

Cytomegalovirus

Latency, tissue injury, congenital infection and immunosuppression

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

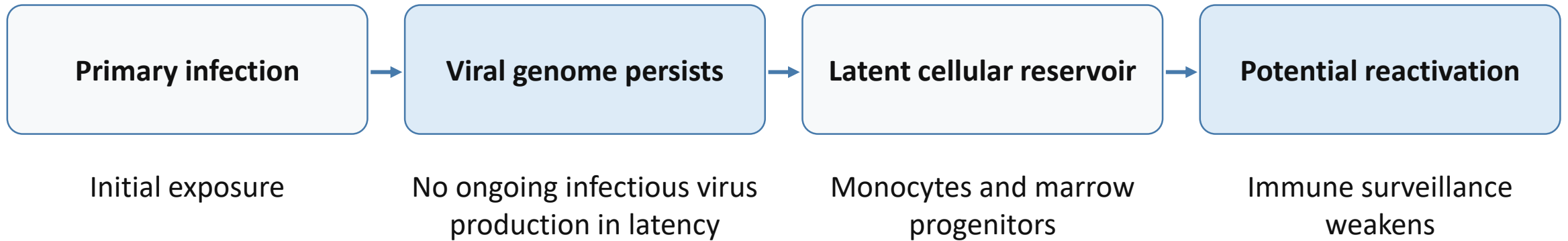
- Explain CMV latency and the importance of cellular immunity.
- Compare congenital, perinatal and postnatal transmission.
- Recognize cytomegalic cells and their characteristic inclusions.
- Link tissue tropism to organ injury and clinical syndromes.
- Select source-supported diagnostic approaches by clinical context.

CMV is a β -herpesvirus

- CMV belongs to the β subgroup of human herpesviruses.
- Herpesviruses produce primary infection followed by persistence and potential reactivation.
- CMV disease is unusually dependent on host age and immune status.
- Cellular and nuclear enlargement gives cytomegalovirus its name.

Virus class and host context both matter

Latency is persistence without infectious virion production



Persistent infection is distinct from continuously productive infection.

Immune status determines the clinical phenotype

Immunocompetent

Usually asymptomatic or mononucleosis-like

Congenital infection

May produce multi-organ injury and lasting deficits

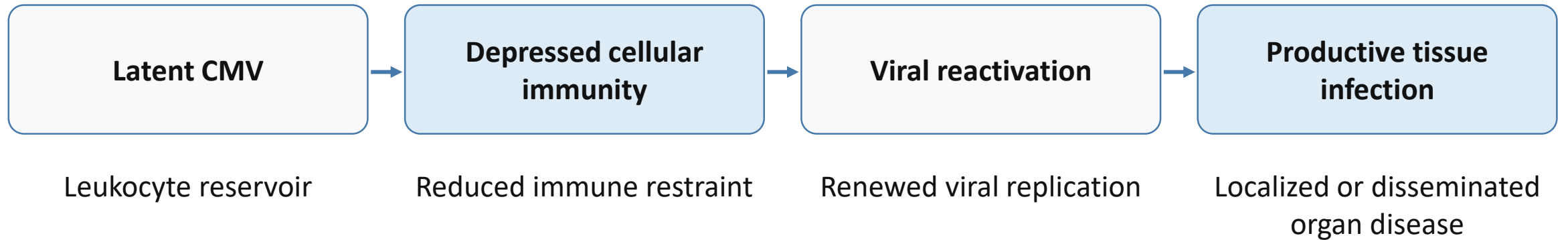
Immunosuppressed

May produce severe disseminated disease

CMV establishes latency in monocyte lineages

- The source identifies monocytes and their bone marrow progenitors as latent reservoirs.
- Latently infected leukocytes retain the virus long after initial illness.
- Symptomatic recovery therefore does not mean virologic eradication.
- Depression of cellular immunity enables reactivation.

Reactivation follows impaired cellular surveillance



The source identifies reactivation as a major pathway to disease in immunosuppressed hosts.

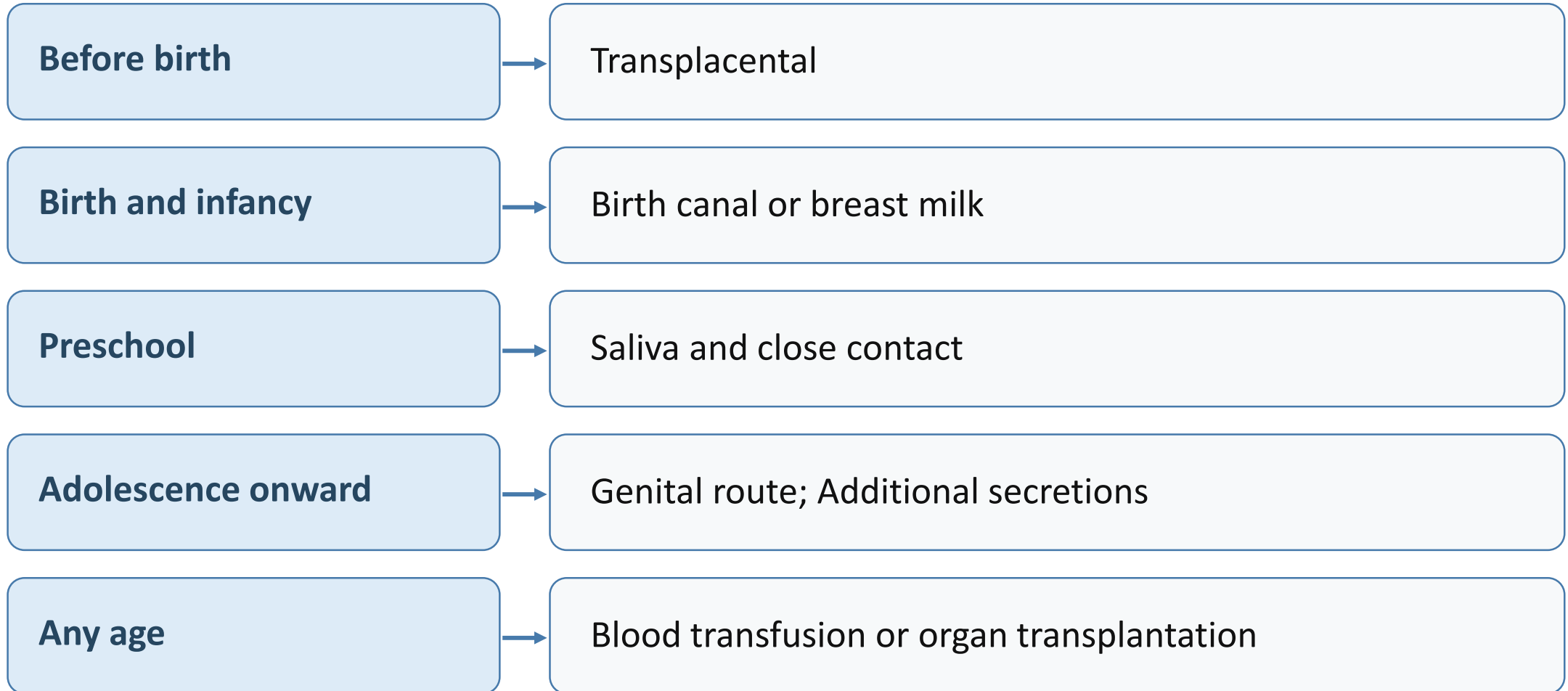
Primary infection, latency and reactivation differ

State	Viral behavior	Clinical implication
Primary infection	New acquisition of CMV	May be asymptomatic or cause illness
Latency	Genome persists without infectious virions	Ongoing lifelong reservoir
Reactivation	Replication resumes from latent infection	Major risk in impaired cellular immunity

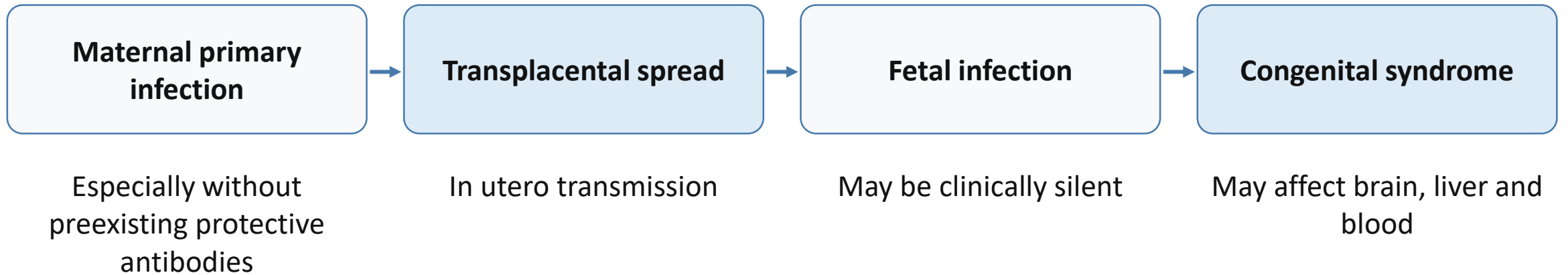
CMV persists after clinical recovery

- Most immunocompetent patients recover without lasting symptoms.
- CMV may continue to be excreted in body fluids for months or years.
- Seropositivity persists throughout life after infection.
- Persistence provides the biological basis for later reactivation.

Transmission routes change with age and exposure



Transplacental infection defines congenital CMV



Not every congenital infection is symptomatic at birth.

Perinatal acquisition is a distinct exposure window

- Exposure can occur to infected cervical or vaginal secretions during delivery.
- Breast milk can transmit CMV after birth.
- These routes differ from infection acquired across the placenta.
- Clinical outcomes are commonly milder because of maternal antibody protection.

Close-contact saliva transmission is important in preschool years

- CMV transmission through saliva occurs in young children, including daycare settings.
- Toddlers with CMV can readily transmit infection to parents.
- Asymptomatic infection does not imply absence of viral shedding.
- This setting connects early childhood infection with household transmission.

Genital and other routes contribute after adolescence

- The genital route is described as dominant after approximately age 15.
- Respiratory secretions and fecal–oral exposure are additional routes.
- The relative role of each route depends on age and exposure context.
- Transmission need not be associated with clinically apparent disease.

Transfusion and organ transplantation are iatrogenic routes

- Transfusion and transplanted organs may transmit CMV at any age.
- A solid-organ recipient may acquire CMV from an infected donor organ.
- Iatrogenic exposure intersects with treatment-related immune suppression.
- New infection and reactivation are both relevant in transplant settings.

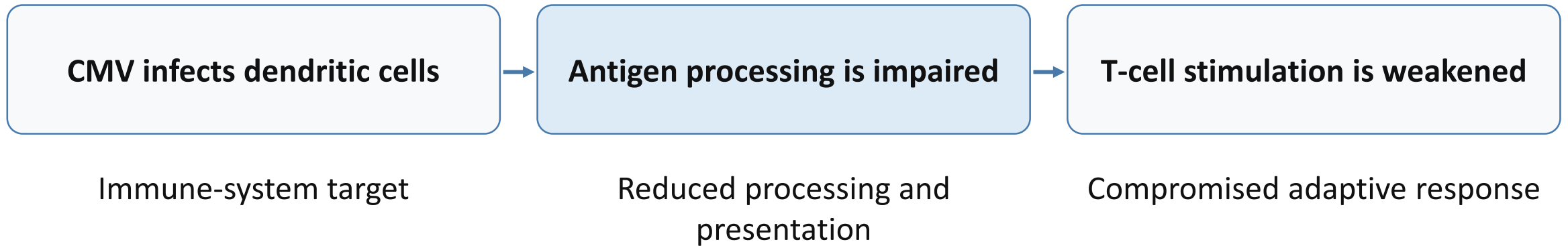
Congenital, perinatal and later exposure: Key distinctions

Context	Main route	Important clinical implication
Congenital	Transplacental	Potential fetal and developmental injury
Perinatal	Delivery secretions / breast milk	Often asymptomatic with maternal antibodies
Childhood / adult	Saliva, genital, other secretions	Commonly silent or mononucleosis-like
Iatrogenic	Organ transplant / blood product	Severe disease when host is immunosuppressed

Cell-mediated immunity is central to CMV control

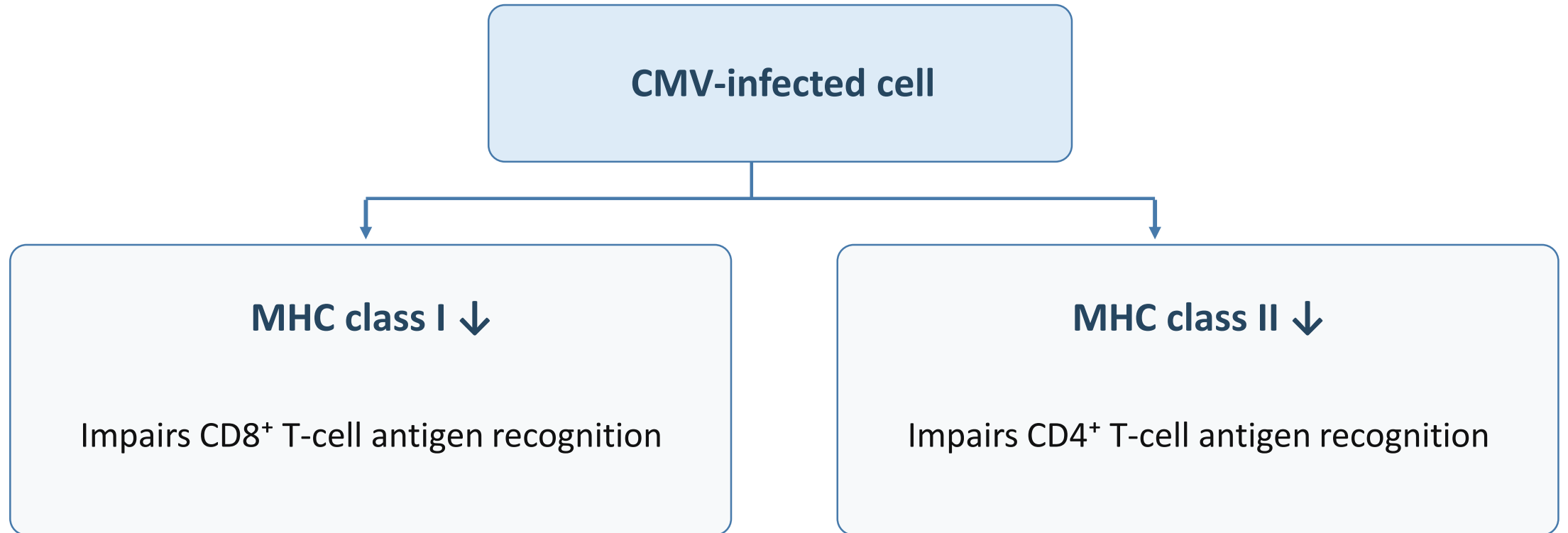
- CMV-specific T-cell responses are important effectors against infected cells.
- The source emphasizes CD8⁺ T lymphocytes as a major effector response.
- CD4⁺ T cells, $\gamma\delta$ T cells and natural killer cells may also contribute.
- Loss of this coordinated response permits reactivation and organ disease.

Dendritic-cell infection impairs antigen presentation



CMV interferes with the initiation of the host antiviral response.

CMV down-modulates MHC class I and II expression

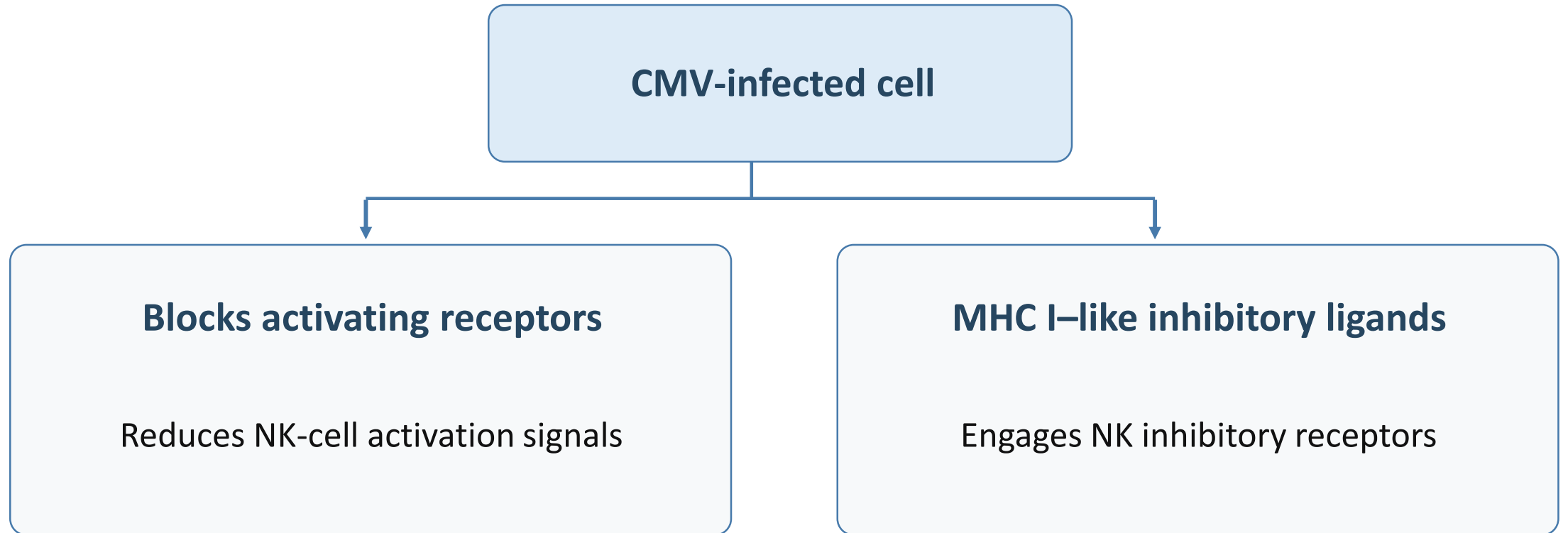


CMV undermines antigen display to both major T-cell compartments.

Viral homologues mimic host immunoregulatory proteins

- CMV produces homologues of tumor necrosis factor receptor superfamily members.
- It also expresses an interleukin-10 homologue.
- MHC class I homologues add another layer of immune deception.
- These are viral immune-evasion products, not evidence that infection has been cleared.

Natural killer cell detection is also evaded



The virus counters NK-mediated detection while also reducing MHC expression.

Viral Fcγ-binding proteins interfere with IgG defense

Viral Fcγ-binding glycoproteins

CMV-encoded immune-evasion proteins



Interference with host Fcγ receptor function

Compete with normal Fcγ-dependent pathways



Inhibition of IgG-mediated immunity

Antibody response becomes less effective

This mechanism targets antibody effector function rather than antigen presentation.

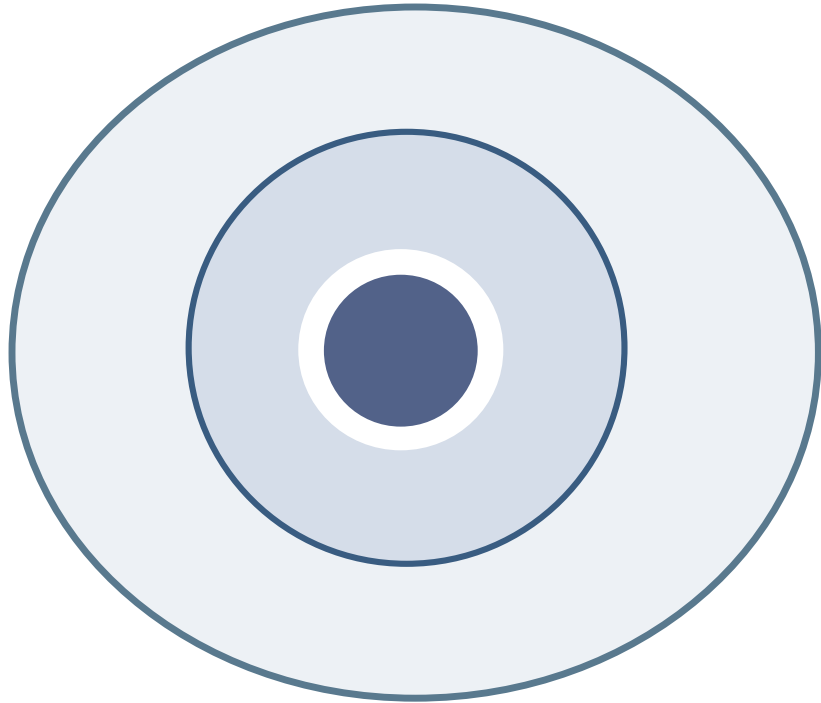
CMV hides from and suppresses immune responses

Targeted defense	CMV strategy	Consequence
Antigen presentation	Dendritic-cell dysfunction; MHC I/II down-modulation	Less effective T-cell recognition
NK surveillance	Blocked activation and enhanced inhibitory engagement	Reduced NK-cell elimination
Antibody effector pathways	Viral Fcγ-binding glycoproteins	Impaired IgG-mediated defense
Immunoregulatory signaling	Viral cytokine/receptor homologues	Further immune modulation

Cytomegaly is the defining cytopathic change

- Infected cells may become strikingly enlarged, often around 40 μm in diameter.
- Both the cytoplasm and nucleus expand and may appear pleomorphic.
- The distinctive appearance is cytopathic rather than a neoplastic diagnosis.
- Histologic interpretation requires recognizing the characteristic viral inclusions.

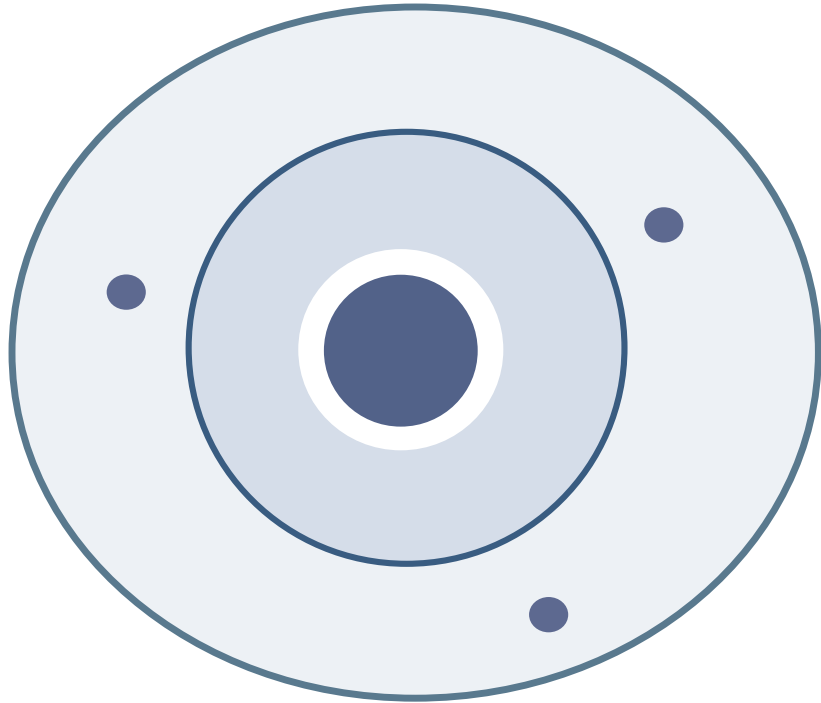
“Owl’s-eye” nuclear inclusion: Defining features



Schematic — not a histologic specimen

- A prominent basophilic inclusion lies within an enlarged nucleus.
- The inclusion may occupy roughly half the nuclear diameter.
- A clear halo separates the inclusion from the nuclear membrane.
- The term “owl’s eye” refers to the nuclear appearance.

Cytoplasmic inclusions accompany nuclear inclusions



Schematic — not a histologic specimen

- Smaller basophilic inclusions can occur in the cytoplasm.
- The cytoplasmic changes may be less sharply outlined than the nuclear inclusion.
- Both compartments should be examined in suspicious enlarged cells.
- The described Robbins lung figure depicts nuclear and cytoplasmic inclusions.

CMV infects multiple tissue compartments

Glandular tissues

Parenchymal epithelial cells

Brain

Neurons

Lung

Macrophages, epithelial and endothelial cells

Kidney

Tubular epithelium and glomerular endothelium

The pulmonary cellular targets explain varied histology

- In the lung, CMV may involve alveolar macrophages.
- Epithelial cells and endothelial cells are also susceptible.
- Pulmonary disease can combine cytomegalic inclusions, interstitial inflammation and necrosis.
- The morphologic picture reflects infection across several resident cell compartments.

CMV can involve renal tubules and glomerular endothelium

Tubular epithelial cells

A parenchymal epithelial target

Glomerular endothelial cells

A vascular compartment target

Interpretive principle

Look for infected cells in more than one renal compartment

Focal necrosis may occur with little inflammation

- Focal necrosis in virtually any organ affected by CMV.
- Inflammatory infiltrates may be minimal despite direct viral injury.
- The degree of necrosis need not parallel a brisk inflammatory response.
- This morphologic mismatch is relevant when reading immunosuppressed tissue biopsies.

Recognize a cytomegalic cell systematically

1. Cellular scale

Identify an unusually enlarged cell



2. Nuclear change

Locate a large basophilic inclusion and clear halo



3. Cytoplasmic change

Look for additional smaller inclusions



Schematic reasoning aid; Not a substitute for a clinical histology section.

Congenital CMV has important population consequences

1 in 200

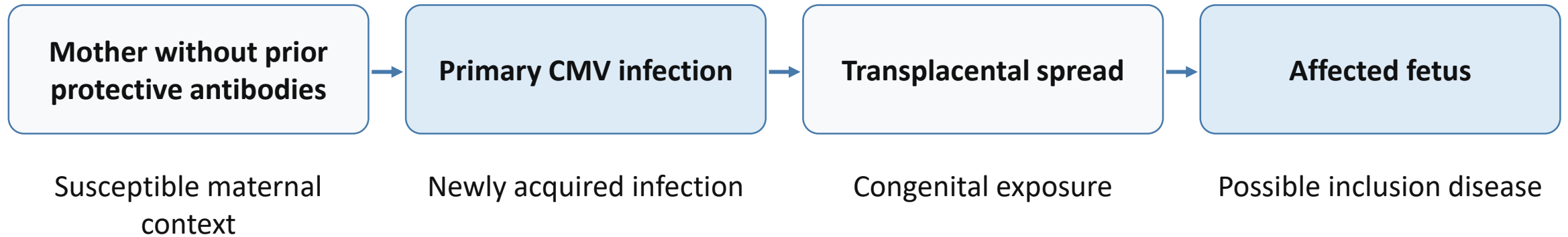
Babies born with congenital CMV

1 in 5

Affected babies with a long-term
health consequence

Approximate estimates reported in the supplied Robbins text; Not newly re-estimated.

Maternal primary infection may cause fetal CMV disease



The source particularly emphasizes primary maternal infection in classic severe congenital disease.

Congenital infection spans silent to severe disease

Asymptomatic at birth

Still at risk of later sequelae in some cases

Milder symptomatic disease Interstitial pneumonitis, hepatitis or hematologic disorder

Classic inclusion disease

Growth restriction, systemic injury and encephalitis

Classic congenital disease can involve several systems

Growth

Intrauterine growth restriction

Liver and spleen

Jaundice, hepatosplenomegaly

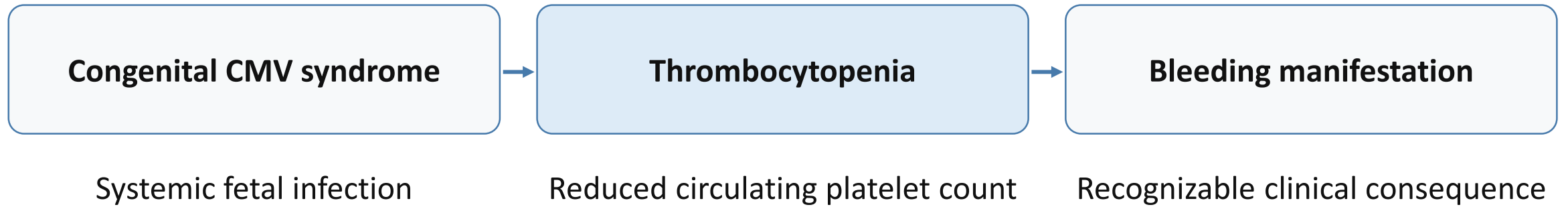
Hematologic

Anemia, thrombocytopenic bleeding

Central nervous system

Encephalitis and neurologic injury

Thrombocytopenia explains congenital bleeding



Anemia and jaundice may coexist with hematologic involvement.

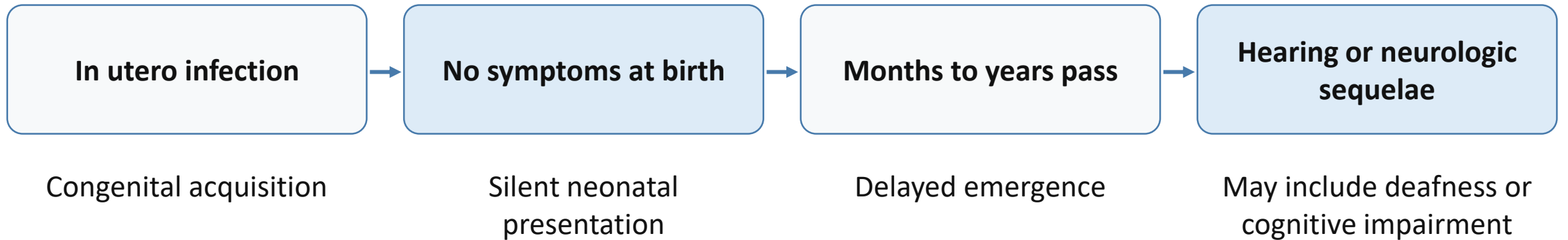
Congenital CNS involvement may be severe

- Encephalitis is part of the classic symptomatic syndrome.
- In fatal cases, the brain may be smaller than normal (microcephaly).
- Foci of intracranial calcification can be present.
- Structural brain injury relates to the risk of lasting neurologic impairment.

Surviving infants may have permanent impairments

- Hearing loss is a major long-term consequence.
- Intellectual disability and other neurologic deficits may persist.
- The severity of initial congenital disease is clinically important.
- Long-term impairment can outlast the period of acute infection.

Initially asymptomatic congenital CMV can declare later

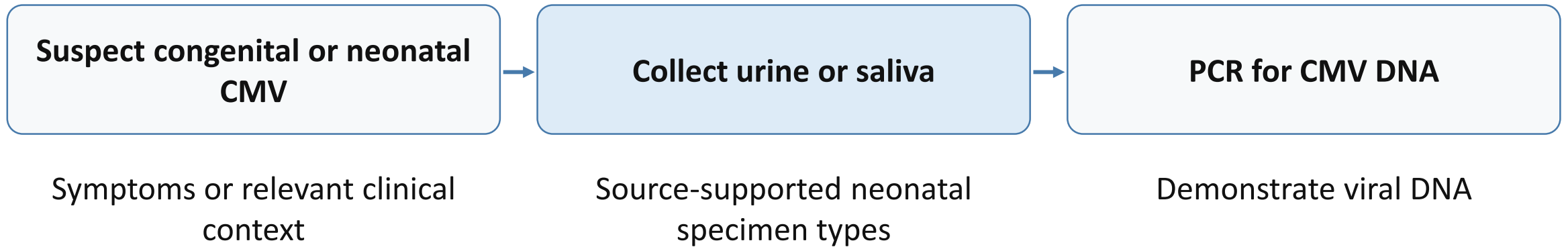


Absence of early clinical findings does not rule out late effects.

Milder congenital forms are not invariably harmless

- Congenital infection may present as interstitial pneumonitis.
- Hepatitis or hematologic manifestations are alternative presentations.
- Most infants with these milder forms recover.
- A minority may develop subsequent intellectual impairment.

Neonatal CMV is diagnosed using viral DNA detection



The excerpt does not specify diagnostic collection deadlines or test cutoffs.

Clinical exercise: Newborn with multi-system findings

Clinical vignette

An infant has intrauterine growth restriction, jaundice, hepatosplenomegaly and thrombocytopenia. Neuroimaging describes a small head size with intracranial calcifications.

- Which congenital viral infection best integrates these findings?
- Which specimen types are identified for neonatal PCR testing?
- Which long-term organ-system consequence is most important to anticipate?

Case reasoning: Congenital CMV inclusion disease

Syndrome recognition

The constellation supports classic symptomatic congenital CMV.

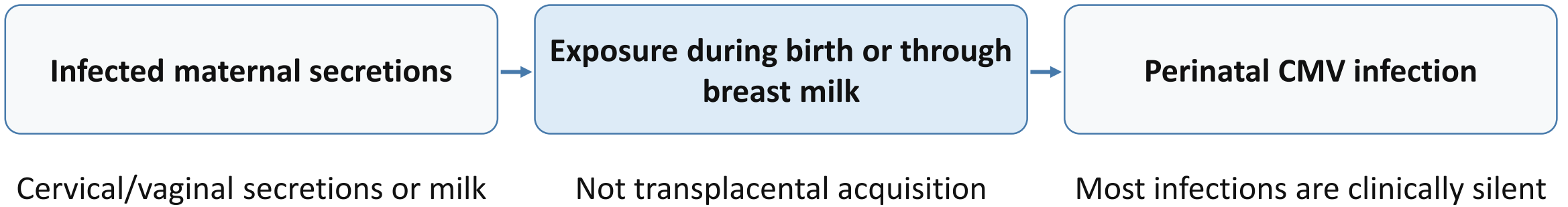
Test selection

Urine or saliva CMV DNA PCR.

Future consequences

Sensorineural hearing and neurologic deficits are major concerns.

Perinatal CMV is acquired during or after delivery



Perinatal and congenital infection are epidemiologically distinct.

Maternal antibodies often protect perinatally infected infants

- Maternal anti-CMV antibodies cross the placenta before delivery.
- These antibodies contribute to the usually asymptomatic perinatal course.
- Protection does not necessarily prevent acquisition or viral excretion.
- The source contrasts this pattern with severe infection from maternal primary CMV.

Perinatal infants may shed virus for a prolonged period

- Even symptom-free infants can continue to excrete CMV.
- Urine and saliva shedding may persist for months to years.
- Clinical well-being is not equivalent to immediate cessation of excretion.
- Longitudinal shedding helps explain transmission during early childhood.

Symptomatic perinatal CMV is less common

- Most infections acquired around birth are asymptomatic.
- Uncommonly, affected infants develop interstitial pneumonitis.
- Failure to thrive, rash and hepatitis are other reported manifestations.
- Some studies have reported subtle later hearing or cognitive effects.

Congenital versus perinatal CMV

Feature	Congenital	Perinatal
Acquisition	Across placenta before birth	Delivery secretions or breast milk
Maternal context	Primary maternal infection emphasized in severe disease	Maternal antibodies often protective
Presentation	Silent to severe multisystem syndrome	Usually silent; rare pneumonitis / hepatitis
Long-term issues	Hearing and neurologic impairment	Subtle effects reported in some studies

CMV infection is often silent in healthy hosts

- Most primary CMV infections in healthy children and adults cause no overt illness.
- The supplied source estimates global seroprevalence at about 80%.
- A highly prevalent persistent infection can therefore be clinically unrecognized.
- When symptomatic, a mononucleosis-like syndrome is the typical presentation.

Immunocompetent CMV may resemble mononucleosis

Systemic

Fever and lymphadenopathy

Peripheral blood

Atypical lymphocytosis

Liver

Hepatomegaly and abnormal liver tests

Typical outcome

Recovery without sequelae

CMV-associated hepatitis contributes to the mono syndrome

- Liver involvement may accompany the systemic febrile illness.
- Hepatomegaly and abnormal liver function tests are described.
- Hepatitis appears with atypical lymphocytosis and lymphadenopathy.
- The syndrome does not imply the severe disseminated disease seen in immunosuppressed patients.

Serology and lifelong positivity shape interpretation

- Serology as the diagnostic approach for CMV mononucleosis.
- Infected people remain seropositive for life.
- Seropositivity alone cannot establish that current tissue symptoms are due to active CMV.
- Persistent latent virus and prolonged shedding require clinical context.

Clinical severity changes with immune competence

Immunocompetent	Immunosuppressed
Usually asymptomatic	New infection or reactivation may be severe
Possible mononucleosis-like illness	Pneumonitis and colitis prominent
Generally recovers	Disseminated, life-threatening infection possible
Serology for mono presentation	Tissue assessment and DNA detection used

Transplant recipients are vulnerable to serious CMV

- Recipients of solid organs are at risk because cellular immunity is compromised.
- Donor organs may introduce CMV into an uninfected recipient.
- Reactivation of previously latent CMV is another pathway.
- CMV-specific cellular immunity is relevant in the stem-cell transplant setting.

Antiretroviral therapy changed CMV in HIV disease

- CMV was previously a leading opportunistic viral pathogen in AIDS.
- Serious CMV infection has decreased markedly with antiretroviral therapy.
- The source nevertheless describes CMV as a continuing contributor to HIV disease.
- Interpret the historical observation in the specific context of modern immune restoration.

Two pathways lead to infection in suppressed hosts

New CMV infection

For example, an infected donor organ



Latent CMV reactivation

Immune control of existing reservoir declines



Shared consequence

Productive infection with possible organ dissemination

Both routes must be considered in transplant and other suppressed populations.

Severe disseminated CMV favors lung and gut

Lungs

Pneumonitis; Potential respiratory failure

Gastrointestinal tract

Colitis, ulcers and necrosis

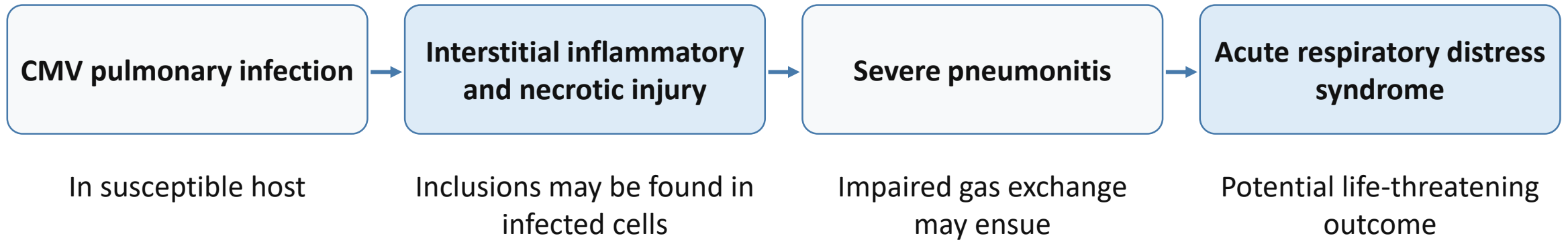
Other associations

Vasculopathy or neurocognitive impairment reported

CMV pneumonitis shows interstitial injury

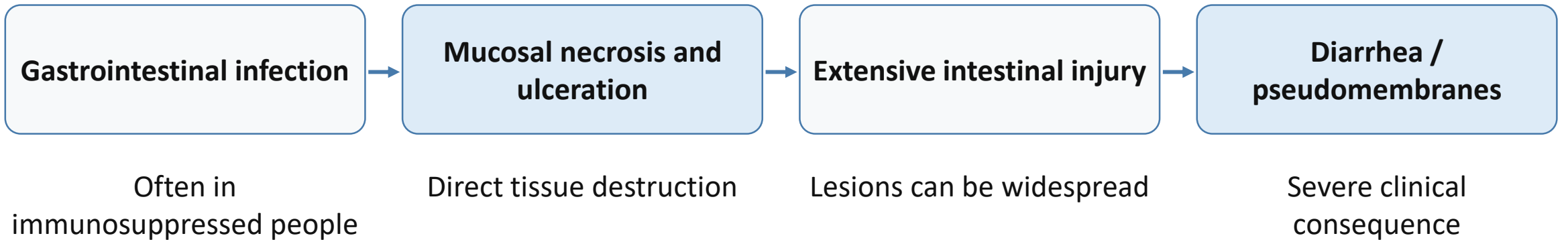
- Pulmonary tissue may show an interstitial mononuclear infiltrate.
- Foci of necrosis accompany the inflammatory changes.
- Cytomegalic enlarged cells with inclusions provide characteristic morphologic evidence.
- The distribution reflects infection in epithelial, endothelial and macrophage populations.

Pulmonary disease can progress to acute respiratory distress



The sequence is a clinical pathophysiologic schematic, not a guaranteed progression.

CMV colitis may be ulcerative and necrotizing



Tissue biopsy morphology matters because GI symptoms alone are nonspecific.

Pseudomembranes can develop after extensive intestinal injury

- CMV-induced intestinal necrosis can be extensive.
- Ulceration may be accompanied by pseudomembrane formation.
- Debilitating diarrhea is a major clinical consequence.
- The lesion must be interpreted in the setting of the patient's immune state.

Other reported CMV associations require caution

- Associations with vasculopathy and neurocognitive impairment.
- Association is not, by itself, proof that CMV caused every vascular or cognitive abnormality.
- A defined organ syndrome, virologic evidence and tissue context strengthen attribution.
- Avoid over-interpreting viral positivity without relevant clinicopathologic findings.

Histology supports diagnosis when inclusions are found

Affected organ tissue

Biopsy or tissue section



Recognizable cytopathic changes

Large nucleus; Owl's-eye inclusion; Other inclusions



Clinicopathologic synthesis

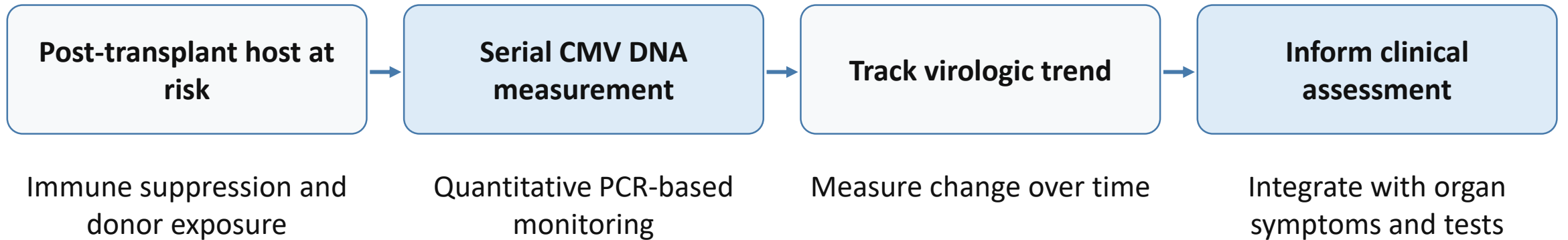
Correlate morphology with symptoms and immune status

Morphology demonstrates tissue involvement; This diagram is not an algorithm with validated accuracy.

CMV diagnostic approaches depend on clinical setting

Clinical situation	Source-supported diagnostic method	Interpretive emphasis
Neonatal infection	Urine / saliva CMV DNA PCR	Evidence of neonatal infection
Mono-like illness	Serology	Compatible systemic syndrome
Organ disease	Characteristic tissue morphology; viral culture	Direct organ assessment
Post-transplant follow-up	Quantitative CMV DNA PCR	Serial viral DNA monitoring

Quantitative PCR transformed transplant surveillance



No viral-load threshold or treatment-trigger value is specified in the source.

Clinical exercise: Transplant recipient with organ dysfunction

Clinical vignette

A solid-organ transplant recipient receiving immunosuppressive therapy develops respiratory symptoms. Tissue assessment identifies strikingly enlarged cells with characteristic nuclear inclusions.

- Which infection unifies host risk and cytopathic appearance?
- What two routes of viral acquisition are relevant?
- Which additional test modality does Robbins emphasize for transplant monitoring?

Case reasoning: CMV pneumonitis after transplantation

Most coherent diagnosis

CMV tissue disease; Lung is a major target in immunosuppressed patients.

Potential origin

New transmission from donor tissue or reactivation of latent CMV.

Monitoring

Quantitative CMV DNA PCR is an important post-transplant assay.

Synthesis: Host context, morphology and testing

Host context	Typical concern	Source-supported evidence
Congenital	Fetal injury; delayed deficits	Urine/saliva CMV DNA PCR
Perinatal	Usually silent acquisition and shedding	Exposure history / clinical context
Immunocompetent	Mono-like syndrome	Serology
Immunosuppressed	Pneumonitis, colitis, dissemination	Inclusions in tissue; viral DNA testing

Questions for clinicopathologic review

- Why can a patient harbor CMV after apparently complete recovery?
- How do congenital and perinatal routes change expected outcomes?
- Which nuclear and cytoplasmic alterations should prompt CMV consideration?
- Why are pneumonitis and colitis especially important after immune suppression?
- Why must PCR results be interpreted alongside organ pathology?

Reference and source limits

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- The lecture is based on the supplied Cytomegalovirus section and its herpesvirus parent context.
- Original textbook micrographs were not available for reuse; teaching illustrations are editable schematics, not clinical specimens.
- All patient scenarios are hypothetical and constructed from findings in the source.