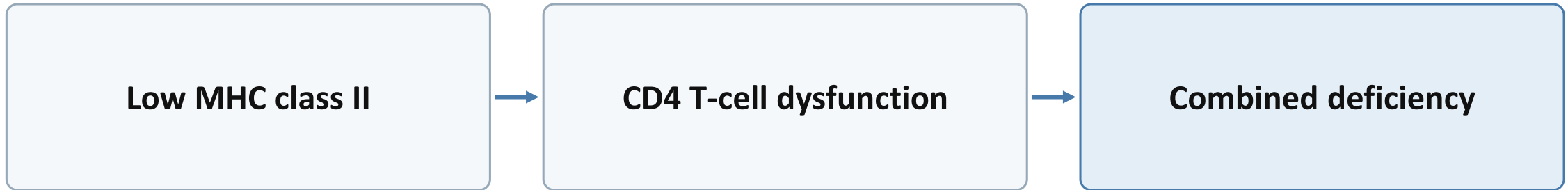
- The thymus is small and lymphocyte-poor in common γ c- and ADA-related SCID.
- X-linked SCID may show immature-appearing thymic epithelial lobules.
- Lymph nodes and other lymphoid tissue exhibit depletion of T-cell and sometimes B-cell zones.

Thymic hypoplasia isolates a T-cell maturation problem



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- DiGeorge syndrome arises from abnormal developmental formation of thymic structures.
 - Reduced thymic T-cell maturation weakens defenses against some viral and fungal infections.
 - Loss of T-cell zones in nodes and spleen may be seen; Immunoglobulin levels vary with severity.

MHC class II deficiency impairs CD4 T-cell development



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- Bare lymphocyte syndrome may follow defects in transcriptional control of MHC class II genes.
 - Without MHC class II, CD4 T-cell maturation and activation fail.
 - Defective T-cell help also impairs B-cell responses, producing combined deficiency.

Antibody deficiency produces recognizable infection patterns

Opsonization

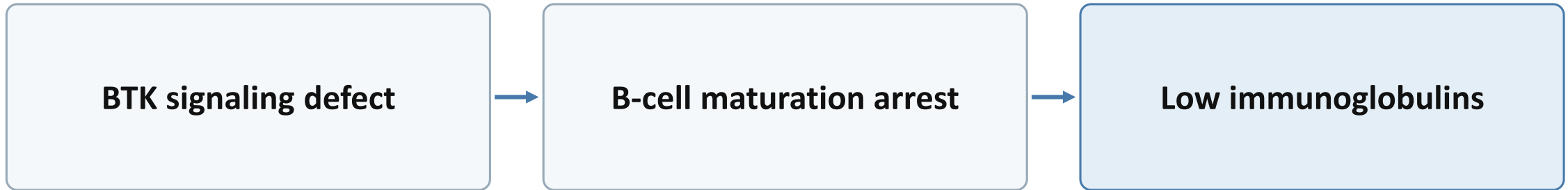
Viral neutralization

Mucosal IgA

B-cell help / class switching

- Antibodies promote opsonization and phagocytic clearance of bacteria.
- Neutralizing antibodies help prevent some viral infections and dissemination.
- Secretory IgA is particularly important at mucosal surfaces.

X-linked agammaglobulinemia: Blocked B-cell maturation



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- BTK mutations arrest development of pre-B cells into mature B cells.
 - Peripheral B cells and circulating immunoglobulins are profoundly reduced.
 - Recurrent infections typically become apparent as maternal Ig protection wanes.

XLA: Bacterial and nonbacterial vulnerabilities

Organism / group	Why it matters
Encapsulated / pyogenic bacteria	Reduced antibody opsonization
Enteroviruses	Impaired neutralization
Giardia lamblia	Insufficient mucosal antibody defense

- Typical respiratory pathogens include *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus*.

XLA morphology mirrors the absent mature B-cell pool

Small germinal centers

Sparse or absent plasma cells

Low mature B cells

Relatively preserved T cells

- Germinal centers in lymph nodes, Peyer patches and tonsils are underdeveloped.
- Plasma cells are absent or markedly depleted across tissues.
- T-cell-mediated responses are relatively normal.

CVID: B cells may be present but ineffective



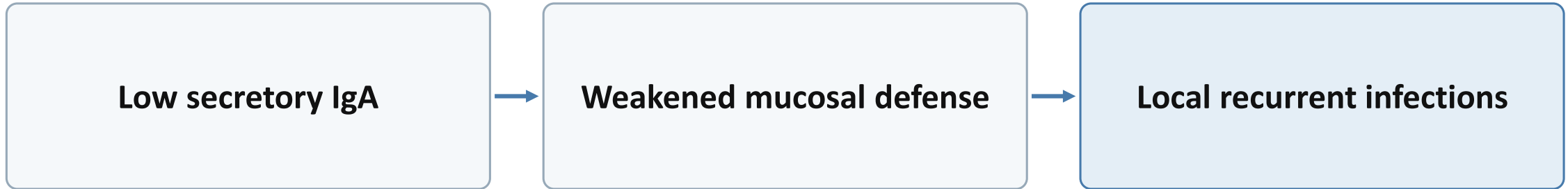
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- Common variable immunodeficiency has heterogeneous mechanisms and hypogammaglobulinemia.
 - Circulating B-cell numbers are often preserved, but plasma-cell differentiation is impaired.
 - Recurrent sinopulmonary pyogenic infections and Giardia-related diarrhea are typical.

XLA and CVID differ in B-cell maturation stage

Feature	XLA	CVID
B-cell count	Markedly reduced	Often near normal
Principal block	Early maturation	Plasma-cell differentiation / function
Germinal centers	Underdeveloped	May be hyperplastic
Infection pattern	Sinopulmonary; enterovirus; Giardia	Sinopulmonary; Giardia; some viral

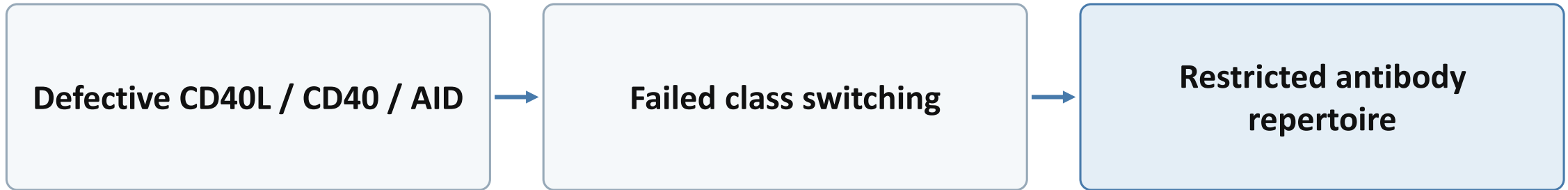
- XLA is an early, BTK-related arrest with few mature B cells.

Selective IgA deficiency exposes mucosal surfaces



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- Failure to generate IgA-producing plasma cells lowers serum and secretory IgA.
 - Most affected individuals have no symptoms.
 - Symptomatic patients may develop recurrent respiratory, gastrointestinal and urogenital infection.

Hyper-IgM syndrome: Class switching is defective



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- IgM is present, whereas IgG, IgA and IgE are deficient.
 - CD40L deficiency in helper T cells is a common X-linked mechanism.
 - Other cases involve CD40 or activation-induced cytidine deaminase (AID).

CD40–CD40L also links antibody and macrophage defense



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- CD40L on activated CD4 T cells engages CD40 on B cells and antigen-presenting cells.
 - This interaction supports antibody class switching and affinity maturation.
 - It also enhances microbicidal activity of macrophages: Loss can therefore impair more than antibodies.

X-linked lymphoproliferative disease: EBV is a clue



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- SAP-associated signaling defects impair NK/T-cell responses to Epstein–Barr virus.
 - Affected patients may develop fulminant mononucleosis and B-cell lymphoproliferation.
 - This illustrates a narrowly patterned pathogen association despite broader immune signaling changes.

Th17 response defects affect mucosal and skin defense



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- Inherited defects of Th17 responses are associated with chronic mucocutaneous candidiasis.
 - Bacterial skin infections may also recur.
 - The infection phenotype directs attention to local barrier-associated lymphocyte responses.

Wiskott–Aldrich: Combined clinical clues

Thrombocytopenia

Eczema

Infections

WASP-related immune defect

- The core phenotype includes thrombocytopenia, eczema and recurrent infection.
- WASP defects alter cytoskeleton-linked immune signaling and cellular responses.
- Peripheral T-cell depletion and poor antibody responses contribute to infection susceptibility.

Ataxia–telangiectasia: DNA repair and immune function



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- ATM deficiency causes impaired DNA-damage responses and disordered immune development.
 - Isotype-switched antibody deficiencies, especially IgA and IgG2, may occur.
 - Bacterial upper and lower respiratory infections are prominent among manifestations.

Immune dysregulation and infection may coexist



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- Some primary immune regulatory disorders cause autoimmunity, infection susceptibility and lymphoproliferation.
 - Defects may change cytokine signaling or regulatory T-cell function.
 - Clinical autoimmunity should not automatically be interpreted as intact antimicrobial immunity.

Secondary deficits arise through several mechanisms

Marrow impairment

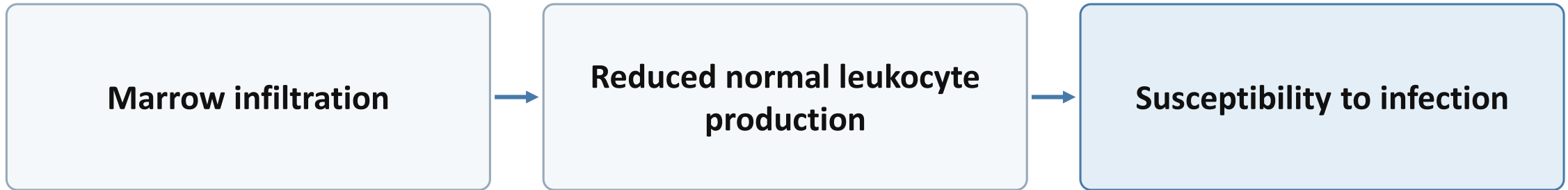
Drug suppression

Infection-associated loss

Nutritional / age effects

- Bone marrow infiltration or injury reduces generation of immune cells.
- Immunosuppressive drugs interfere with lymphocyte and other immune responses.
- Infection, malnutrition, aging or systemic disease can also reduce host defense.

Leukemia can suppress hematopoietic defense



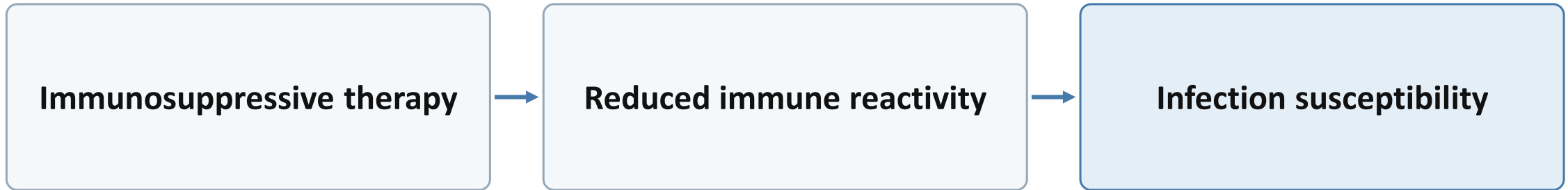
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- Infiltration of bone marrow by malignant cells can impair normal blood-cell production.
 - Reduced functional leukocyte output diminishes protection against infection.
 - This is acquired immunodeficiency arising from another disease process.

Cancer therapy may diminish host immunity



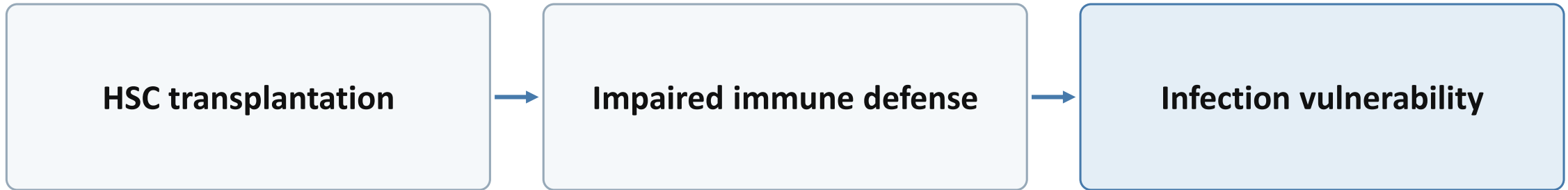
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- Chemotherapy and radiation therapy can injure hematopoietic and immune compartments.
 - Some cancer treatments produce lymphocyte depletion or suppress immune activity.
 - The timing and degree of immunosuppression influence infection vulnerability.

Drug immunosuppression is an intended effect with a cost



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- Autoimmune disease treatments suppress harmful immune activity but may weaken antimicrobial defense.
 - Solid-organ transplant recipients often require immunosuppressive drugs to prevent graft rejection.
 - Suppressing immunity against host or graft antigens can simultaneously expose patients to infections.

Hematopoietic stem cell transplantation changes defense



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- The source includes hematopoietic stem cell transplantation among contexts of acquired immunodeficiency.
 - The immune compartment may be quantitatively or functionally impaired in the transplantation setting.
 - The transplantation context must be considered when interpreting a new infection.

HIV-related immune suppression is a central example



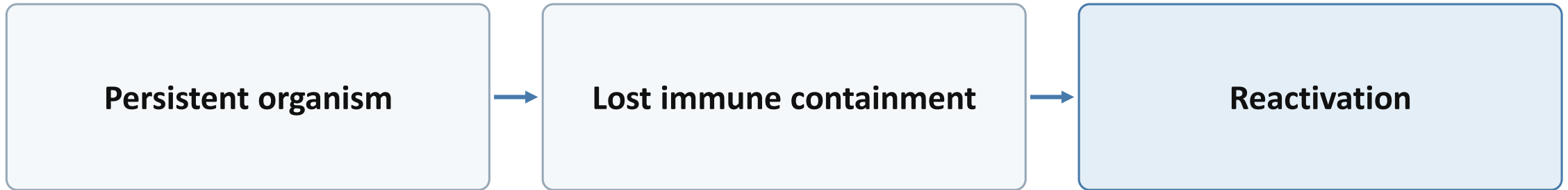
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- HIV infection causes acquired immunodeficiency syndrome (AIDS).
 - AIDS features profound immunosuppression and susceptibility to opportunistic infections.
 - Tumors and neurologic manifestations also contribute to the pathologic spectrum of AIDS.

Different acquired causes can converge on one phenotype

Context	Major immune disturbance
HIV/AIDS	Virus-associated immunosuppression
Leukemia	Bone marrow infiltration / reduced output
Cancer therapy	Marrow / immune injury
Transplant treatment	Drug-mediated immune suppression

- HIV-related immunodeficiency follows an infectious cause.

Why suppressed immunity reactivates latent pathogens



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- Some microbes persist after primary infection despite apparent clinical recovery.
 - Effective immunity prevents their renewed proliferation.
 - Reduced surveillance can release this containment, producing reactivated infection.

Herpesviruses and tuberculosis illustrate latency

Latent example	Event when control declines
Herpesviruses	Viral reactivation
Mycobacterium tuberculosis	Reactivated mycobacterial infection

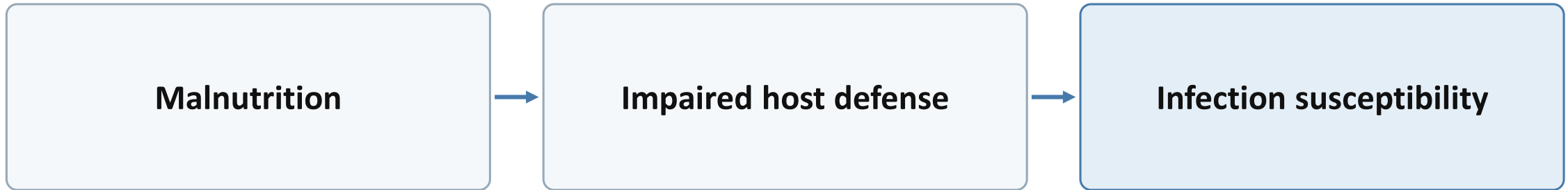
- Herpesviruses are among the latent infections capable of reactivation.

Immunosenescence contributes to acquired susceptibility



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- Host immune responses decline with aging.
 - The source links this age-related decline to increased infections in older adults.
 - Chronologic age is contextual information rather than a pathogen-specific diagnosis.

Malnutrition impairs antimicrobial defense



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- Inadequate nutrition can compromise immune defenses.
 - Malnutrition is included among causes of secondary immunodeficiency.
 - Nutritional and disease-related vulnerabilities may coexist and compound infection susceptibility.

Not all infection susceptibility is immune-cell failure

Mucociliary / epithelial function

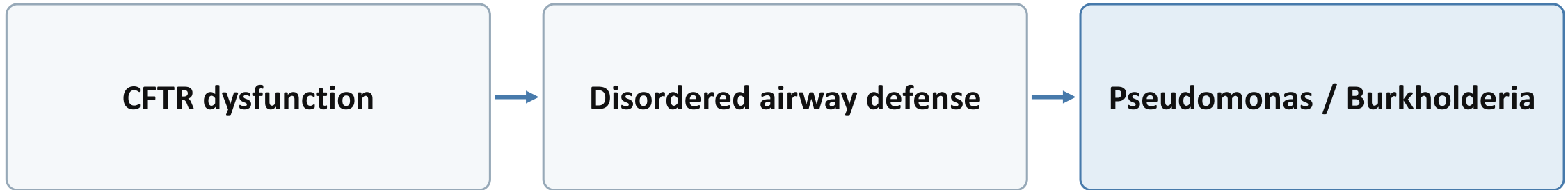
Splenic clearance

Skin barrier

Immune-cell function

- An intact immune system still depends on barriers, clearance mechanisms and organ function.
- Cystic fibrosis, sickle cell disease and burns are examples of nonimmune settings associated with infection.
- Identifying the damaged host function explains the organism association.

Cystic fibrosis: Altered airway host defense



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- A defective CF transmembrane conductance regulator underlies cystic fibrosis.
 - The source identifies *Pseudomonas aeruginosa* and *Burkholderia cepacia* as notable infections.
 - This exemplifies infection risk from abnormal organ function, not necessarily intrinsic leukocyte failure.

Sickle cell disease: Loss of splenic protection



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- Loss of functional splenic activity impairs protective host clearance.
 - *Streptococcus pneumoniae* is a highlighted infection in sickle cell disease.
 - A disease of erythrocytes can therefore present a major infectious vulnerability.

Burns: Disruption of the physical barrier



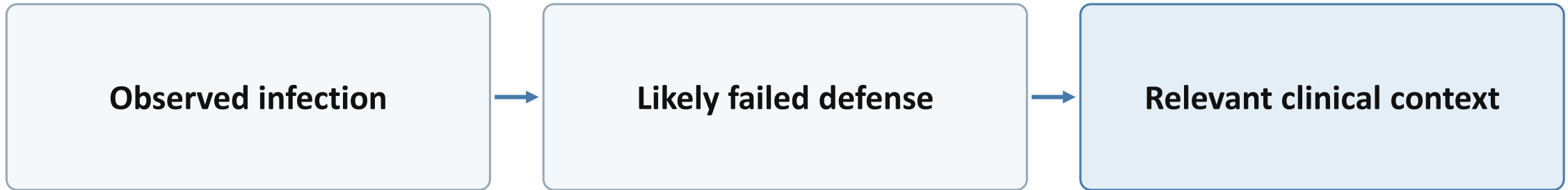
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- Severe burn injury disrupts the skin barrier that normally blocks microbial entry.
 - *Pseudomonas aeruginosa* is an example highlighted by Robbins.
 - The proximate defect is barrier failure rather than a defining inherited immunodeficiency.

The same organism can accompany different host defects

Clinical setting	Primary vulnerability
Cystic fibrosis	Disease-associated airway defense defect
Burn injury	Disrupted epithelial barrier
SCID	Severe combined immune deficit

- Pseudomonas appears in the source examples for burns, cystic fibrosis and SCID.

From infection phenotype back to mechanism



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- Define whether infections are recurrent, severe, persistent or reactivated.
 - Localize the defense component suggested by pathogen group and involved organ.
 - Review inherited conditions, treatments, malignant disease, nutrition and barrier injuries.

An infection association is not a diagnosis

Observed clue	Mechanistic possibilities
Recurrent bacterial respiratory infection	Antibody, phagocyte or other defenses
Severe herpes simplex encephalitis	TLR3-linked signaling defects
Recurrent Neisseria	Terminal complement deficiency
Candida + broad severe infections in infancy	SCID / combined defect

- Complement, phagocyte and antibody defects can all present with bacterial infection.

Lymphoid morphology can localize developmental failure

Condition	Source-described morphologic pattern
SCID	Hypoplastic thymus / T-cell zones
X-linked agammaglobulinemia	Poorly formed germinal centers; few plasma cells
CVID	Potentially hyperplastic germinal centers

- SCID can produce a small, lymphocyte-poor thymus and depleted lymphoid zones.

Application: Severe multisystem infection in infancy

CLINICAL CLUE

Infant with thrush, rash, poor growth and recurrent severe infections

MECHANISM TO RECOGNIZE

Consider SCID: Both cellular immunity and antibody responses are compromised.

- Illustrative case: An infant has thrush, extensive diaper rash and failure to thrive.
- Several organism groups cause recurrent, severe infections.
- The pattern is more consistent with combined than isolated humoral deficiency.

Application: Recurrent bacterial infection with granulomas

CLINICAL CLUE

Recurrent infection accompanied by macrophage-rich granulomas

MECHANISM TO RECOGNIZE

CGD: Phagocyte oxidase deficiency → inadequate oxidative microbial killing.

- Illustrative case: Recurrent bacterial infections occur in a child with granulomatous inflammation.
- A phagocyte oxidative burst disorder can explain failed early killing.
- Macrophage-rich granulomas develop during persistent microbial stimulation.

Application: Recurrent Neisseria infection

CLINICAL CLUE

Repeated episodes involving Neisseria species

MECHANISM TO RECOGNIZE

Terminal components C5–C9, required for the membrane attack complex.

- Illustrative case: Recurrent Neisseria meningitidis infections suggest a selective defect in serum bacterial lysis.
- Terminal complement activity is important in membrane attack complex formation.
- The association supports assessment of complement function rather than presuming an antibody defect.

Application: Pneumococcal infection in sickle cell disease

CLINICAL CLUE

Sickle cell disease with *Streptococcus pneumoniae* infection

MECHANISM TO RECOGNIZE

Functional asplenia / loss of splenic protection.

- Illustrative case: A patient with sickle cell disease develops invasive pneumococcal infection.
- The source associates this with loss of splenic function.
- This is a functional organ-defense problem, not necessarily a primary lymphocyte defect.

Synthesis: Four questions organize the topic

Defense function

Type of defect

New vs latent

Clinical context

- What defense normally prevents the organism from causing disease?
- Is that defense genetically defective, secondarily suppressed, or mechanically impaired?
- Is the event a new infection or reactivation of a latent organism?
- Which features of timing, pathogen and tissue response support the proposed mechanism?

Principal source and contextual sections

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 8, Infectious Diseases: Infections in People With Immunodeficiencies (p. 308).
- Chapter 6, Diseases of the Immune System: Immunodeficiency Diseases (pp. 213–219).
- Text derived from supplied project Markdown; original chapter PDF was not provided for page-image verification.