

General Principles of Microbial Pathogenesis

Host barriers • entry • dissemination • transmission • microbial–host
interactions

Core processes governing infectious disease

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Learning outcomes: Explain how infection is established

- Identify portals of microbial entry and the defenses operating at each site.
- Distinguish localized infection from lymphatic, hematogenous, and neural dissemination.
- Relate transmission pathways to microbial exit and the next host's entry.
- Interpret the roles of microbiota, virulence, and immune evasion in disease.

Microbial disease is an interaction—not simply exposure



An effective barrier or immune response may interrupt the process at multiple points.

Virulence and host defenses jointly determine infection

Microbial factors

- Ability to attach or penetrate surfaces
- Virulence mechanisms that overcome defenses
- Capacity to persist and disseminate

Host factors

- Integrity of epithelial barriers
- Local innate antimicrobial mechanisms
- Effective adaptive immune responses

An organism can cause disease through high virulence or weakened host resistance.

Infectious microbes are acquired from multiple sources

Humans

Symptomatic or asymptomatic sources

Animals

Direct zoonotic contact or bites

Arthropods

Vector-mediated introduction

Environment

Contaminated water, food, or other exposures

Portals of entry are linked to particular defenses

Skin

Keratinized epithelium, low pH, fatty acids

GI tract

Acid, mucus, IgA, enzymes, microbiota

Respiratory tract

Mucociliary clearance; Alveolar phagocytes

Urogenital tract

Urine flow; Vaginal acidic microbiota

Intact mucosa and injured skin present different challenges

Intact mucosal surfaces

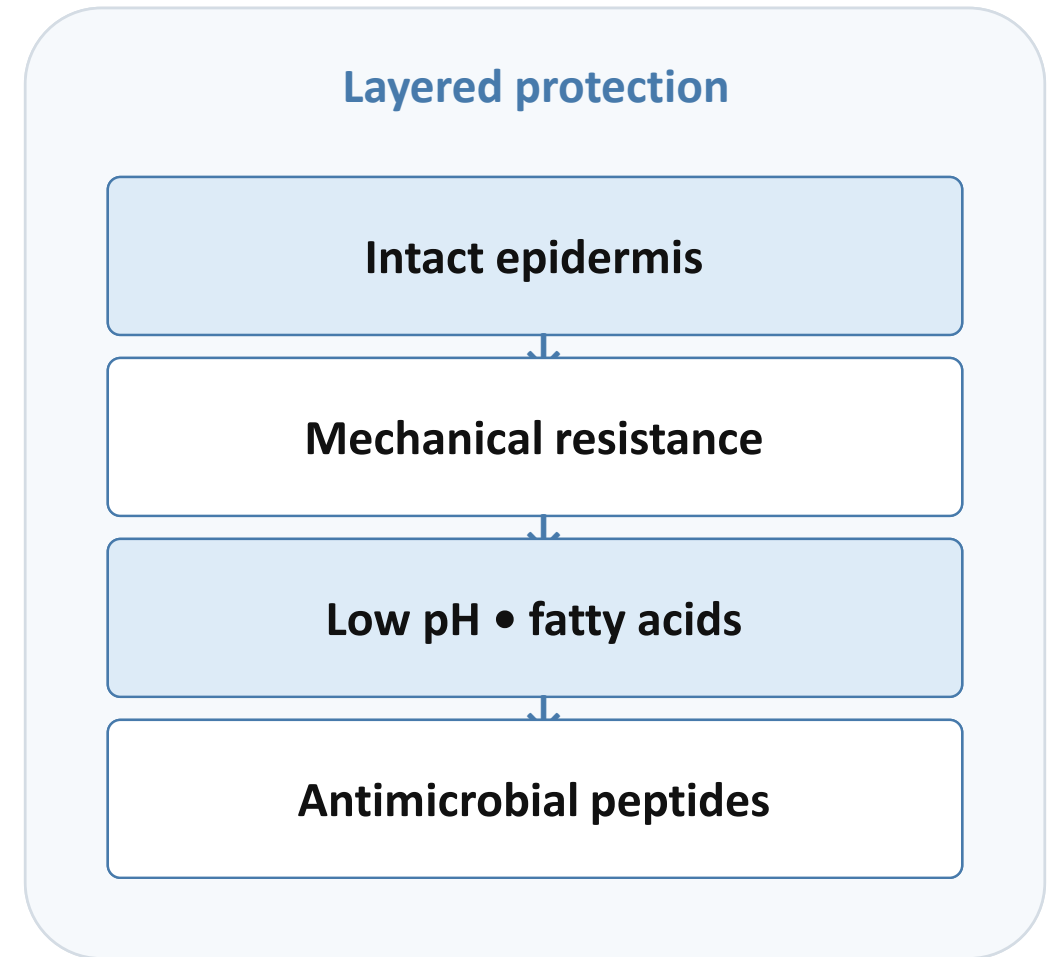
- Respiratory, GI, and genitourinary portals
- Successful pathogens can adhere or penetrate
- Local replication can occur despite intact epithelium

Skin after breach

- Trauma, burn, ulcer, or intervention opens entry
- Infections usually exploit disruption
- Needlesticks and bites bypass the surface barrier

Healthy skin presents mechanical and chemical defenses

- Keratinized epidermis resists microbial penetration.
- Surface acidity and antimicrobial fatty acids inhibit organisms.
- Defensins contribute direct antimicrobial activity.
- Physical injury removes multiple protective mechanisms.



Skin infection commonly follows loss of barrier integrity

Barrier disruption	Pathogen example	Mechanistic interpretation
Burns / ulcers	S. aureus; P. aeruginosa	Exposed tissue enables microbial entry
Needlestick	HIV; HBV; HCV	Inoculation bypasses epidermis
Arthropod / animal bite	Plague; rabies; malaria	Vector or bite directly introduces agent

Some pathogens penetrate skin without an obvious wound

- Most pathogens require a cutaneous defect or vector-associated puncture.
- Schistosoma larvae provide an important exception.
- Larval enzymes disrupt adhesive proteins joining keratinocytes.
- The route of entry reflects pathogen-specific capabilities.

Direct penetration — schematic

Schistosoma larva



Enzymatic cleavage of adhesion



Passage through epidermis

The gastrointestinal tract has overlapping barriers

Chemical

Gastric acidity; Bile; Pancreatic enzymes

Surface

Mucus and epithelial barrier

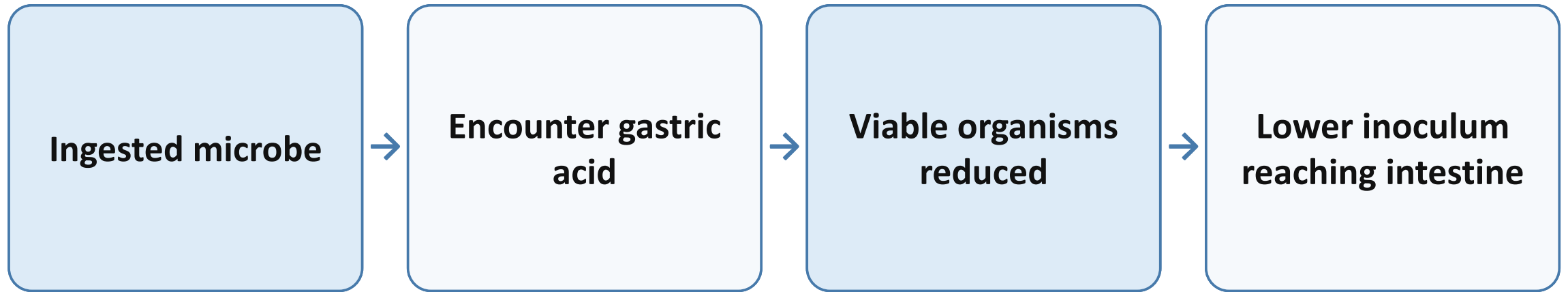
Immune

Secretory IgA and defensins

Ecologic / mechanical

Microbiota and peristalsis

Gastric acidity can sharply restrict infectivity

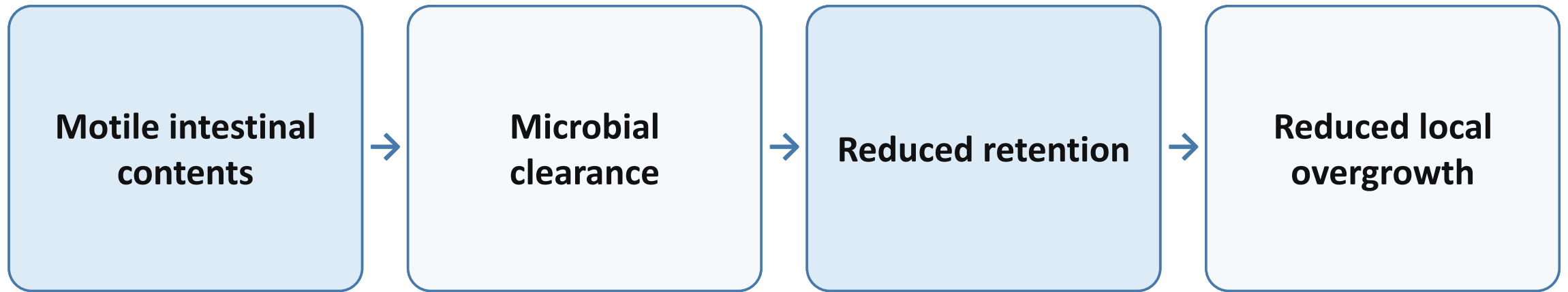


Markedly increased *V. Cholerae* infectivity after experimentally neutralizing gastric acid.

Mucus, secretory IgA, and defensins have different roles

Local defense	Principal protective role
Superficial mucus	Physical separation of organisms from epithelium
Secretory IgA	Mucosal antibody-mediated protection
Defensins	Antimicrobial peptide activity
Epithelial integrity	Barrier to invasion

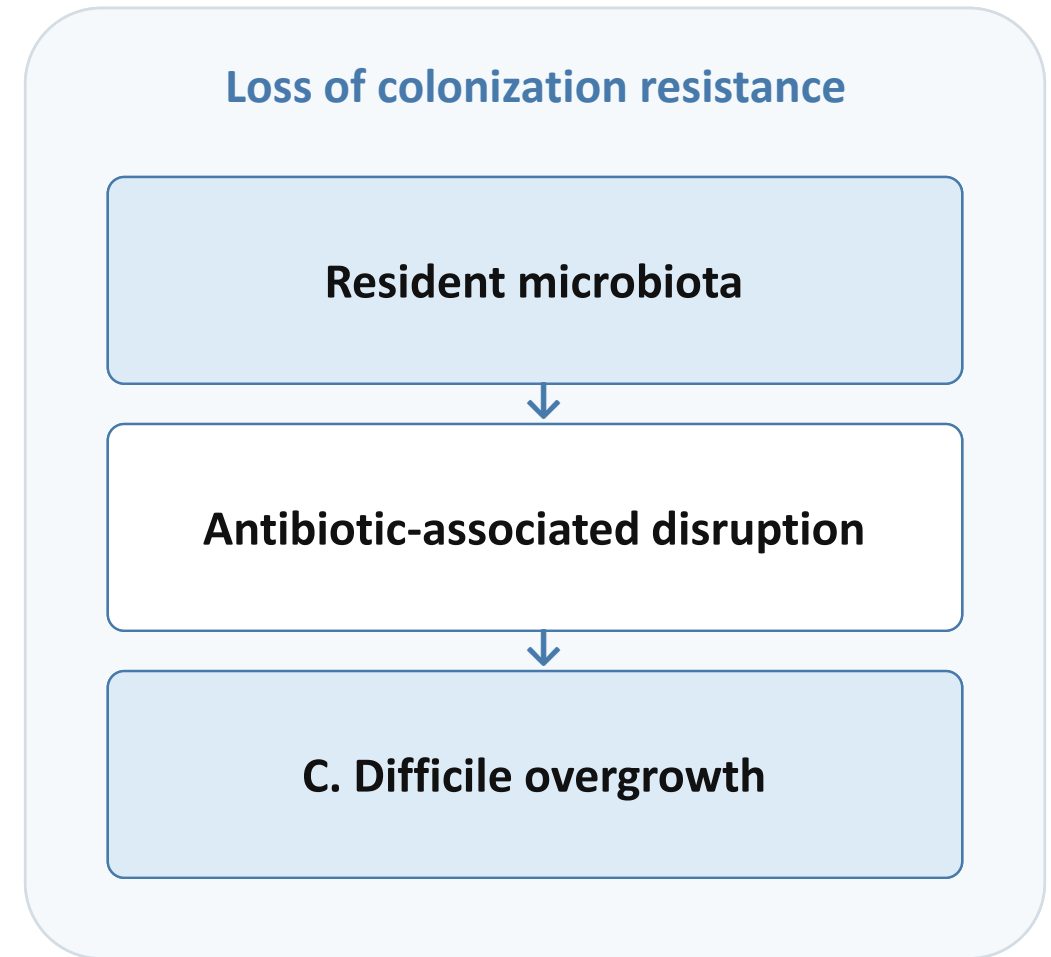
Peristalsis limits microbial residence and overgrowth



Obstruction, ileus, or postsurgical adhesions may permit excessive growth of mixed gut bacteria.

Commensal microbiota constrain opportunistic colonization

- Resident gut organisms competitively inhibit pathogens.
- Broad-spectrum antibiotic exposure can disrupt colonization resistance.
- *Clostridioides difficile* is a central clinical example.
- Thus antimicrobial treatment can indirectly favor infection.



Enteric pathogens succeed by distinct barrier-evasion routes

Route / defense defeated	Examples	Pathogenic advantage
Attachment and proliferation	V. cholerae; Giardia	Persistence at epithelial surface
Local invasion	Shigella; Salmonella	Passage into mucosal tissue
Acid-resistant forms	Protozoal cysts; helminth eggs	Survival through stomach
Resistance to luminal factors	Norovirus	Survival despite bile / enzymes

Gastrointestinal entry: Differentiate exposure from disease

Two individuals ingest an enteric pathogen; One has recently received broad-spectrum antibiotics.

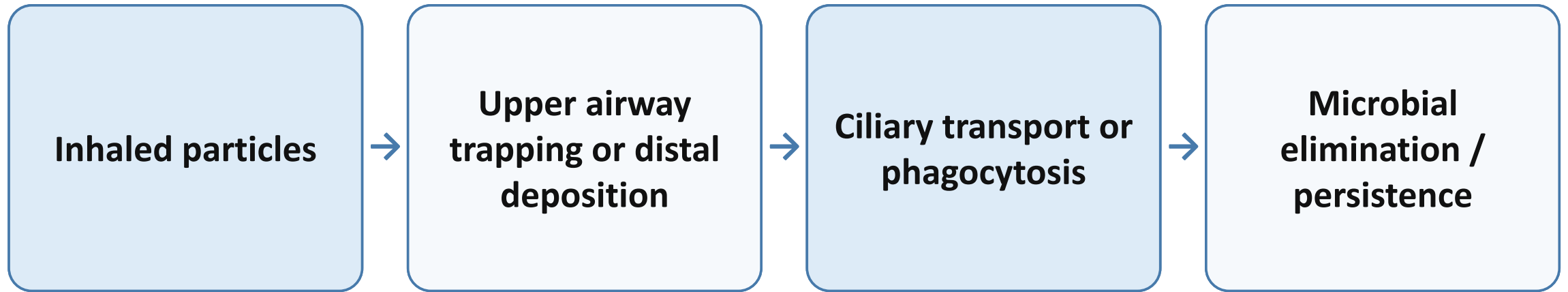
Interpretation question

Which local mechanism may differ even when exposure is similar?

Mechanistic answer

Disruption of colonization resistance can permit pathogen expansion, particularly for *C. Difficile*.

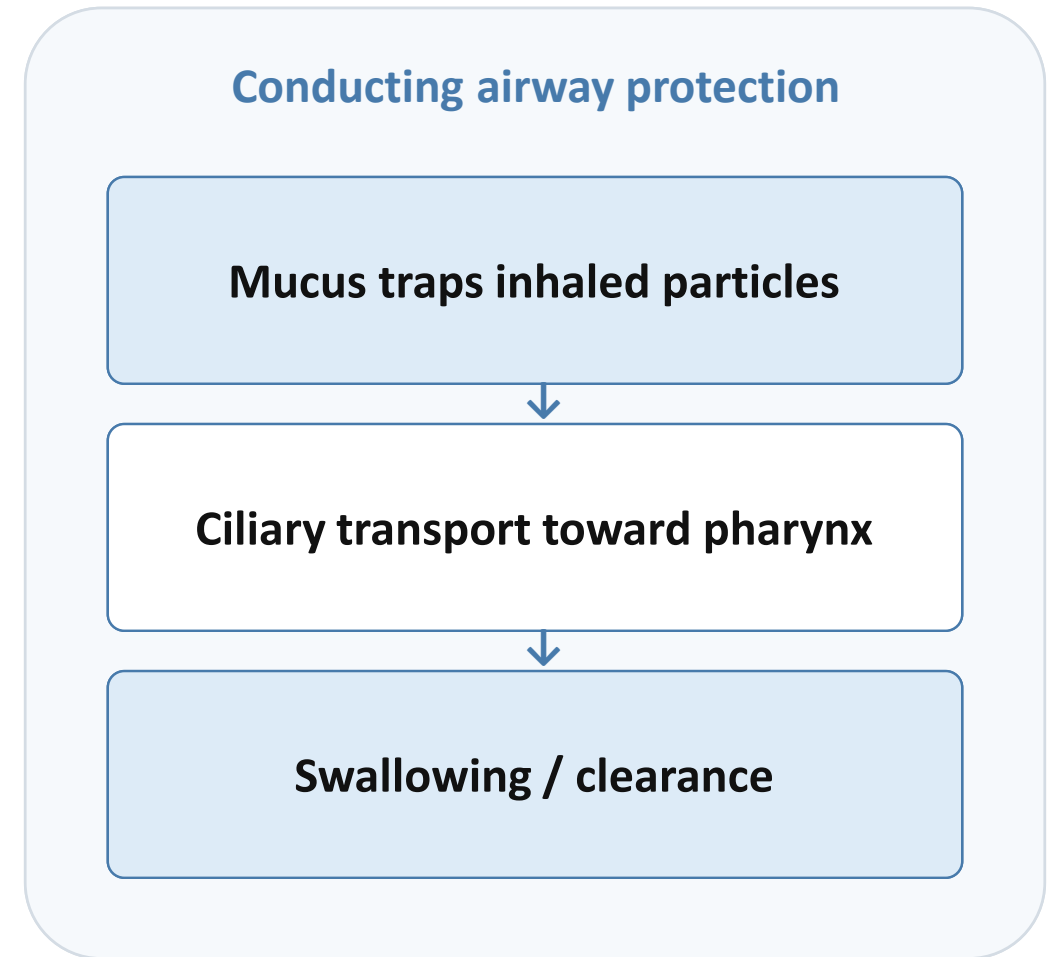
Respiratory entry begins with inhaled particles



Particle size influences deposition; Failure to clear organisms permits establishment.

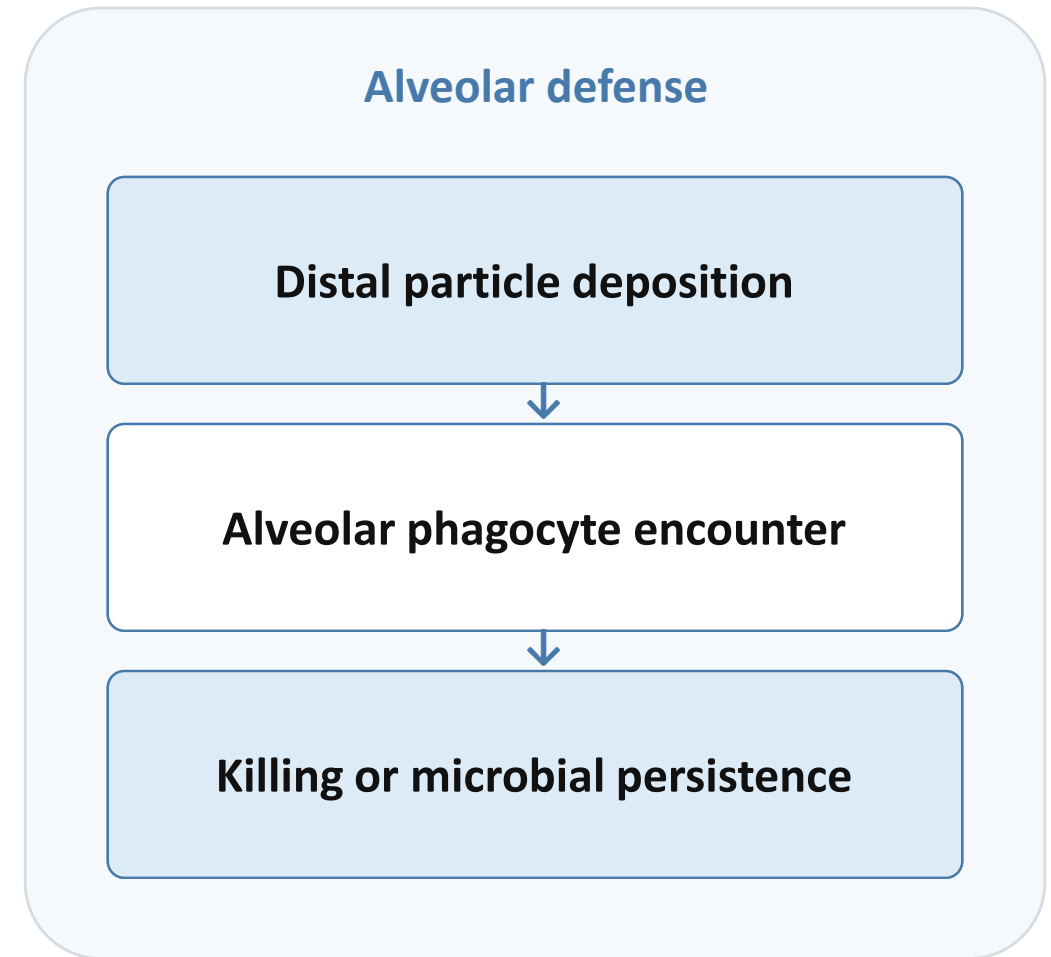
Mucociliary clearance protects the conducting airways

- Larger inhaled particles are trapped in airway mucus.
- Coordinated ciliary activity moves mucus toward the pharynx.
- Swallowing removes trapped microorganisms from the airway.
- Organisms that inhibit ciliary activity evade this defense.

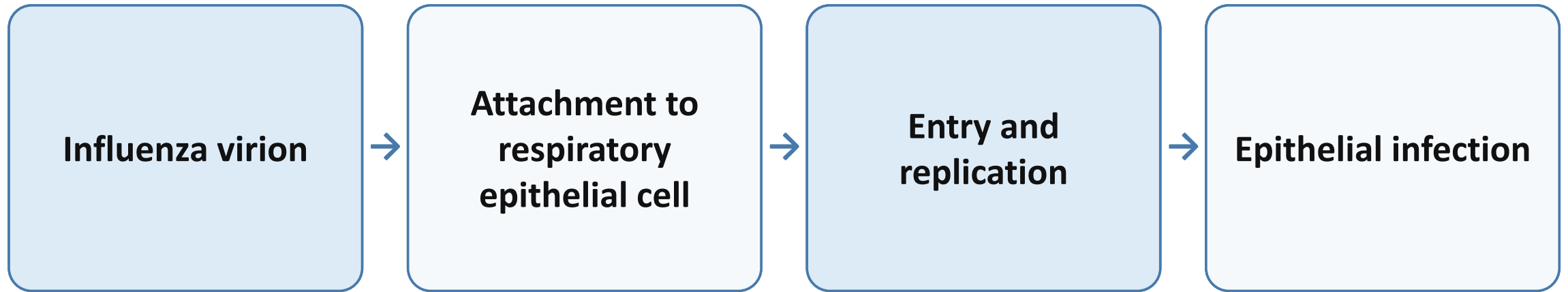


Particles reaching alveoli confront phagocytes

- Fine particles can penetrate to distal airspaces.
- The source describes particles $<5\text{ }\mu\text{m}$ reaching alveoli.
- Alveolar leukocytes and macrophages phagocytose organisms.
- Intracellular survival becomes an effective evasion strategy.



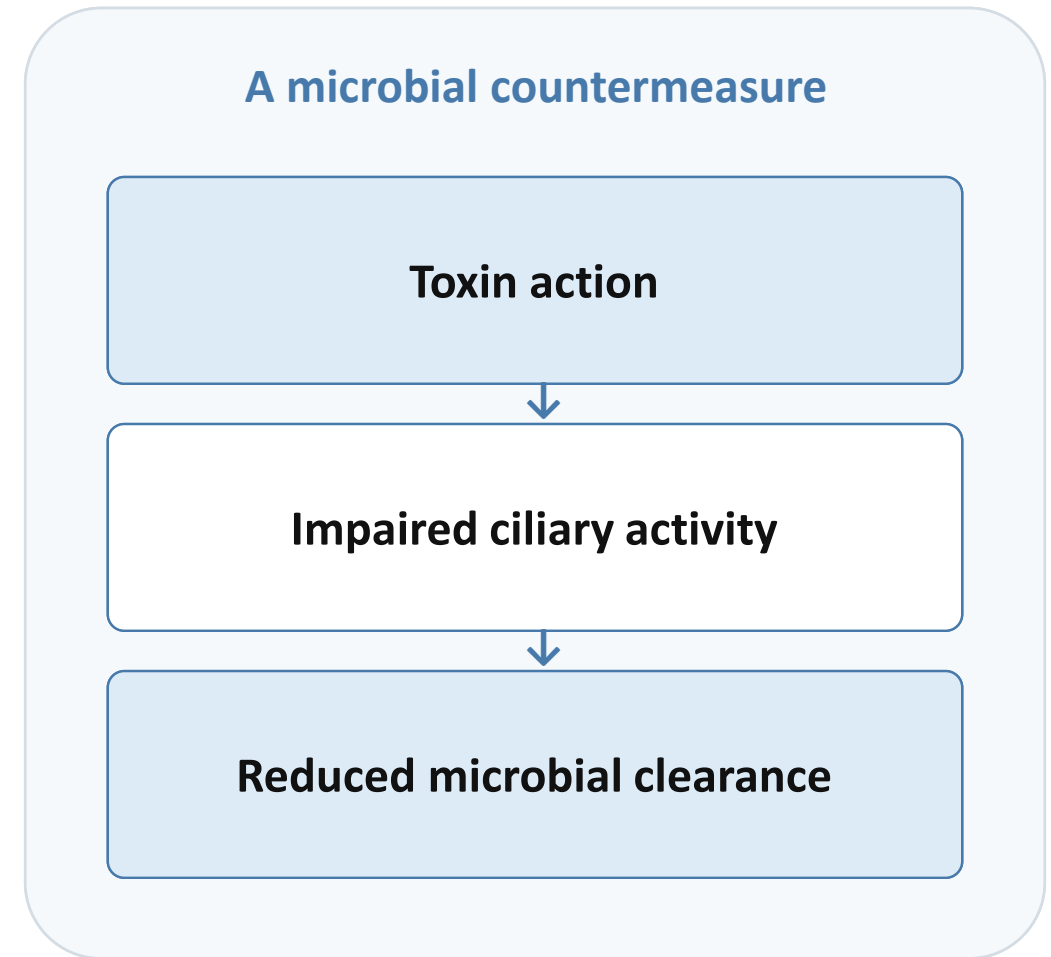
Respiratory viruses can exploit epithelial cells directly



Successful local entry can overcome clearance even without an overt barrier wound.

Bacterial toxins can undermine mucociliary protection

- Bordetella pertussis produces factors that impair ciliary function.
- Reduced clearance increases airway retention of organisms.
- Mucociliary dysfunction therefore aids establishment of infection.
- This is a functional barrier failure rather than a skin-like breach.



Phagocytosis does not ensure microbial elimination

Usual outcome

- Alveolar uptake of an organism
- Phagocyte antimicrobial activity
- Elimination of the microbe

Pathogen survival

- Mycobacteria resist intracellular killing
- Persistence in macrophages
- Potential progression of infection

Impaired airway clearance predisposes to secondary infection

Influenza

Damages airway defenses

Smoking

Compromises clearance

Cystic fibrosis

Defective mucociliary clearance

Ventilation

Altered airway protection

Systemic immune impairment changes pulmonary susceptibility

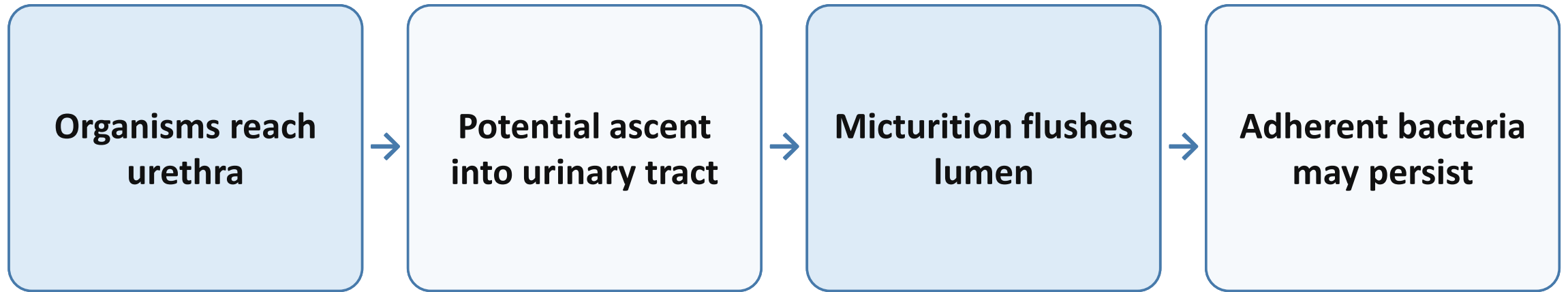
Intact host defense

- Alveolar phagocyte activity
- Mucociliary removal
- Systemic antimicrobial immunity

Immunodeficient host

- Opportunistic respiratory pathogens emerge
- Examples include *Pneumocystis jirovecii*
- *Aspergillus* spp. May cause disease

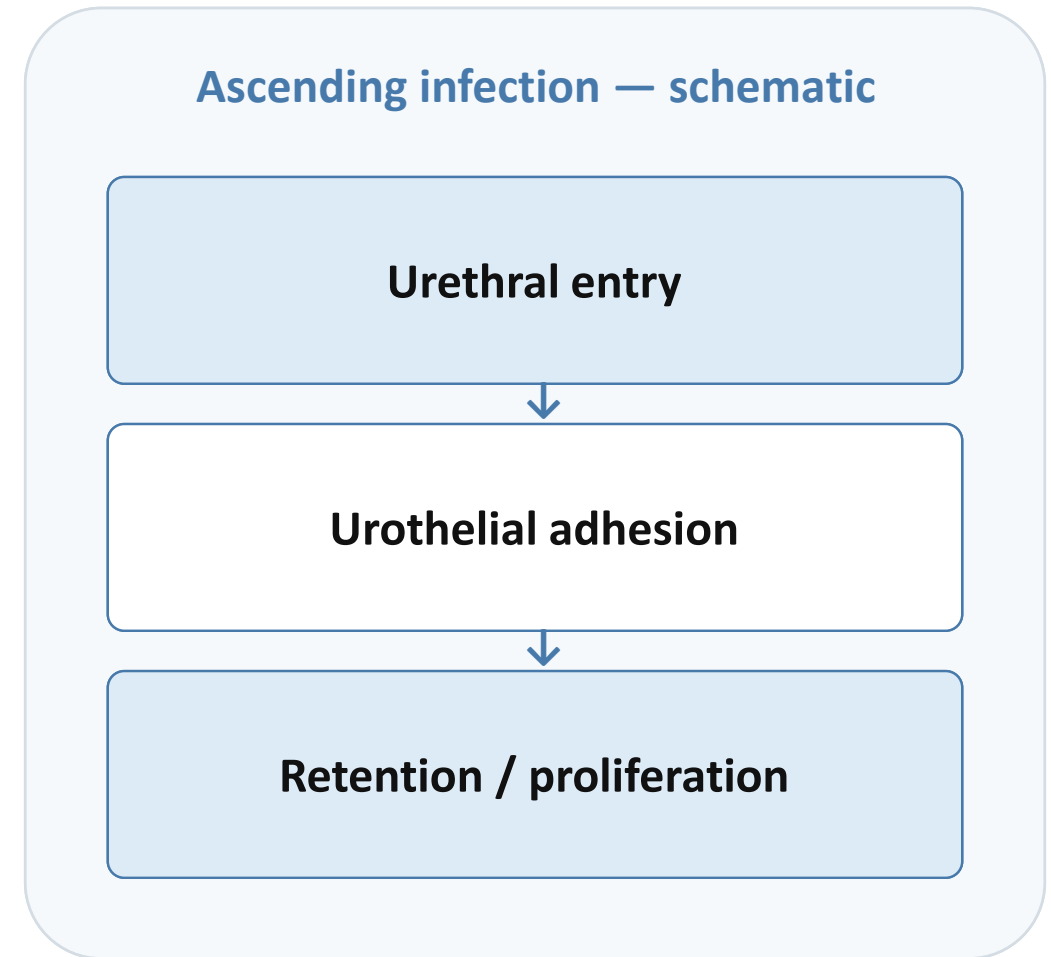
Urinary flow mechanically limits colonization



Bacterial attachment to urothelium counteracts repeated washout.

Adhesion is central to ascending urinary infection

- Most urinary tract pathogens enter through the urethra.
- Escherichia coli is a representative organism.
- Attachment to urothelial surfaces resists urinary flushing.
- Local proliferation may follow successful adherence.



Obstruction and reflux compromise urinary defense

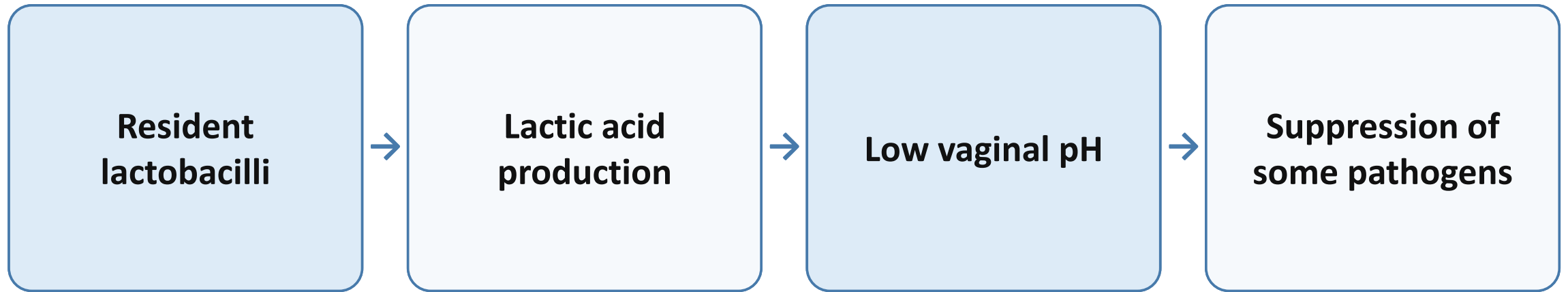
Effective urine flow

- Regular emptying of the urinary tract
- Washout of nonadherent microbes
- Reduced opportunity for growth

Impaired drainage

- Obstruction slows flushing
- Vesicoureteral reflux favors persistence / spread
- Predisposition to urinary tract infection

Vaginal lactobacilli maintain a protective acidic niche

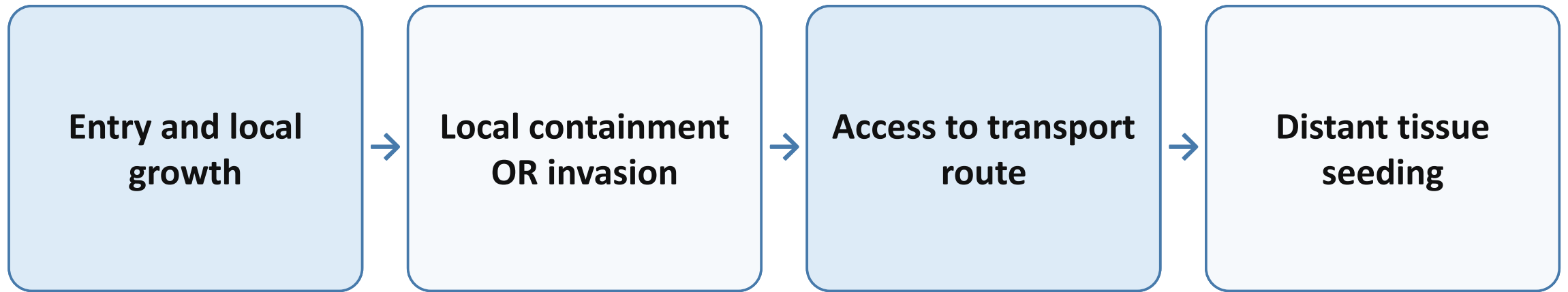


Antibiotic-associated disruption of vaginal microbiota may permit *Candida* overgrowth.

Portal-specific failures predict likely entry mechanisms

Portal	Protective mechanism	Representative failure
Skin	Epidermal integrity	Trauma or vector puncture
Gut	Acid; motility; microbiota	Acid resistance; ileus; antibiotics
Airway	Mucociliary clearance; phagocytes	Toxins; intracellular persistence
Urogenital	Urination; lactobacilli	Adhesion; obstruction; antibiotic use

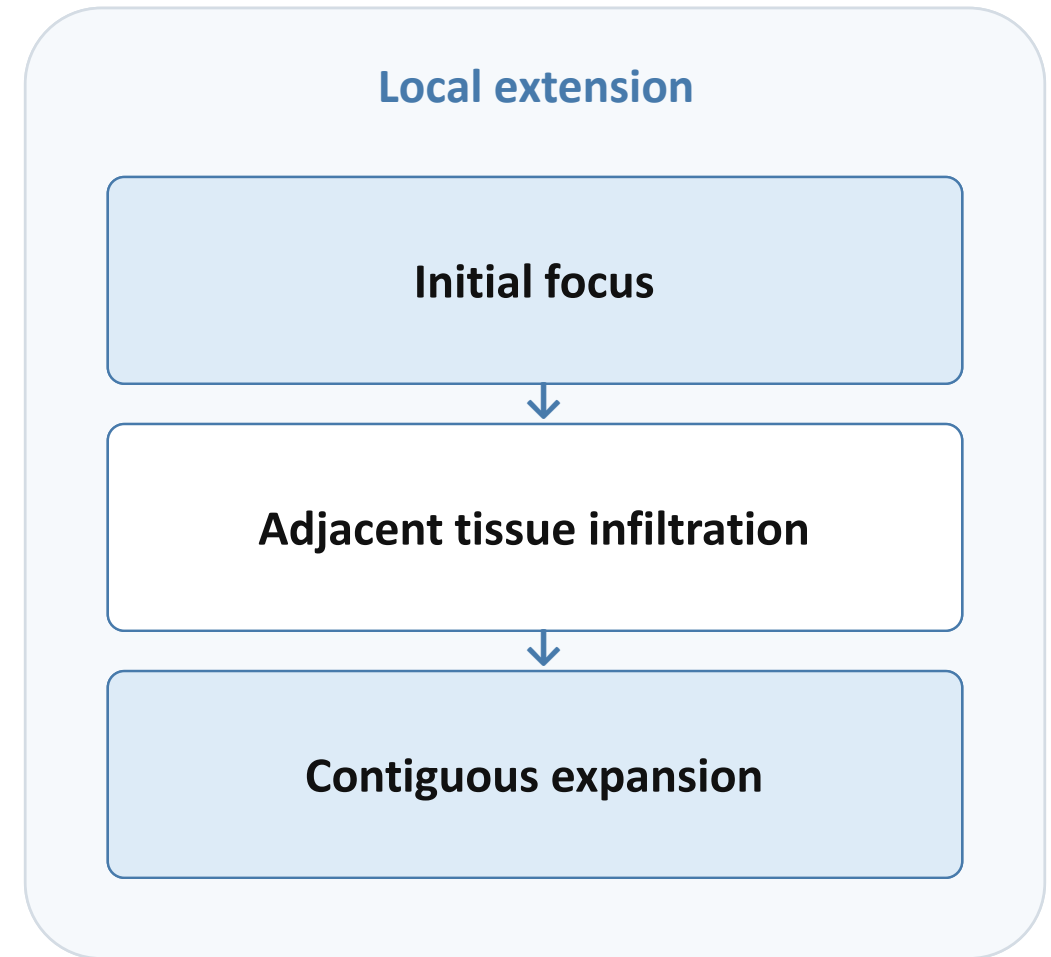
Local infection and dissemination are distinct outcomes



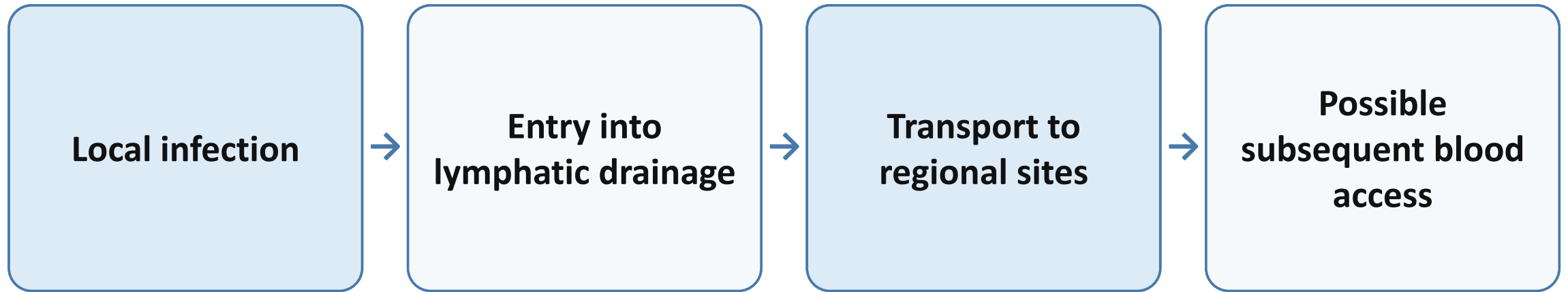
Successful entry need not imply systemic infection; The capacity to spread is pathogen-dependent.

Contiguous spread follows direct tissue invasion

- Some pathogens expand from the initial focus into adjacent tissue.
- Microbial enzymes can disrupt tissue barriers.
- No bloodstream step is necessary for direct extension.
- Anatomic continuity explains the distribution of lesions.

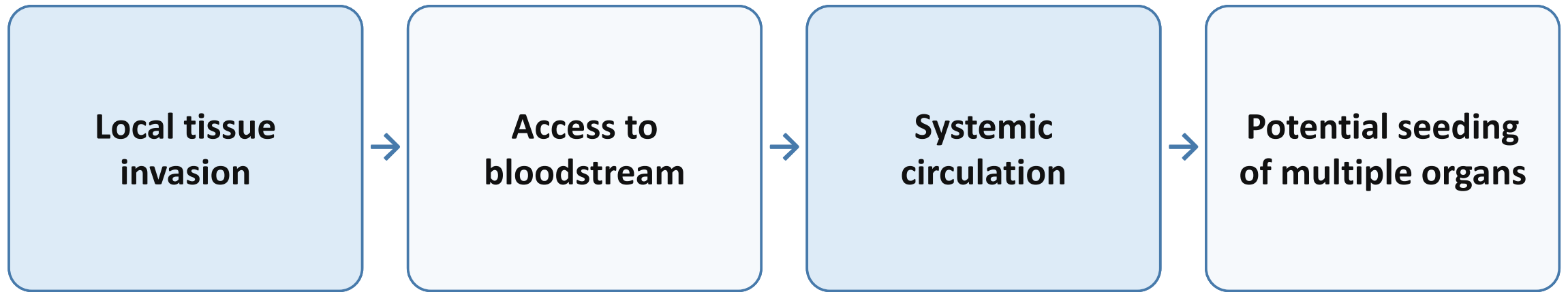


Lymphatic channels can transport microorganisms



Organisms may transit lymph freely or in inflammatory cells.

Bloodstream dissemination provides widespread access



The bloodstream as the most common and efficient long-distance route.

Bacteremia, tissue seeding, and sepsis are not identical

Distribution and seeding

- Microbes enter blood
- Organ-specific vascular delivery
- Focal tissue infection may develop

Systemic clinical syndrome

- Disseminated infection can trigger sepsis
- Fever, hypotension, and coagulopathy
- Severe cases can progress to organ failure

Nerves permit directed dissemination by selected microbes

- Some viruses exploit axonal transport.
- Rabies virus and varicella-zoster virus are textbook examples.
- Neural routes differ from hematogenous distribution.
- The route of transport helps explain target-organ disease.

Neural dissemination — schematic

Peripheral inoculation



Axonal transport

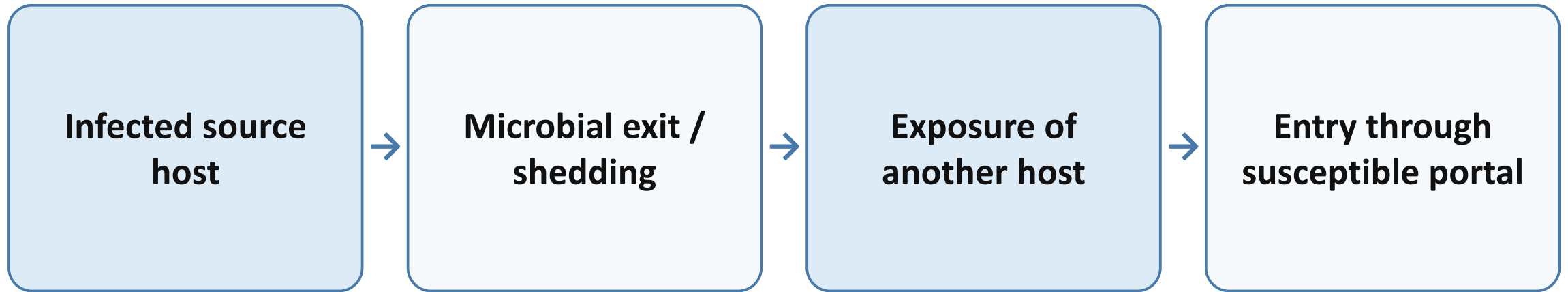


Central nervous system / ganglia

Transport routes provide different anatomical opportunities

Pathway	Mechanism	Consequence
Contiguous	Local enzymatic invasion	Extension to adjacent structures
Lymphatic	Transport in lymph or cells	Regional spread; potential blood access
Hematogenous	Circulation in blood	Distant organ seeding
Neural	Axonal transport	Spread along neuronal pathways

Transmission completes the pathogen life cycle



Shedding and successful entry are both needed for host-to-host propagation.

Microbial shedding varies in timing and duration

Brief

Short period of release

Intermittent

Release during disease flares

Persistent

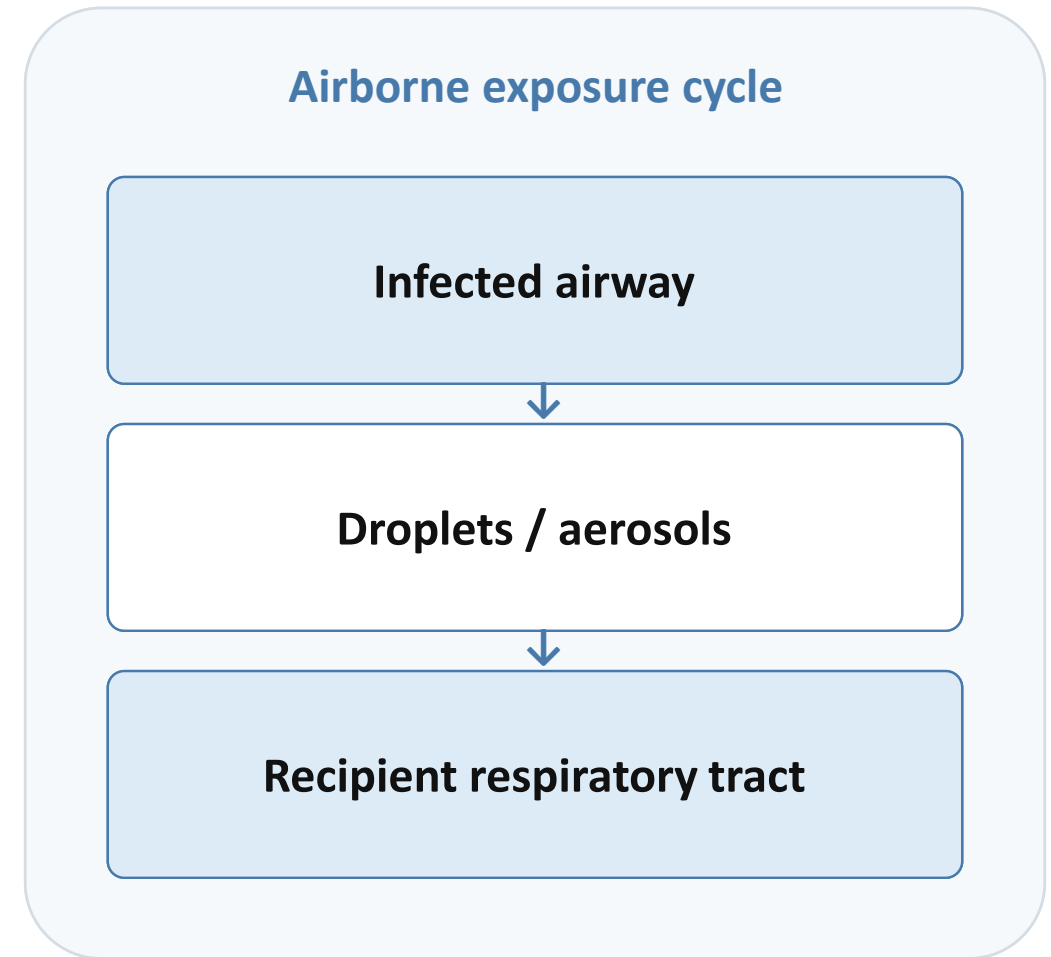
Long-duration shedding

Asymptomatic

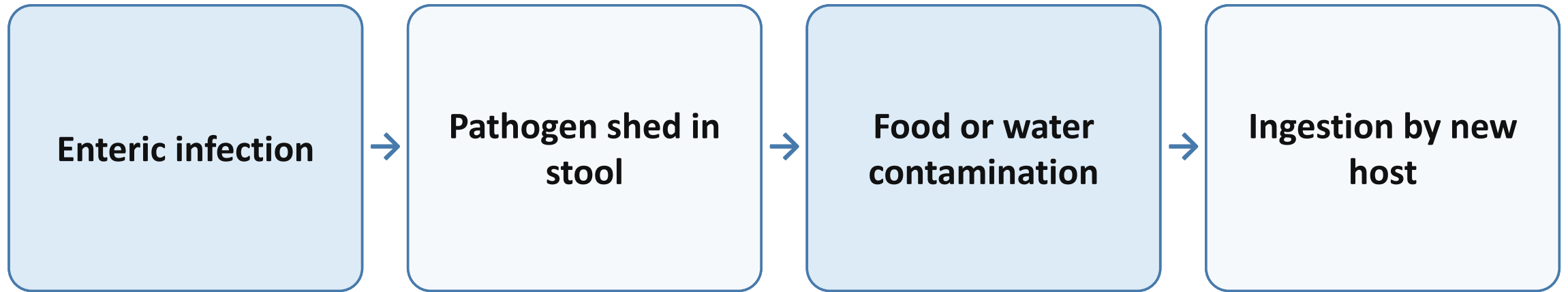
Transmission without overt illness

Respiratory transmission requires release into air

- Infected hosts expel pathogens in respiratory particles.
- Particle characteristics influence travel and deposition.
- Influenza and tuberculosis illustrate different patterns.
- Respiratory release links directly to airway entry in the recipient.



Fecal–oral transmission joins excretion and ingestion



Examples include hepatitis A/E viruses, rotavirus, cholera, Shigella, and Salmonella.

Sexual transmission exploits mucosal or intimate contact

Agent group	Representative organism
Viruses	HSV; HIV; HPV
Bacteria	N. gonorrhoeae; T. pallidum
Protozoa	Trichomonas vaginalis
Arthropods	Phthirus pubis

Vertical transmission has three distinct windows

In utero

Placental–fetal transmission

At delivery

Exposure during passage through birth canal

After birth

Transmission through maternal milk

Clinical implication

Timing can alter fetal or neonatal manifestations

Animal reservoirs and vectors expand transmission routes

Zoonotic pathways

- Direct animal contact / bites
- Exposure to infected animal products
- Vector-mediated transmission

Other pathways

- Arthropod blood meals carry some protozoa
- Saliva can transmit agents such as EBV
- Not every infection requires person-to-person spread

Transmission and entry must be matched

Exit / transmission	Portal in next host	Example
Respiratory particles	Respiratory mucosa	Influenza
Fecal contamination	Gastrointestinal tract	V. cholerae
Sexual contact	Genital mucosa	N. gonorrhoeae
Vector bite	Skin	Malaria
Maternal transmission	Fetal / neonatal interface	Rubella; CMV

The microbiome comprises resident microbial communities

- The human microbiome includes microorganisms living on or within the body.
- It encompasses bacteria, fungi, viruses, and protozoa.
- Communities differ across skin, gut, oral, lung, and vaginal niches.
- Each broad niche contains multiple site-specific microenvironments.

Microbial communities differ by anatomical niche

Oral

Distinct tooth, tongue, gingival, and salivary communities

Gut

Nutritional and metabolic interactions

Skin

Organisms adapted to cutaneous niches

Vaginal

Microbes can regulate local acidity

Commensal microbes influence host physiology

Nutrition

Microbes generate some vitamins and amino acids

Metabolism

Host physiology responds to microbial processes

Immunity

Microbiota modulate host immune function

Protection

Commensals can limit pathogen colonization

Microbiome–organ axes describe intersite relationships

Gut–lung

Cross-site associations with respiratory function

Gut–skin

Reported links between intestinal and cutaneous niches

Gut–brain

Investigated connections with neural function

Interpretation

Specific causal mechanisms are often uncertain

Dysbiosis may be a cause, consequence, or modifier

Association observed

- Microbiome differs between groups
- Disease may alter diet, physiology, or ecology
- Confounding can explain part of the signal

Causal role established?

- Direction of effect must be tested
- Specific responsible species often unknown
- Association alone cannot prove causation

Species-level associations demand cautious interpretation

Microorganism	Association / biological property	Interpretive limit
Ruminococcus gnavus	IBD flares	Association; causation not established
Prevotella copri	Rheumatoid arthritis	Correlation, not sole cause
Akkermansia muciniphila	Mucin degradation; barrier effects	Context-dependent host interaction

Culture-independent methods extend microbiome analysis

Method	What it contributes	Constraint
Culture	Growth of viable organisms	Many organisms difficult to culture
Sequencing	Taxonomic / genomic community profiling	Requires bioinformatic analysis
Metabolomics	Microbial and host-associated metabolites	Interpreting sources and functions is complex

Microbiome therapy has unequal levels of support

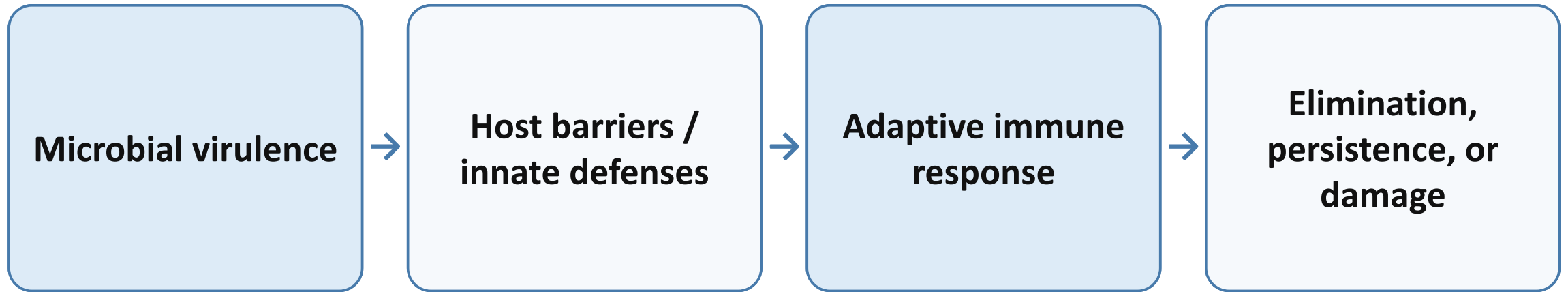
Textbook-supported application

- Fecal microbiota transplantation can treat recurrent *C. Difficile* infection
- Donor-stool-derived bacterial spore therapy is described

Investigational extension

- Trials in chronic noninfectious diseases have mixed results
- Engineered microbes, phages, and metabolites remain exploratory

Outcome depends on pathogen potency and host immunity



The immune response may both protect the host and contribute to tissue injury.

Protective immunity is multilayered

Physical

Intact epithelium and mechanical clearance

Innate

Phagocytes, complement, peptides, interferons

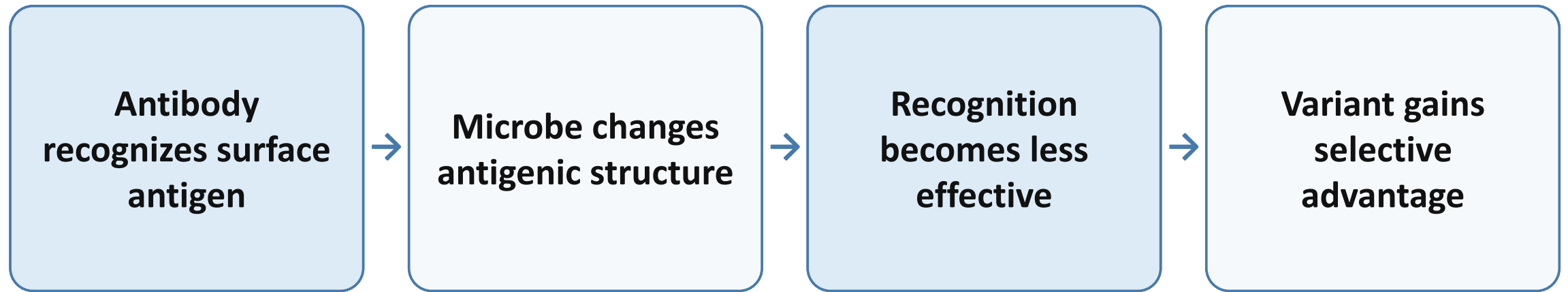
Adaptive humoral

Antibodies constrain extracellular microbes

Adaptive cellular

T cells recognize and control infected cells

Antigenic variation can defeat existing antibody recognition



Borrelia, trypanosomes, influenza, and other variable pathogens.

Antigenic variation arises through several mechanisms

Mechanism	Examples	Underlying change
High mutation rate	HIV; SARS-CoV-2	Sequence variation
Genome reassortment	Influenza; rotavirus	Exchange of genome segments
Genetic rearrangement	N. gonorrhoeae; Borrelia	Altered expressed antigen
Serotype diversity	Rhinoviruses; S. pneumoniae	Pre-existing antigenic heterogeneity

Antimicrobial peptide resistance counters innate killing

Usual peptide action

- Host cationic peptides bind microbial surfaces
- Peptide insertion can disrupt membranes
- Innate peptides therefore contribute to killing

Resistance strategies

- Change surface charge or hydrophobicity
- Secrete peptide-inactivating enzymes
- Export peptides using efflux pumps

Capsules and antibody-binding proteins deter phagocytosis

Polysaccharide capsule

- Inhibits phagocytic uptake
- Examples: Pneumococci, meningococci, H. Influenzae
- Barrier to effective opsonization / engulfment

Staphylococcal protein A

- Binds antibody Fc region
- Interferes with Fc-receptor-mediated uptake
- Illustrates a distinct anti-phagocytic strategy

Intracellular pathogens may survive after phagocytosis

Strategy	Example	Cellular consequence
Block phagosome–lysosome fusion	Mycobacteria	Reduced phagolysosomal killing
Escape phagosomal membrane	Listeria monocytogenes	Growth in cytosol
Survive within host cells	Leishmania; other protozoa	Persistence despite cell uptake

Intracellular survival includes manipulation of cell fate

Apoptosis

Some viruses delay infected-cell death

Autophagy

Microbes evade degradative trafficking

Host signaling

Viral proteins alter cellular pathways

Persistence

Altered cell fate extends replication opportunities

Microbes can interfere with interferon signaling

Usual interferon response

- Host cells produce interferons
- Receptor signaling activates JAK–STAT pathways
- Antiviral effectors include PKR

Viral interference

- Soluble receptor homologues act as decoys
- Viral factors inhibit JAK–STAT signaling
- Other factors block or inactivate PKR

Antigen presentation is an immune-evasion target

Normal recognition

- MHC class I presents to CD8⁺ T cells
- MHC class II presents to CD4⁺ T cells
- Cell-mediated immunity detects infected cells

Viral interference

- Some herpesviruses alter MHC I trafficking
- Other mechanisms affect MHC II
- Reduced presentation impairs T-cell recognition

Latency and immune-cell infection promote persistence

Latency

- Few viral genes may be expressed
- HSV / VZV persist in neurons
- EBV can persist in B lymphocytes

Immune-cell targeting

- HIV infects and destroys CD4⁺ T cells
- Loss of helper function compromises immunity
- Persistent infection changes host defense

Different immune deficits expose distinct vulnerabilities

Defective defense	Characteristic susceptibility
Antibodies	Encapsulated / extracellular bacteria
Terminal complement (C5–C9)	Neisseria species
Neutrophil function	S. aureus; selected bacteria and fungi
T-cell immunity	Intracellular pathogens, viruses, some parasites

Direct microbial and host-mediated mechanisms cause injury

Direct

Microbes infect cells and alter viability

Toxins

Secreted products cause injury at a distance

Tissue invasion

Enzymes / vascular injury produce necrosis

Immune-mediated

Antimicrobial responses damage host tissue

Clinical application: Integrate portal, defense, and outcome

A patient with impaired urinary outflow develops an infection caused by an adherent strain of E. Coli.

Interpretation question

Explain the microbial and host contributions to infection.

Mechanistic answer

E. Coli attachment opposes urinary washout, while obstruction further reduces a major local mechanical defense.

Clinical application: Distinguish spread from transmission

A neurotropic virus enters following an animal bite and later produces neurological disease.

Interpretation question

Which mechanism explains movement within the original host?

Mechanistic answer

Neural transport is an intrahost dissemination route; The bite was the original exposure / entry mechanism.

Integrative map: Where pathogenesis can be interrupted



Each transition requires compatible microbial traits and host conditions.

Core principles to retain

- Portal-specific physical, chemical, ecological, and immune defenses govern initial infection.
- Virulence factors and deficient host immunity are alternative ways to overcome defenses.
- Local invasion, blood, lymph, and nerves create different distributions of disease.
- Microbiome associations and immune responses require careful mechanistic interpretation.

Primary reference and source boundaries

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 8, Infectious Diseases.

General Principles of Microbial Pathogenesis and adjacent sections, printed pp. 304–308.

Original educational schematics are native PowerPoint shapes; source figures and photographs have not been reproduced.