

Spirochete Infections

Syphilis: pathogenesis, morphology, clinical stages and diagnosis

An integrated clinicopathologic lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraisakhri.com

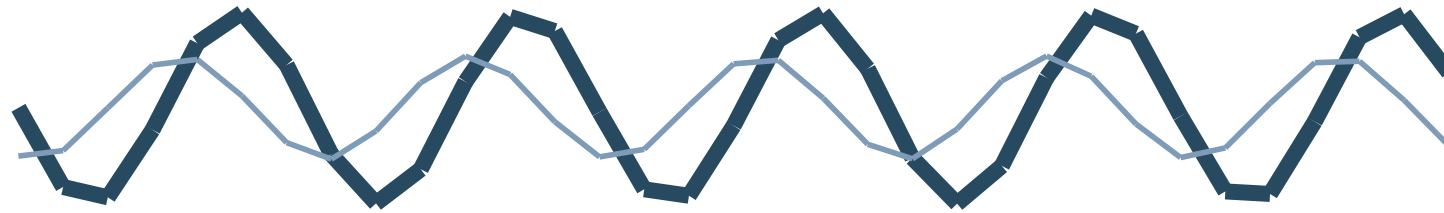
Learning outcomes

- Explain spirochete structure and the biologic basis of treponemal persistence.
- Relate proliferative endarteritis and inflammation to organ injury in syphilis.
- Distinguish acquired stages and congenital manifestations using morphology.
- Interpret the complementary roles of treponemal and nontreponemal tests.

Etiologic identity of syphilis

- *Treponema pallidum* subsp. *Pallidum* causes chronic, multisystem sexually transmitted infection.
- The organism is slender, microaerophilic and difficult to propagate in routine culture.
- The clinical spectrum reflects dissemination, host inflammation and potential persistence.
- Transplacental infection creates a distinct pattern of fetal and childhood disease.

Spirochete architecture: Movement within an outer sheath



Slender helical body

Periplasmic flagella

Outer sheath

Schematic: Corkscrew-shaped gram-negative bacteria; Axial flagella lie between the protoplasm and outer sheath.

Closely related treponemes: Distinct diseases

Organism	Associated disease
T. Pallidum subsp. Pallidum	Syphilis
T. Pallidum subsp. Pertenuae	Yaws
T. Pallidum subsp. Carateum	Pinta

Why routine bacterial visualization is difficult

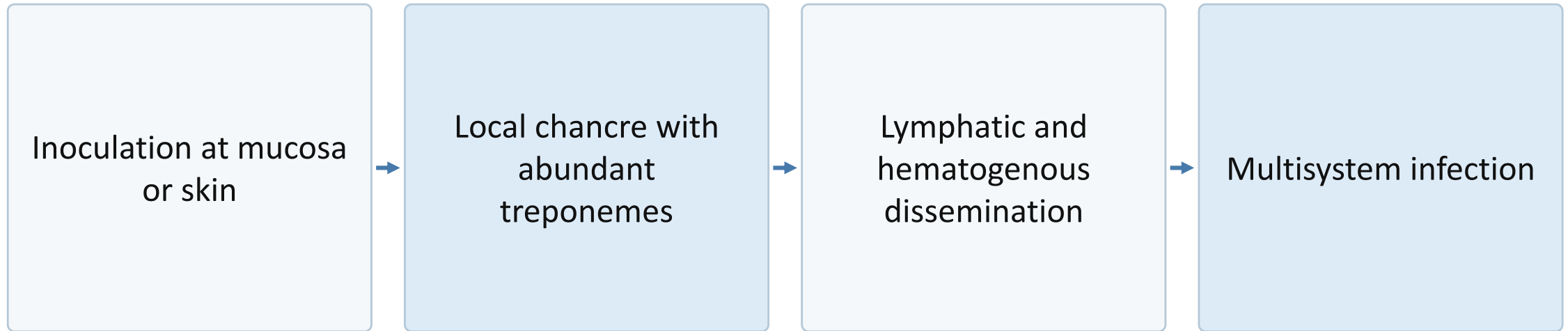
Direct tissue visualization

- Too slender for conventional Gram-stain recognition
- Silver stains can highlight organisms in tissue
- Immunofluorescence techniques may demonstrate bacteria

Laboratory growth

- *T. Pallidum* is not easily maintained in standard culture
- Diagnosis therefore relies heavily on serologic testing
- Results need clinical and stage-specific interpretation

Routes of treponemal spread



Schematic — conceptual sequence based on the source text

Disease expression follows both organism and host

Microbial behavior

- Early local multiplication
- Widespread dissemination
- Prolonged persistence

Host-mediated injury

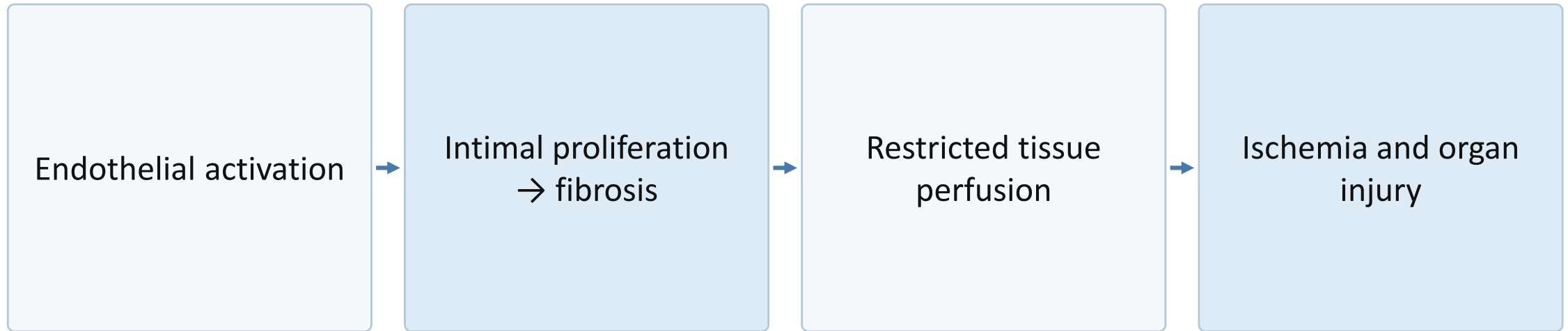
- Plasma cell–rich inflammation
- Proliferative endarteritis
- Ischemia and eventual scarring

An initially limited lesion does not exclude systemic infection.

The defining lesion: Proliferative endarteritis

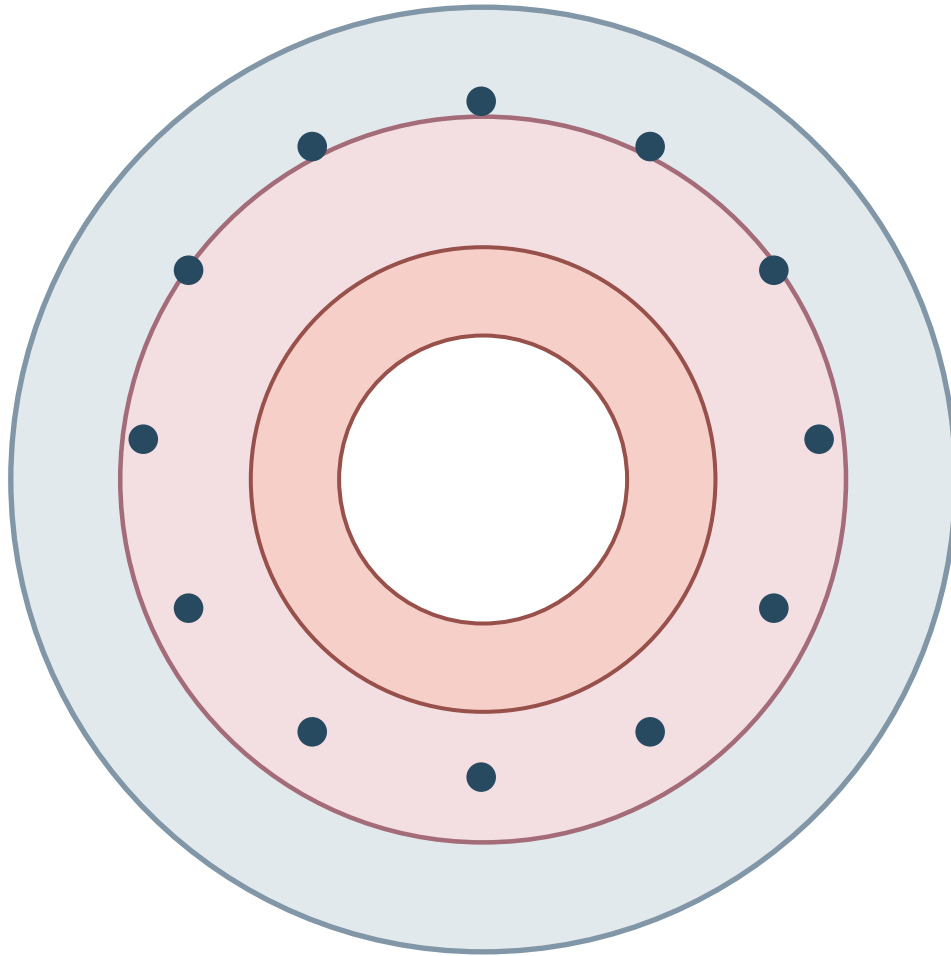
- Small vessels develop endothelial activation and intimal proliferation.
- A surrounding chronic inflammatory infiltrate is characteristically rich in plasma cells.
- Progressive intimal fibrosis may narrow or obliterate the vascular lumen.
- This vascular reaction contributes to lesions at multiple clinical stages.

From endarteritis to ischemic tissue injury



Schematic — conceptual sequence based on the source text

An inflamed small artery develops luminal narrowing



Intimal proliferation + inflammation

Progressive narrowing of lumen

Downstream tissue ischemia

Simplified vascular cross-section — schematic, not histology or a scale drawing

Why plasma cells matter histologically

- Plasma cells are a recurring component of the inflammatory reaction in syphilis.
- Primary chancres show plasma cells mixed with macrophages and lymphocytes.
- Secondary lesions commonly retain this pattern, sometimes less intensely.
- Plasma cell predominance supports consideration of syphilis but is not pathogen-specific.

Cellular response at superficial infection sites

T lymphocytes

- Prominent infiltrate
- CD4+ Th1 cells participate
- Protection remains incomplete

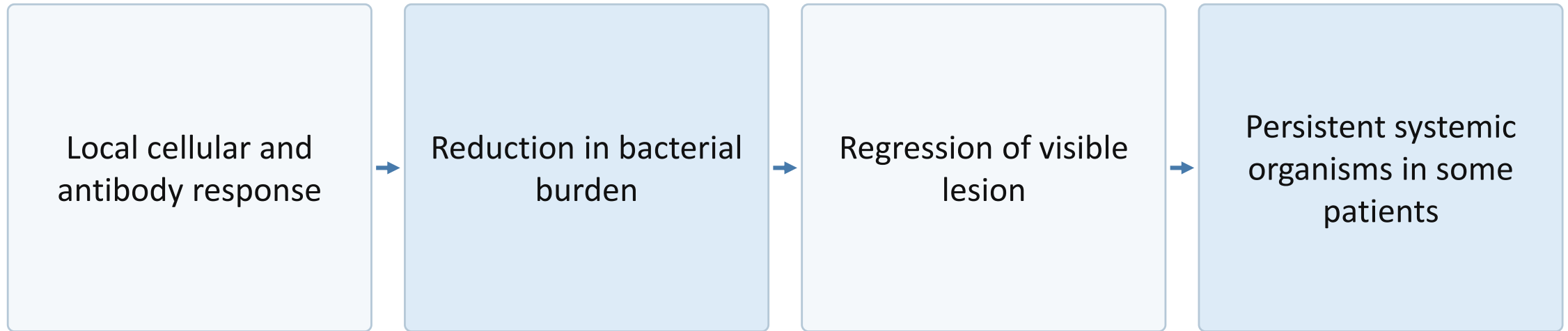
Macrophages

- Infiltrate infected tissue
- Engulf antibody-opsonized treponemes
- Contribute to local microbial control

Plasma cells / antibodies

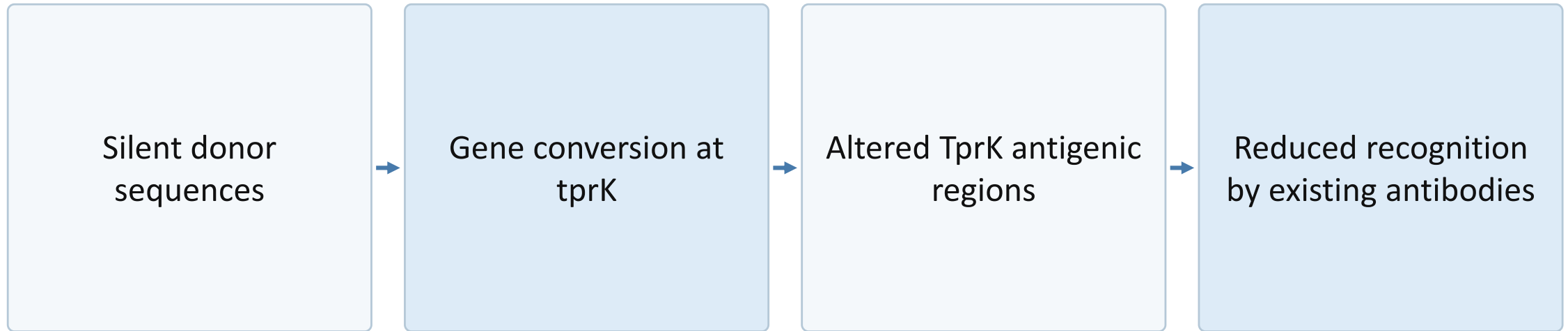
- Specific antibodies develop
- Complement activation
- Facilitate phagocytosis

Immune containment is not necessarily eradication



Schematic — conceptual sequence based on the source text

Antigenic diversification of TprK



Schematic — proposed contribution to antibody escape, not proof of a single causal mechanism

Persistence: Several reinforcing processes

- Treponemes can disseminate despite a prominent local inflammatory infiltrate.
- Host immunity reduces organism numbers but does not consistently sterilize infection.
- TprK variation is a proposed mechanism of antibody escape.
- T. Pallidum attachment to activated platelets may contribute to dissemination; This remains a suggested mechanism.

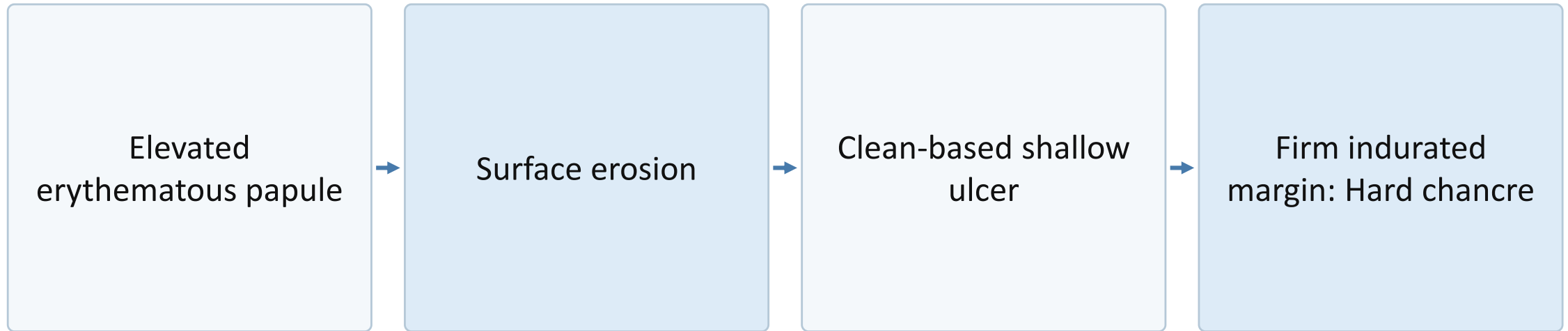
Three acquired stages and an intervening latent phase

Phase	Dominant clinical picture	Central pathologic concept
Primary	Painless indurated chancre	Local treponemes and endarteritis
Secondary	Multisite mucocutaneous lesions	Hematogenous spread and inflammation
Latent	No overt active lesions	Persistent infection with seroreactivity
Tertiary	Aortitis, neurosyphilis, gummas	Chronic inflammatory injury and scarring

Primary syphilis: Onset and anatomic distribution

- Classically appears approximately 2–6 weeks after infection.
- The first lesion develops at the site of initial treponemal invasion.
- Common sites include genital mucosa and skin, cervix, vagina and anus.
- Lesion healing does not imply microbiologic cure.

Chancre: The gross morphology of a firm ulcer



Schematic — conceptual sequence based on the source text

Histology of the primary chancre

- A dense infiltrate of plasma cells with lymphocytes and macrophages occupies the lesion.
- Small vessels show proliferative endarteritis.
- Endothelial activation is followed by progressive intimal fibrosis.
- Treponemes are numerous in the primary lesion and permit transmission.

Regional lymph nodes in primary infection

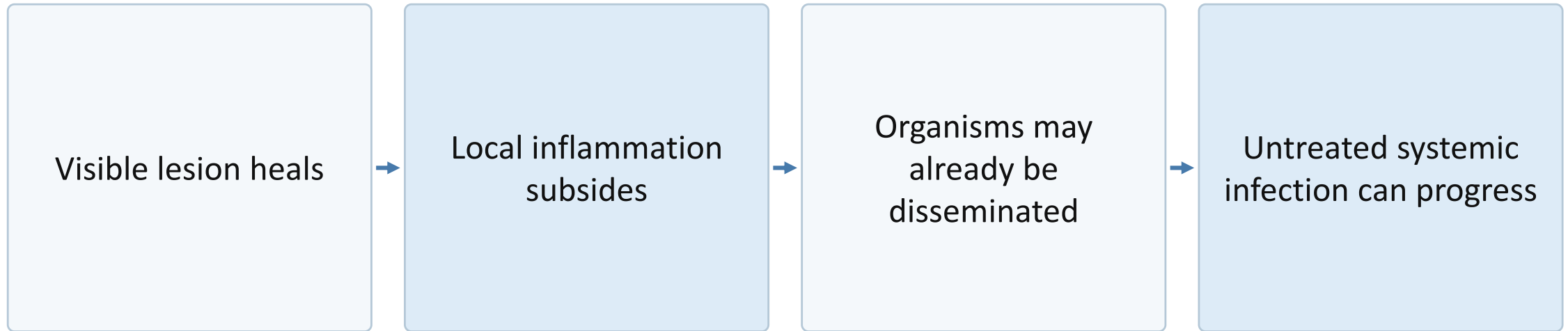
Clinical consequence

- Regional lymphadenopathy may accompany the chancre
- Nodal changes often reflect reactive inflammation

Microscopic reactions

- Acute or chronic nonspecific lymphadenitis
- Plasma cell–rich infiltrates may be seen
- Granulomatous responses are also described

Why disappearance of a chancre is misleading



Schematic — conceptual sequence based on the source text

Case: A painless indurated genital ulcer

An adult presents with a solitary painless, firm genital ulcer.

Findings to interpret

- A clean superficial ulcer lies within an indurated base.
- The lesion arose weeks after a potential exposure.
- The associated local node is enlarged.

Primary syphilis is a major clinicopathologic consideration.

Secondary syphilis: Clinical transition

- Secondary manifestations follow dissemination from the primary focus.
- They typically arise weeks after the original chancre in untreated infection.
- Lesions are widely distributed on skin and mucous membranes.
- Systemic inflammatory symptoms commonly accompany the eruption.

Secondary rash: More than one morphology

Common appearances

- Discrete red-brown macules
- Maculopapular eruption
- Scaly or annular lesions

Other patterns

- Follicular lesions
- Pustular variants
- Distribution may be widespread

Palms and soles are diagnostic clues

- Cutaneous lesions frequently affect palmar and plantar surfaces.
- These sites are informative when evaluating an otherwise nonspecific eruption.
- Morphology is variable: Macular, papular, scaly or pustular.
- The distribution should be interpreted together with mucosal changes and serology.

Condylomata lata: Broad moist plaques

Clinical setting

- Moist intertriginous or anogenital sites
- Inner thighs and axillae may also be affected

Lesion identity

- Broad-based elevated plaques
- Part of secondary syphilitic mucocutaneous disease
- Distinguish conceptually from a primary chancre

Secondary mucosal involvement

- Superficial silvery-gray erosions can involve oral, pharyngeal or genital mucosa.
- Lesions may be painless and easy to overlook without examination.
- Red mucosal lesions may harbor many organisms and be especially infectious.
- Mucosal disease and skin lesions often coexist.

Systemic inflammatory manifestations

Lymphatic

- Generalized lymphadenopathy
- Local inflammatory reactions

Constitutional

- Low-grade fever and malaise
- Possible weight loss

Neurologic

- CNS invasion may occur early
- May be asymptomatic

Microscopic pattern in secondary lesions

- Plasma cell–rich chronic inflammation resembles the reaction in the primary chancre.
- Small-vessel obliterative endarteritis can persist as a central microscopic clue.
- The density of the infiltrate may be lower than in primary lesions.
- Clinical distribution is essential because microscopic findings alone are not specific.

CNS dissemination need not await tertiary disease

- Treponemes can involve the CNS during relatively early infection.
- Some infections are neurologically silent despite CSF changes.
- Symptomatic disease may include meningitis, visual disturbance or hearing change.
- The classic tertiary categories do not define the earliest possible timing of CNS involvement.

Clinical case: Rash plus mucosal lesions

A patient has a generalized eruption involving palms and soles.

Findings to interpret

- Broad, moist plaques are present in the anogenital region.
- A painless superficial oral lesion is noted.
- The patient reports malaise and generalized lymphadenopathy.

Secondary syphilis integrates the distribution, mucosal lesions and systemic findings.

Latency: Persistent infection without florid lesions

What changes

- Chancre and secondary lesions may regress
- The patient may become clinically asymptomatic

What does not follow

- Disappearance does not prove organism elimination
- Serologic investigation remains central
- Late organ manifestations can arise in untreated infection

Tertiary syphilis: Three major patterns

Cardiovascular

- Syphilitic aortitis
- Aortic root / arch sequelae

Neurologic

- Meningovascular disease
- Tabes dorsalis / general paresis

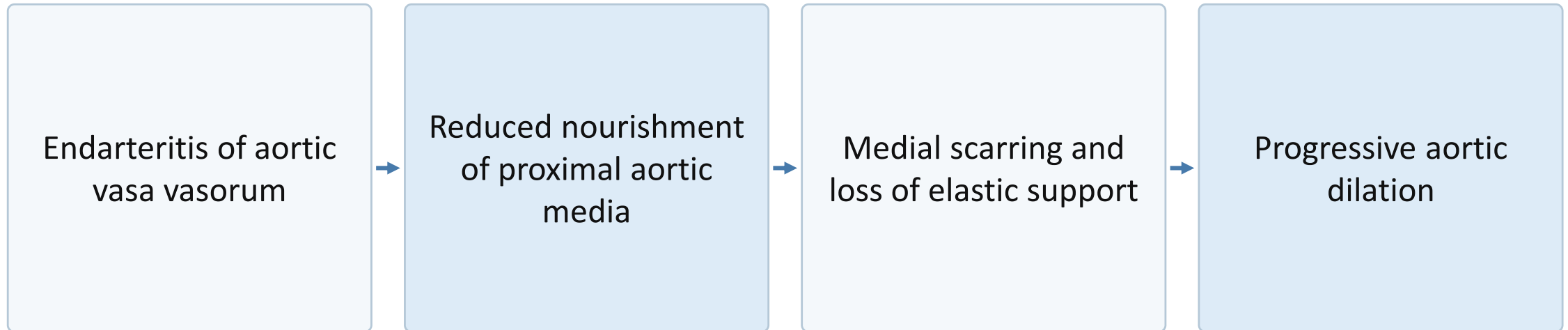
Gummatous

- Nodular necrotizing lesions
- Skin, bones and internal organs

Tertiary injury may follow years of latency

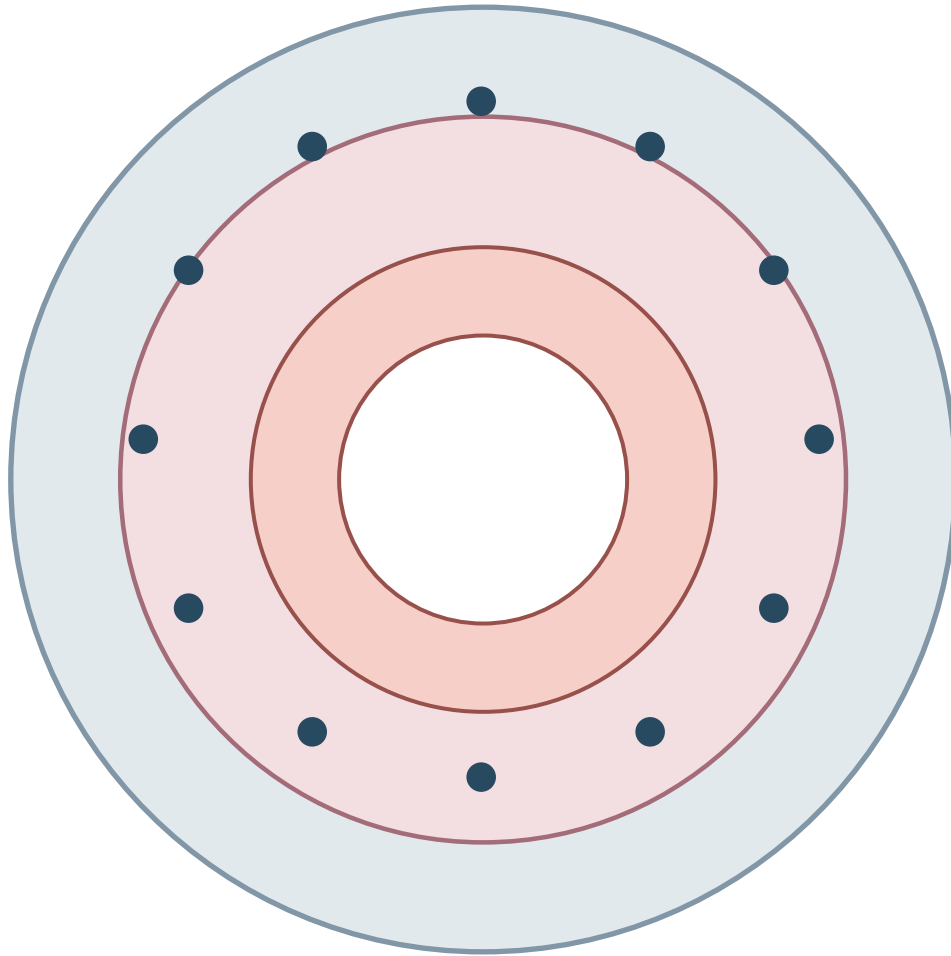
- Tertiary disease can emerge after a prolonged clinically latent interval.
- Cardiovascular, neurologic and gummatous manifestations may occur separately or together.
- The scarcity of organisms in some late lesions highlights the importance of host inflammation.
- Treatment has made gummatous complications less frequent.

Syphilitic aortitis: The relevant vascular target



Schematic — conceptual sequence based on the source text

Vasa vasorum occlusion initiates medial injury



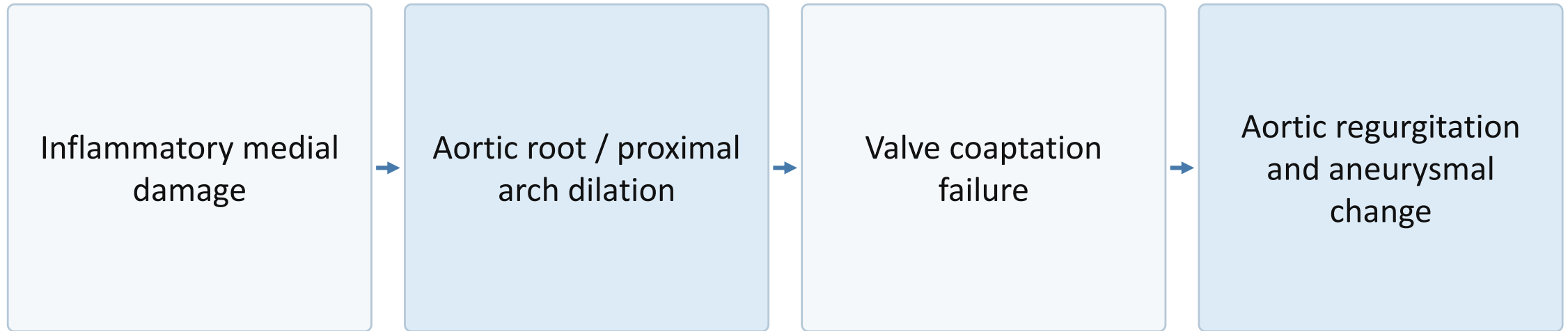
Intimal proliferation + inflammation

Progressive narrowing of lumen

Downstream tissue ischemia

Simplified vascular cross-section — schematic, not histology or a scale drawing

Aortic root dilation: Major functional outcomes



Schematic — conceptual sequence based on the source text

Coronary ostial narrowing in aortitis

- Subintimal scarring may constrict the coronary arterial openings.
- Ostial narrowing limits myocardial blood supply.
- Ischemic manifestations may therefore coexist with proximal aortic dilation.
- Both consequences arise from chronic remodeling rather than simply a bacterial mass.

Neurosyphilis: Diverse presentations

Form	Recognized manifestation
Asymptomatic	CSF inflammatory or serologic abnormalities without recognized neurologic symptoms
Meningovascular	One designated form of symptomatic neurosyphilis
Tabes dorsalis	One designated late neurologic form
General paresis	One designated late neurologic form

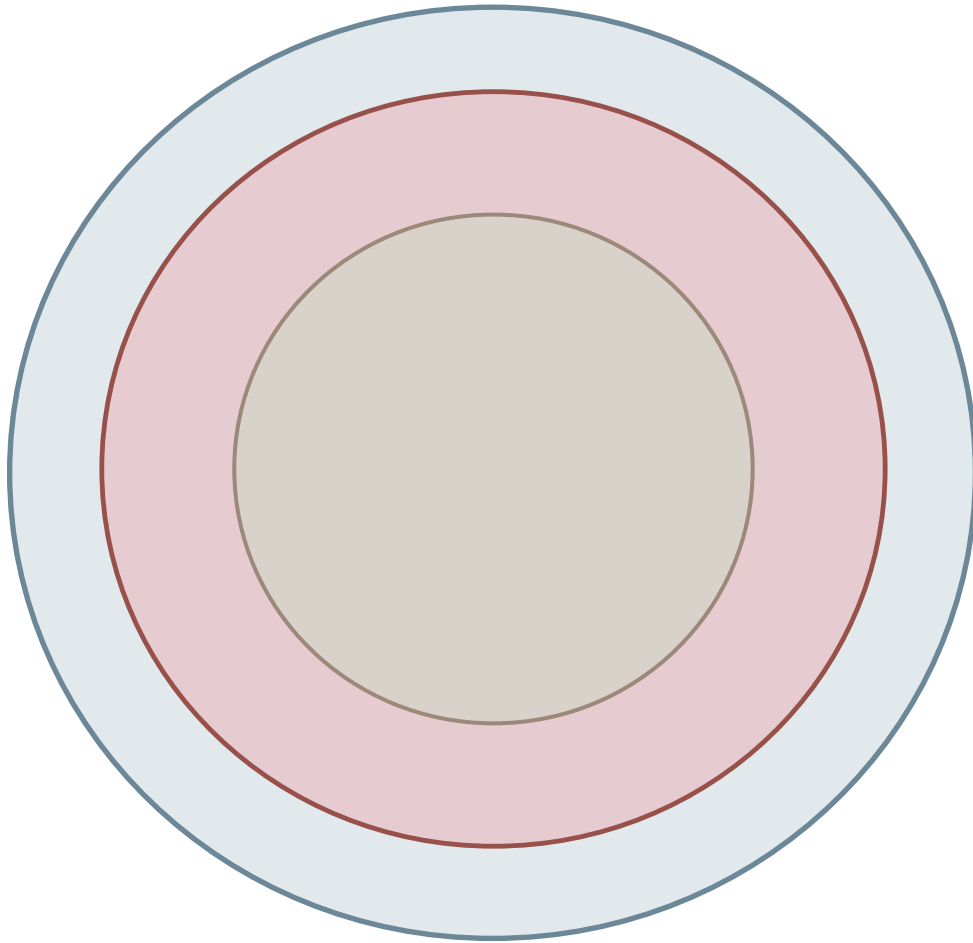
Asymptomatic neurosyphilis: CSF clues

- Inflammatory CSF abnormalities may precede obvious neurologic symptoms.
- Described changes include pleocytosis, increased protein or reduced glucose.
- CSF testing for syphilis-associated antibodies supports the diagnostic assessment.
- Neurosyphilis evaluation matters because central nervous system involvement changes clinical management.

Gummas: The distribution and gross lesion

- Gummas are rubbery, white-gray lesions varying from microscopic foci to tumorlike masses.
- They can occur singly or in multiples.
- Favored locations include skin, subcutis, bone, joints and other viscera.
- They may cause tenderness, swelling, ulceration or pathologic fracture depending on site.

Gumma: Central necrosis and reactive margin



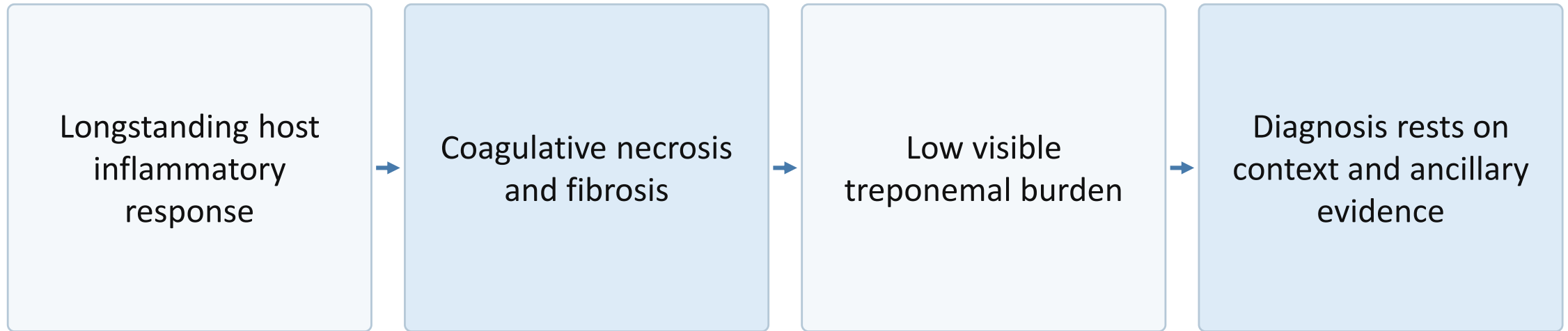
Central coagulated necrotic material

Palisading macrophages + fibroblasts

Outer mononuclear infiltrate: Plasma cells

Schematic of described architecture; Treponemes are sparse in established gummas

Why organisms are hard to find in a gumma



Schematic — conceptual sequence based on the source text

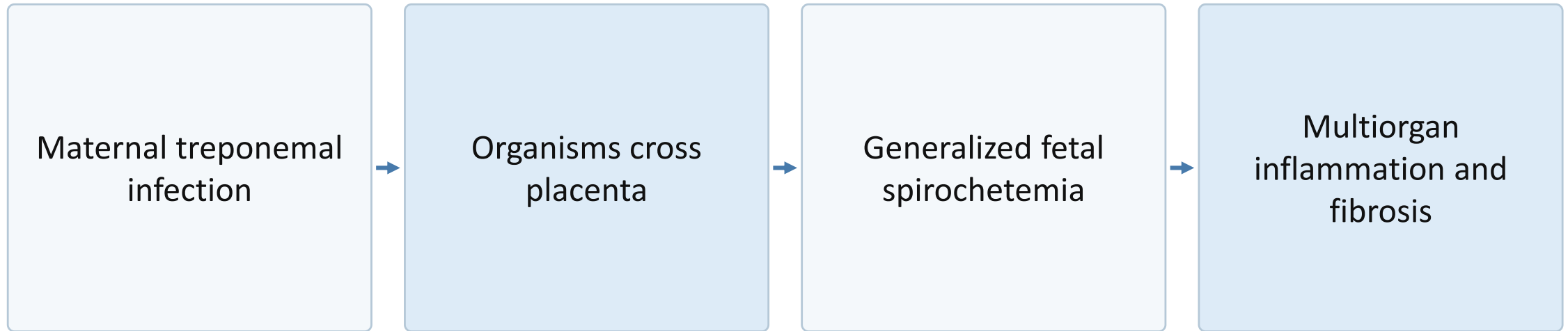
Hepar lobatum: Gummatous hepatic scarring

- Hepatic gummas can heal with irregular scarring.
- The resulting distortion produces the characteristic lesion termed hepar lobatum.
- The source illustration uses trichrome to highlight fibrosis; The actual image is not included here.
- This is a tertiary manifestation, distinct from diffuse congenital hepatic fibrosis.

Tertiary patterns: Lesion and consequence

Pattern	Pathologic lesion	Main consequence
Aortitis	Vasa vasorum endarteritis; Medial scarring	Root dilation, valve regurgitation, aneurysm
Neurosyphilis	CNS inflammatory disease	Variable neurologic syndrome
Gumma	Necrotic center; Macrophages, fibrosis, plasma cells	Focal destruction and scarring

Congenital infection: Transplacental spread



Schematic — conceptual sequence based on the source text

Why maternal disease stage matters

- Congenital transmission is most frequent with maternal primary or secondary syphilis.
- Organism burden is greatest during these clinically active phases.
- The fetal effects may include pregnancy loss and severe neonatal illness.
- That appropriate maternal penicillin treatment greatly reduces transmission and adverse outcomes.

Untreated congenital syphilis: Fetal outcomes

Pregnancy consequences

- Late abortion
- Stillbirth or perinatal death
- Severe fetal infection

Surviving infants

- Early multisystem inflammation
- Skin and bone involvement
- Potential later stigmata

Early congenital syphilis: Snuffles

- Nasal discharge and obstruction may develop during the first months of life.
- This presentation is traditionally termed snuffles.
- Nasal mucosal involvement accompanies systemic congenital infection.
- It must be interpreted with maternal history, infant examination and appropriate testing.

Infantile skin injury can be severe

- A bullous or desquamating eruption may involve palms and soles.
- Epidermal sloughing can also affect perioral and perianal skin.
- The rash is often more severe than typical acquired secondary syphilis.
- Cutaneous changes should trigger consideration of disseminated fetal infection.

Congenital skeletal abnormalities: Two mechanisms

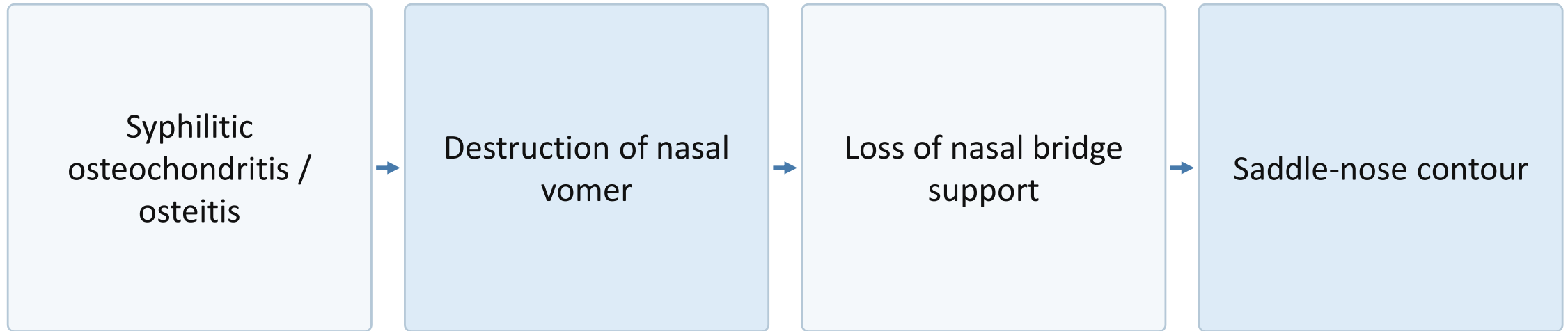
Osteochondritis

- Disturbed endochondral bone formation
- Epiphyseal widening and disordered cartilage position

Periostitis

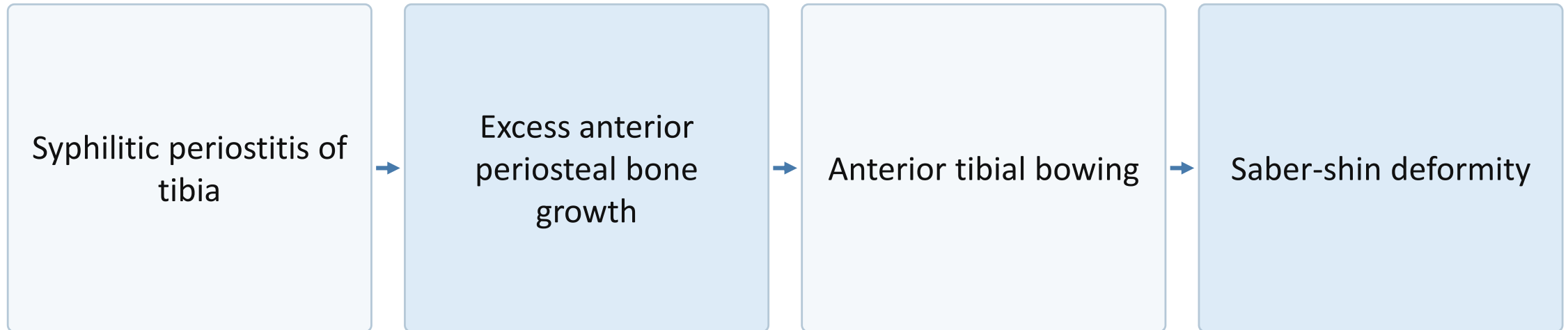
- New bone formation on long-bone surfaces
- Prominent lesions in lower legs
- Characteristic deformities can follow

Vomer injury and saddle-nose deformity



Schematic — conceptual sequence based on the source text

Tibial periostitis and saber shin



Schematic — conceptual sequence based on the source text

Congenital hepatic disease: Diffuse fibrosis

- The liver may show fibrosis that traverses lobules and separates hepatocytes into small nests.
- Lymphoplasmacytic inflammation and vascular abnormalities accompany the fibrosis.
- Hepatomegaly is a frequent clinical correlate.
- Early hepatic gummas are possible but diffuse fibrosing injury is the central pattern.

Pneumonia alba: Fetal pulmonary involvement

- Congenital infection may produce diffuse pulmonary interstitial inflammation and fibrosis.
- In an affected stillborn infant, the lungs may appear pale and airless.
- This gross appearance is termed pneumonia alba.
- The process is part of systemic spirochetemia rather than an isolated airway infection.

Other affected fetal organs

Visceral involvement

- Pancreas and kidneys
- Heart and spleen
- Endocrine organs

Immune / nervous sites

- Thymus
- Central nervous system
- Diffuse interstitial inflammation

Late congenital syphilis: Hutchinson triad

Eye

- Interstitial keratitis
- Corneal inflammatory injury

Dentition

- Hutchinson teeth
- Small, notched incisors

Hearing

- Eighth-nerve deafness
- Neurologic tissue injury

Additional late congenital features

- Ocular changes may include choroiditis and abnormal retinal pigmentation.
- Hutchinson incisors are reduced in size, peg- or screwdriver-shaped and may be notched.
- Eighth-nerve injury and optic atrophy may arise in the setting of meningovascular disease.
- Late manifestations reflect damage that becomes evident during childhood.

Congenital disease differs by time of expression

Infantile / early	Childhood / later
Snuffles and bullous rash	Interstitial keratitis and hearing loss
Osteochondritis or periostitis	Saddle nose and saber shin may persist
Hepatic and pulmonary fibrosis	Characteristic Hutchinson teeth

Syphilis diagnosis: Combine clinical stage and serology

- Serologic assays are the principal laboratory approach.
- Treponemal and nontreponemal tests measure different antibody responses.
- Diagnostic algorithms use both classes rather than relying on one test alone.
- Test performance and interpretation vary by disease stage and treatment history.

Nontreponemal tests: Reaction to a lipid antigen

Antigenic target

- Cardiolipin–cholesterol–lecithin complex
- Not exclusive to *T. Pallidum*

Common tests

- Rapid plasma reagin (RPR)
- Venereal Disease Research Laboratory (VDRL)

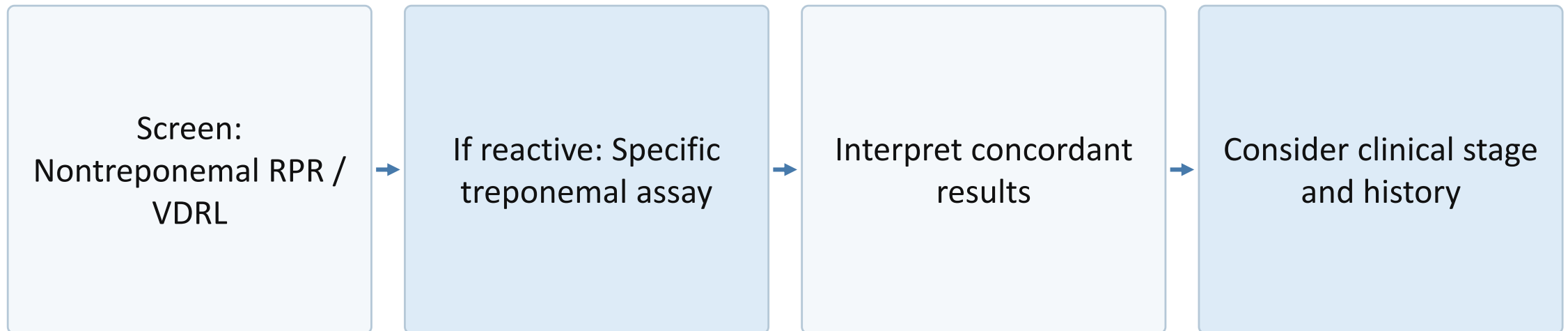
Clinical interpretation

- Results can be quantified as titers
- Useful for response monitoring

Treponemal tests identify organism-directed antibodies

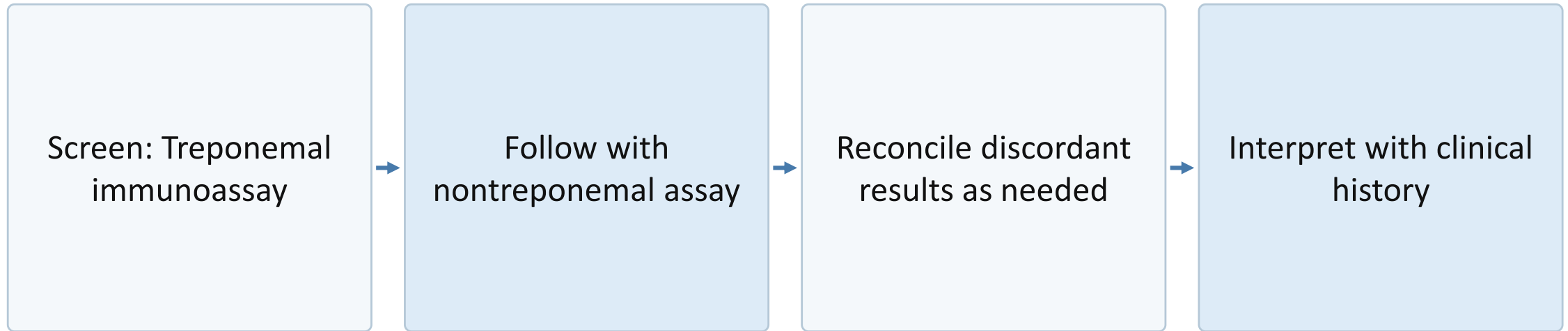
- These assays detect antibodies directed against *T. Pallidum* antigens.
- Examples in the source include the fluorescent treponemal antibody absorption test.
- *T. Pallidum* enzyme immunoassays also serve as treponemal tests.
- Many treponemal tests remain reactive after adequate therapy and are not suitable for monitoring treatment response.

Traditional syphilis serologic algorithm



Schematic — conceptual sequence based on the source text

Reverse-sequence serologic algorithm



Schematic — conceptual sequence based on the source text

Test sensitivity depends on clinical phase

Early infection

- Antibody tests may not yet be reliably reactive
- A negative early test does not settle a strong clinical suspicion
- Clinical follow-up and repeat evaluation may be required

Established infection

- Both classes of tests perform well in secondary disease
- Treponemal tests generally remain useful in latent or tertiary disease
- Prior treatment changes serologic interpretation

Follow-up: Antibody titers are not interchangeable

Nontreponemal assays	Treponemal assays
Quantitative titers can be followed	Commonly provide qualitative reactivity
Titers often fall after successful treatment	Reactivity may persist after treatment
Useful for monitoring response	Useful for evidence of exposure/infection history

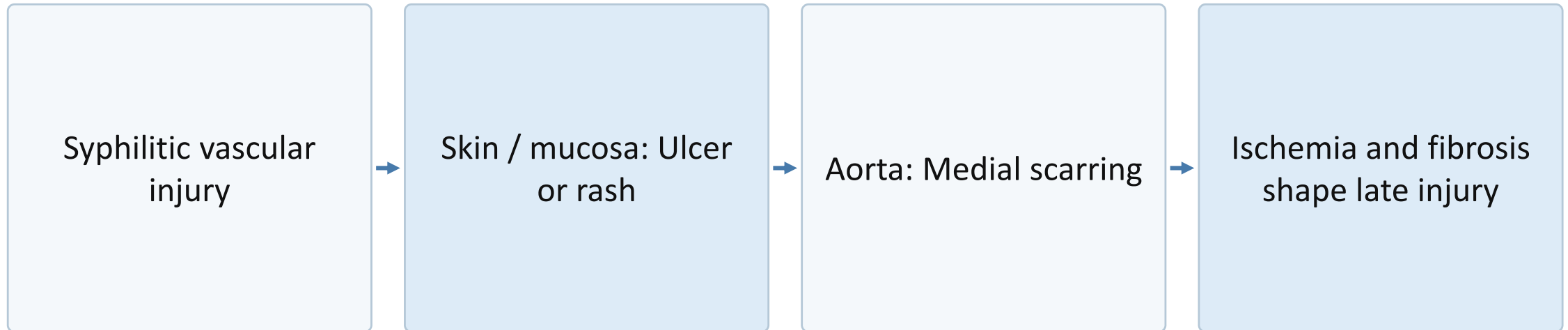
False positives and discordant tests

- Nontreponemal antibody responses are not fully specific to *T. Pallidum*.
- False-reactive results can accompany pregnancy, autoimmune disease or other infections.
- Treponemal tests can also produce false-positive results.
- Discrepant serology requires interpretation of both assays and the clinical context.

Histopathology across acquired stages

Stage	Typical lesion	Shared microscopic features
Primary	Hard chancre	Plasma cells; Proliferative endarteritis
Secondary	Skin / mucosal eruption	Plasma cells; Obliterative endarteritis
Tertiary	Aortic lesions or gumma	Vessel injury / necrosis / fibrosis; Organisms often sparse

Interpretation: The same vascular lesion, different organs



Schematic — conceptual sequence based on the source text

Case: Chronic ascending aortic disease

A patient with untreated historical infection has progressive proximal aortic dilation.

Findings to interpret

- Vasa vasorum show chronic obliterative vascular injury.
- The proximal aortic media is scarred.
- The aortic valve has become incompetent.

Syphilitic aortitis links vasa vasorum disease to root dilation and regurgitation.

Case: Congenital multisystem involvement

A neonate has nasal discharge, a bullous palmar eruption and hepatomegaly.

Findings to interpret

- Maternal syphilis was active during pregnancy.
- The rash is accompanied by prominent skin desquamation.
- Bone abnormalities appear on clinical evaluation.

The combination supports congenital syphilis with systemic involvement.

Clinicopathologic synthesis: five anchors

- *T. pallidum* is difficult to culture and can persist despite host immunity.
- Plasma cell–rich inflammation and proliferative endarteritis recur across stages.
- Chancres, disseminated mucocutaneous disease and late organ injury form a spectrum.
- Congenital infection preferentially produces skin, bone, liver, lung and later sensory lesions.
- Clinical stage and paired serologic test classes are crucial for interpretation.