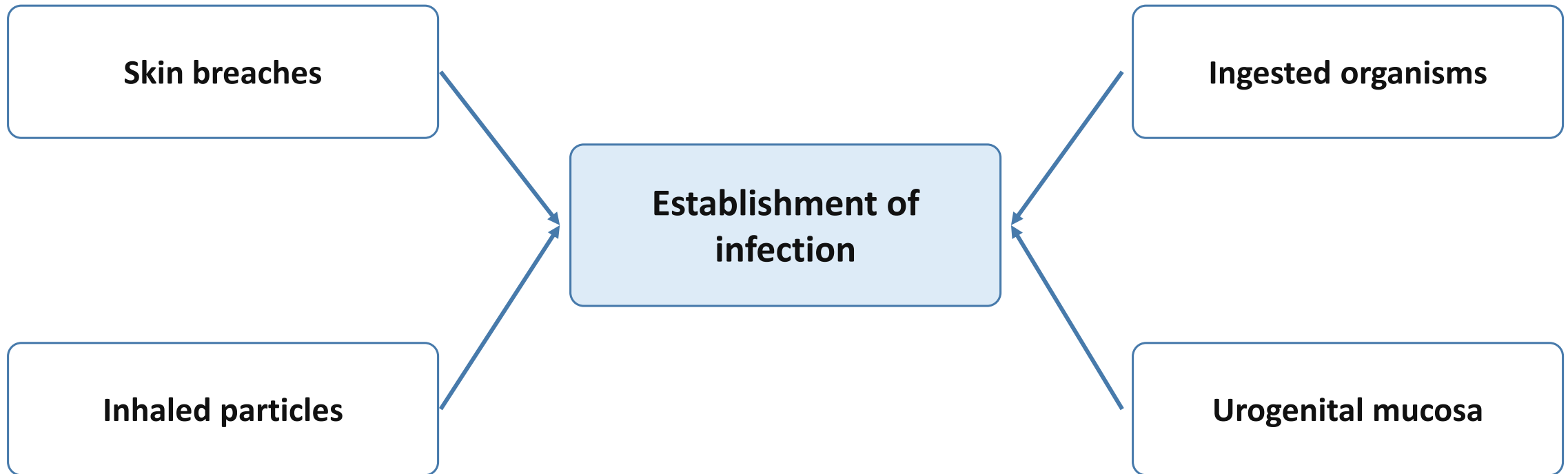


Routes of entry of microbes

Four principal entry contexts in human infectious disease



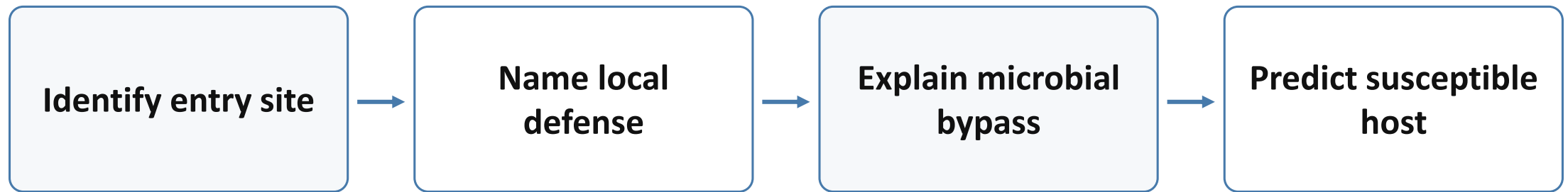
Dr Abu Suraih Sakhri

Entry depends on the portal's barrier and the microbe's ability to bypass it.

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Learning goals: Analyze a portal of infection

Use the same causal framework for every anatomical portal.



Causal sequence — schematic

Entry, dissemination and transmission are different events

Entry into a host

- Crosses skin or mucosal defenses
- Establishes a local foothold
- May remain localized

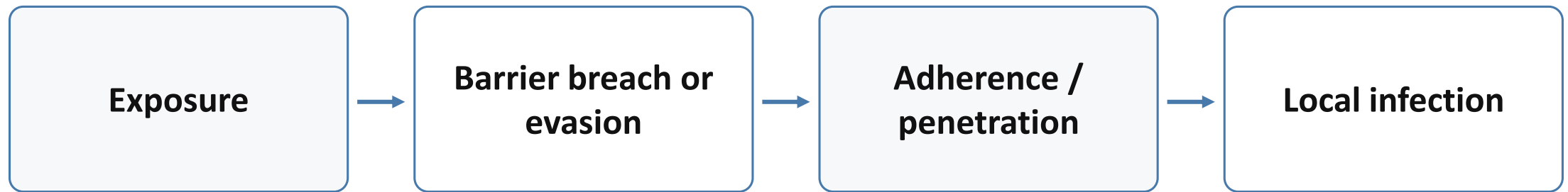
After entry

- Spread may occur within tissues, blood, lymphatics or nerves
- Exit and transmission occur by separate processes

A portal of entry does not determine whether infection becomes systemic.

A pathogen must establish a foothold

Exposure is necessary but does not, by itself, establish disease.



Causal sequence — schematic

Two routes to successful invasion

Intact mucosal surface

- Respiratory, intestinal and genital pathogens may bind intact epithelium
- Virulence enables adherence, entry or proliferation

Disrupted skin barrier

- Most skin infections follow epidermal injury
- Trauma or procedures provide direct access

The route reflects both microbial capabilities and anatomical vulnerability.

Major local defenses differ by portal

Portal	Principal defense	Representative vulnerability
Skin	Keratinized epidermis; Low pH; Peptides	Trauma, puncture, burn or ulcer
Gut	Acid; Mucus; IgA; Motility; Microbiota	Resistance, invasion, obstruction, antibiotics
Airway	Mucociliary clearance; Macrophages	Epithelial infection or impaired clearance
Urogenital	Urine flow; Vaginal microbiota; Mucosa	Adhesion, obstruction, antibiotics, trauma

Barrier failure may be host-driven or microbial

Microbial strategies

- Adherence or tissue penetration
- Resistance to hostile secretions
- Survival after phagocytosis

Host vulnerabilities

- Tissue trauma or altered anatomy
- Reduced clearance or disturbed microbiota
- Systemic immunodeficiency

A normal commensal can become pathogenic when a local defense is severely weakened.

The epidermis is a multilayered defense

For skin infection, a break in the epithelial shield is the predominant predisposing event.

1. Keratinized surface prevents access

2. Low surface pH inhibits organisms

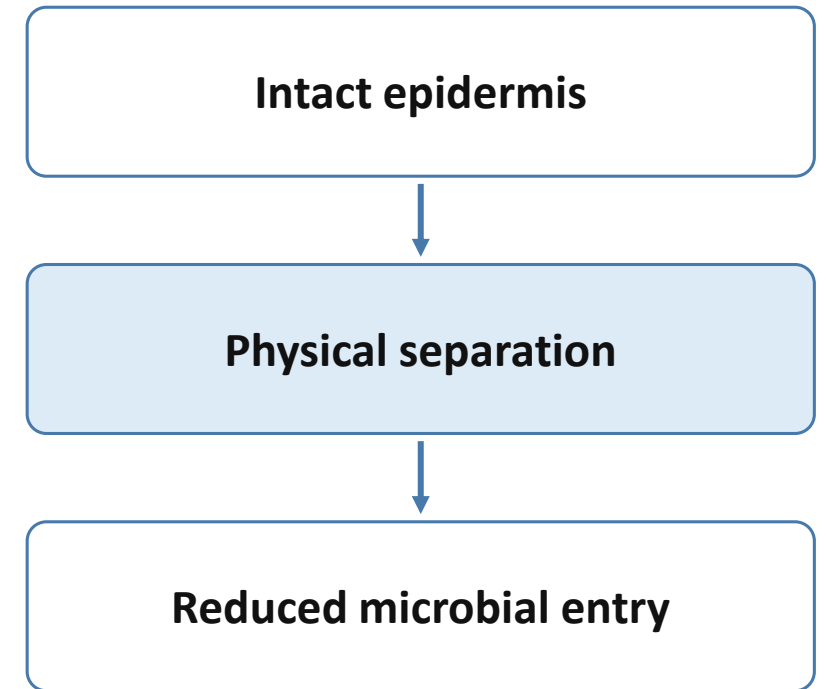
3. Fatty acids and defensins are antimicrobial

4. Barrier injury removes the main protection

Intact skin: Physical exclusion

- Keratinized epidermis creates a durable mechanical barrier.
- Most pathogens cannot traverse an undamaged skin surface.
- Punctures, ulcers, trauma and burns create entry opportunities.

PROTECTIVE SEQUENCE



Skin surface chemistry restricts microbes

Low surface pH

- Inhibits organisms poorly adapted to acid
- Acts with the physical epidermal barrier

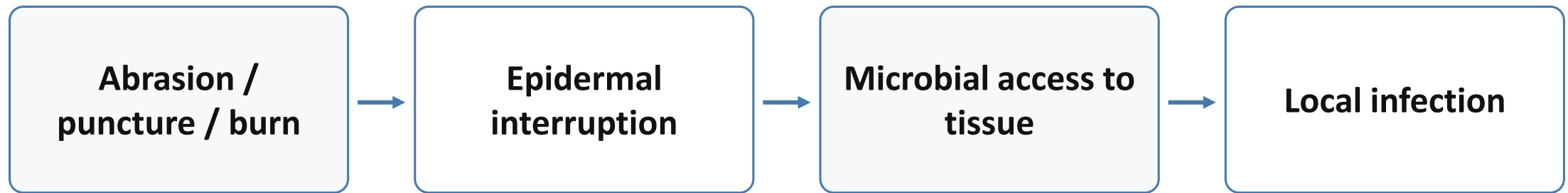
Endogenous antimicrobials

- Antimicrobial fatty acids
- Defensins: Small bacteria-toxic peptides

Skin protection is both structural and biochemical.

Trauma converts exposure into inoculation

A structural defect can bypass defenses without requiring an organism to invade intact keratinized epithelium.



Causal sequence — schematic

Burns, ulcers and punctures create distinct breaches

Breach	Barrier defect	Illustrative pathogen
Burn or extensive surface injury	Loss of intact epidermis	Pseudomonas aeruginosa
Cut, puncture or local wound	Direct route into skin or soft tissue	Staphylococcus aureus
Needle stick	Percutaneous inoculation	HIV; Hepatitis B or C viruses

Needle injury bypasses the epidermal barrier

- A penetrating needle introduces material beneath intact surface defenses.
- Blood-borne viruses are relevant to this inoculation route.
- HIV and hepatitis B and C viruses are examples of percutaneous pathogens.

PERCUTANEOUS PORTAL

Contaminated needle



Direct inoculation



Host exposure

Arthropod bites act as inoculation portals

Entry event	Example disease or agent	Key interpretation
Arthropod bite	Malaria	Inoculation through skin by a vector
Arthropod bite	Yellow fever; Plague; Lyme disease	Vector-associated breach of skin
Animal bite	Rabies	Direct pathogen introduction through bite

Animal bites are not equivalent to vector bites

Vector-mediated entry

- Arthropod introduces an infectious agent
- Examples include malaria and Lyme disease

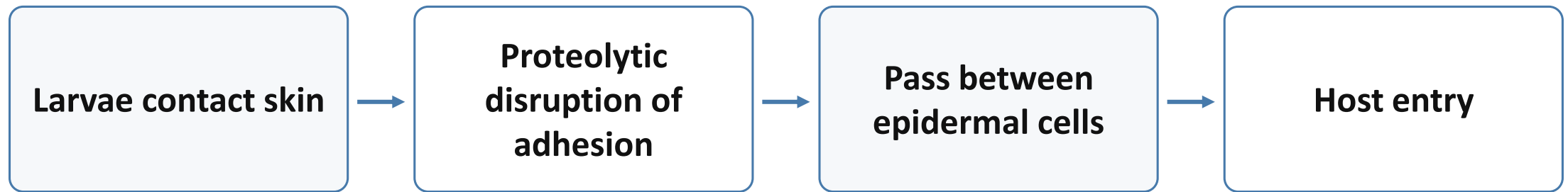
Animal bite entry

- Mechanical injury breaches skin
- Rabies is a listed example

Both bypass skin, but their reservoirs and transmission cycles differ.

Schistosome larvae can penetrate unbroken skin

A parasite-specific mechanism overcomes a skin barrier that remains grossly intact.



Causal sequence — schematic

Skin entry: Injury versus direct penetration

Predominant pattern

- Most cutaneous infection begins at an injured epidermis
- Staphylococci and Pseudomonas are examples

Notable exception

- Schistosoma larvae traverse intact skin
- Enzymes disrupt proteins joining keratinocytes

Do not assume every skin infection requires a visible wound.

Clinical reasoning: Infected puncture wound

An otherwise healthy patient develops a localized infection after a puncture wound.

Mechanistic question

What defense failed, and why was the portal permissive?

Mechanical interruption of keratinized epidermis provides access to deeper tissue; This differs from invasion through intact mucosa.

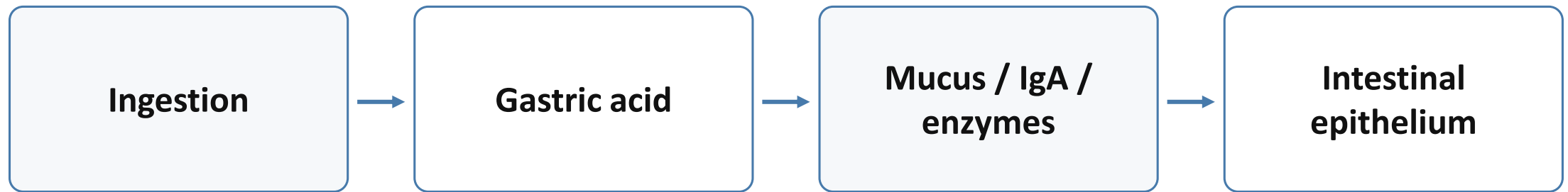
Examples of wound-associated pathogens include *S. Aureus* and *P. Aeruginosa*.

Skin portal: Synthesis across entry mechanisms

Mechanism	Defense defeated	Examples
Surface injury	Mechanical epidermal barrier	S. Aureus; P. Aeruginosa
Needle puncture	Percutaneous inoculation	HIV; HBV; HCV
Bite	Cutaneous barrier + inoculation	Rabies; Vector-borne pathogens
Enzymatic entry	Interkeratinocyte adhesion	Schistosoma spp.

Gastrointestinal entry requires surviving serial barriers

An enteric organism encounters several defenses before it can establish infection.



Causal sequence — schematic

Fecal contamination is a major exposure pathway

- Many gastrointestinal pathogens arrive in food or drinking water contaminated with fecal material.
- Failure of hygiene increases opportunity for fecal–oral acquisition.
- Ingestion does not guarantee infection: Local defenses still act.

EXPOSURE ROUTE

Contaminated food / water



Ingestion



GI exposure

Gastric acid is a powerful microbial barrier

The text highlights gastric acidity as particularly important among gastrointestinal defenses.

1. Acidic gastric secretion damages susceptible organisms

2. Only surviving microbes enter distal bowel

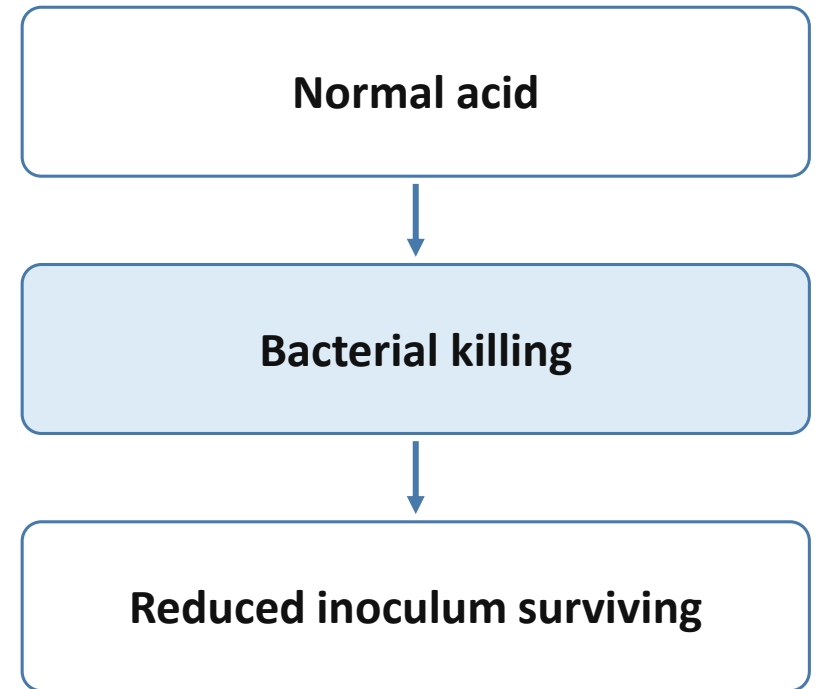
3. Microbial acid tolerance alters infectivity

4. Neutralization reduces this protective filter

Gastric pH can determine *Vibrio* infectivity

- *Vibrio cholerae* is an illustrative organism whose infectivity is strongly constrained by gastric acidity.
- Neutralizing gastric acid greatly increased *V. Cholerae* infectivity in healthy volunteers.
- This links one host defense to the probability of establishing an infection.

HOST DEFENSE



Mucus and secretory IgA defend the intestinal surface

Superficial mucus

- Separates luminal organisms from epithelium
- Provides a local protective layer

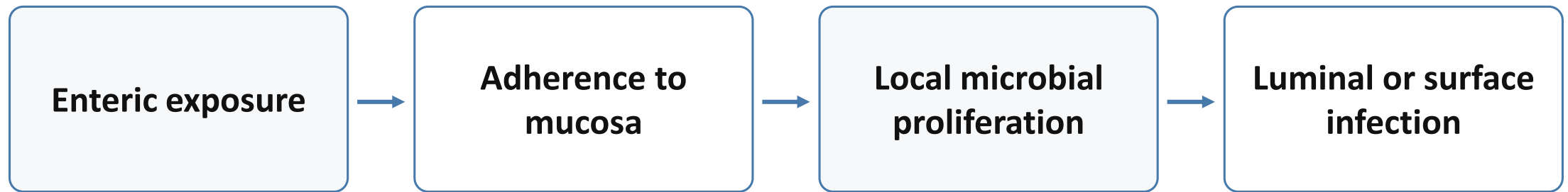
Secretory IgA and defensins

- Mucosal immunologic defense
- Antimicrobial peptides limit susceptible microbes

Organisms must circumvent more than gastric acidity.

Attachment can establish infection without invasion

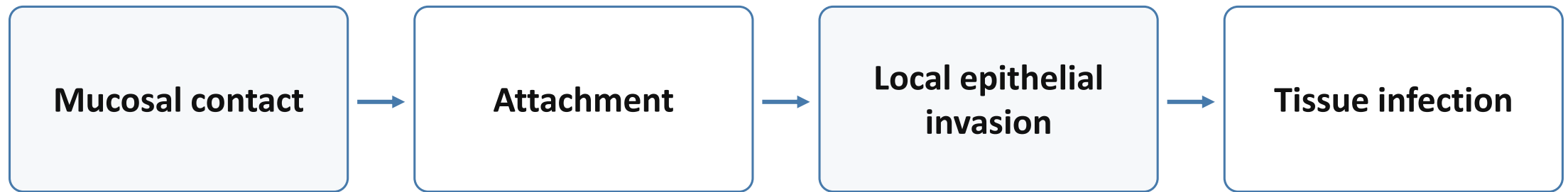
Table 8.1 lists *V. Cholerae* and *Giardia duodenalis* as examples of attachment with local proliferation.



Causal sequence — schematic

Other enteric bacteria adhere and invade

Shigella, Salmonella and Campylobacter exemplify local invasion after entry.

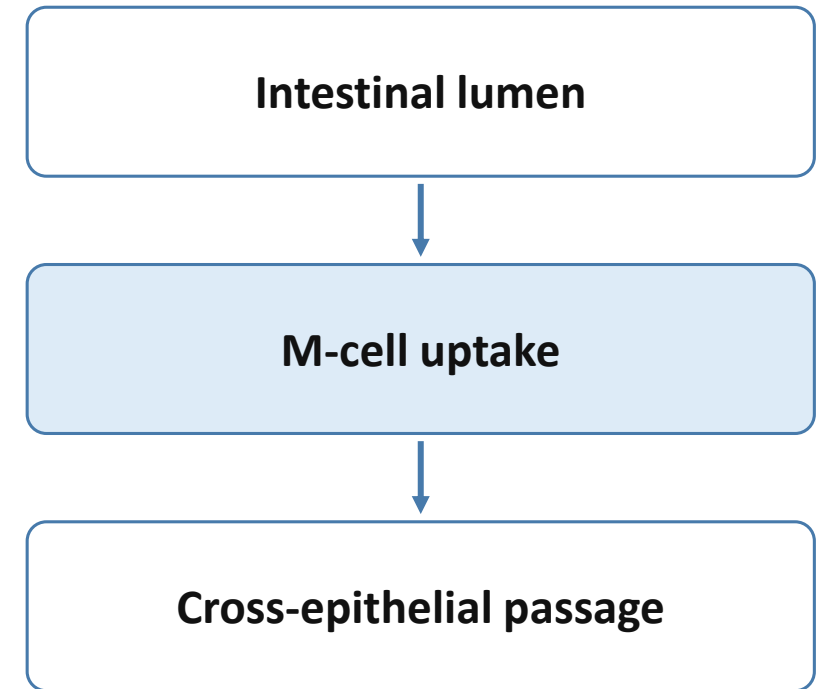


Causal sequence — schematic

M cells provide a specialized uptake route

- M cells represent a route by which microbes can be taken across intestinal epithelium.
- Poliovirus, Shigella and Salmonella exemplify uptake through M cells.
- Uptake through an epithelial specialization differs from simple surface colonization.

ALTERNATIVE EPITHELIAL ENTRY



Enteric entry can follow three epithelial patterns

Pattern	Representative organisms	Key distinction
Attachment + proliferation	V. Cholerae; G. Duodenalis	Surface colonization
Attachment + local invasion	Shigella; Salmonella; Campylobacter	Crosses or damages epithelium
Uptake through M cells	Poliovirus; Shigella; Salmonella	Specialized epithelial uptake

Acid-resistant cysts and eggs survive ingestion

Protozoal cysts

- Resistant outer coats
- Permit survival through gastric acidity

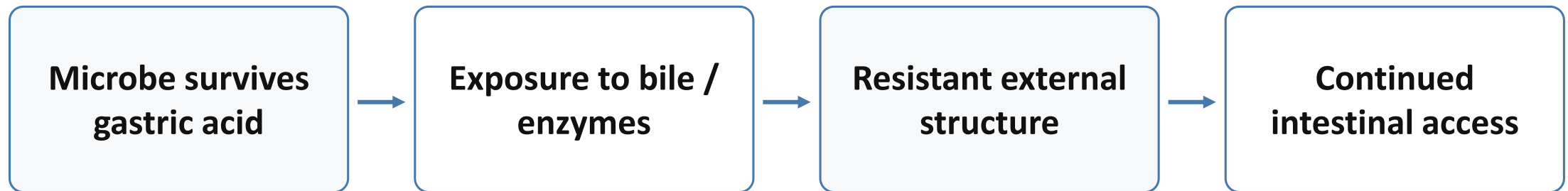
Helminth eggs

- Protective external coats
- Support passage through the stomach

Structural resistance is a microbial answer to a chemical host defense.

Bile and pancreatic enzymes create additional selection

Hepatitis A virus, rotavirus and norovirus exemplify resistance to luminal defenses.



Causal sequence — schematic

Norovirus resists gastrointestinal defenses

- Norovirus is resistant to gastrointestinal acid, bile and pancreatic enzymes.
- The absence of a lipid envelope contributes to resistance.
- This illustrates how viral structure affects success after ingestion.

VIRION PROPERTIES

No lipid envelope



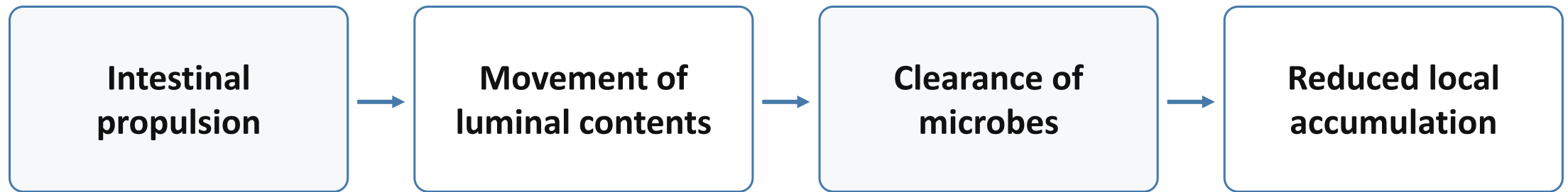
Enzyme / bile resistance



Persistence through gut

Peristalsis mechanically limits overgrowth

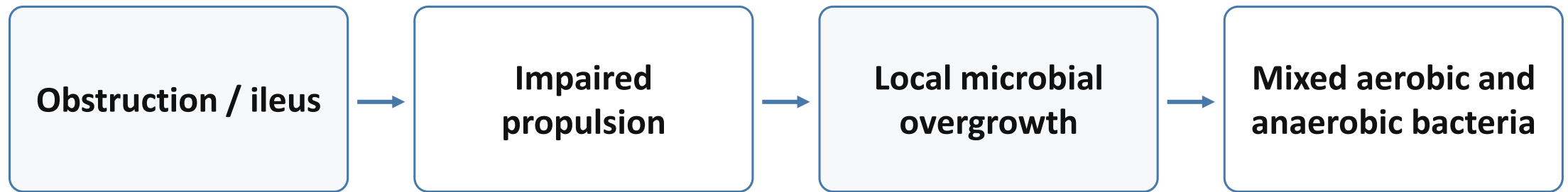
Normal motility is a protective process, not merely a digestive function.



Causal sequence — schematic

Obstruction or ileus defeats intestinal clearance

Postsurgical adhesions can also obstruct the normal clearance of luminal organisms.



Causal sequence — schematic

The intestinal microbiota resists colonization

Normal microbiota

- Occupies ecological niches
- Competitively inhibits potential pathogens

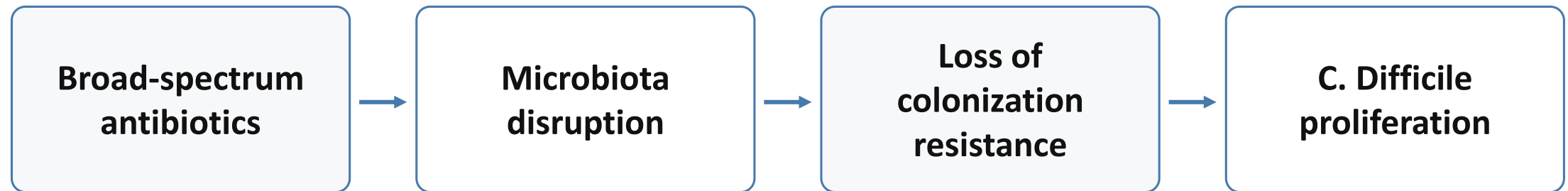
Disturbed microbiota

- Antibiotic exposure can remove competitors
- Opportunistic overgrowth becomes possible

Microbial communities are themselves an important mucosal defense.

Antibiotics permit C. Difficile overgrowth

Loss of ecological competition explains susceptibility even without epithelial trauma.



Causal sequence — schematic

GI disease is possible without a highly invasive organism

Direct microbial adaptation

- Acid-resistant external structures
- Epithelial adherence or invasion
- Resistance to enzymes

Compromised host environment

- Impaired peristalsis
- Antibiotic-disrupted microbiota
- Weakened local defenses

The relative contribution of pathogen and host varies across enteric infections.

Clinical reasoning: Diarrhea after antibiotics

Diarrheal illness follows broad-spectrum antibiotic exposure.

Mechanistic question

Which local defense has been disrupted?

The intestinal microbiota normally prevents colonization and overgrowth; Antibiotic disruption permits *C. Difficile* proliferation.

The explanatory mechanism is ecological rather than a mechanical epithelial breach.

Clinical reasoning: Contaminated drinking water

Multiple people develop enteric illness after ingesting fecally contaminated drinking water.

Mechanistic question

Identify the exposure route and the earliest major host barrier.

Fecal–oral acquisition; Gastric acidity is an early defense, followed by mucosal and luminal defenses.

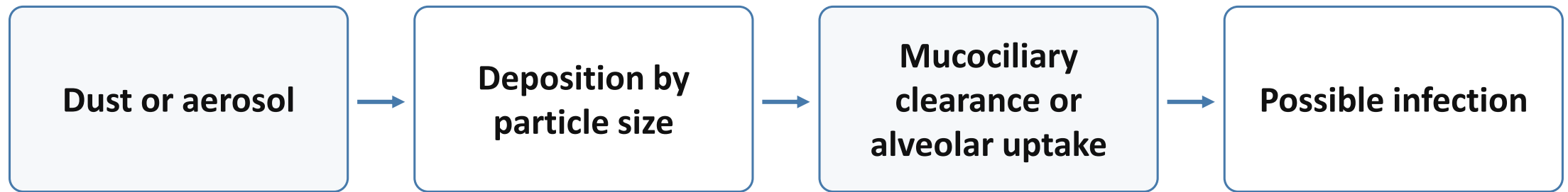
Different enteric organisms survive by acid resistance, adherence or invasion.

Gastrointestinal defense failures in one view

Defense	Failure / bypass	Illustrative organism
Gastric acid	Resistant cyst or egg	Protozoa; Helminths
Epithelial barrier	Adherence; Invasion; M cells	Vibrio; Shigella; Salmonella
Peristalsis	Obstruction or ileus	Mixed enteric bacteria
Microbiota	Broad-spectrum antibiotics	C. Difficile

Respiratory exposure begins with inhalation

Most daily inhaled microbes are removed before establishing infection.



Causal sequence — schematic

Particle size influences where organisms deposit

Larger inhaled particles

- Caught in upper-airway mucociliary layer
- Moved to pharynx and swallowed

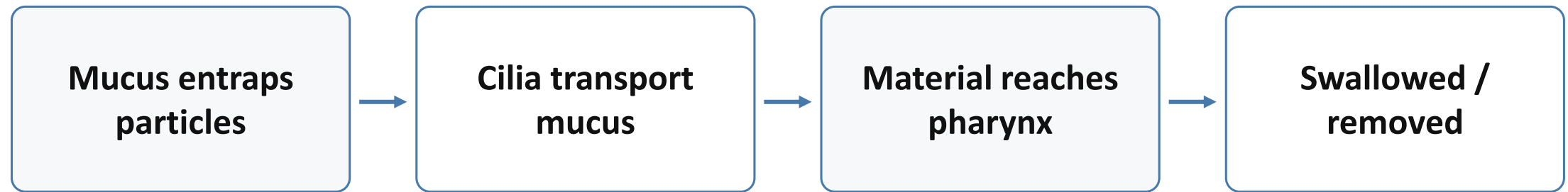
Small particles (<5 μm)

- May reach the alveoli
- Encounter resident macrophages and leukocytes

Particles under 5 μm can be carried into the alveoli.

Mucociliary clearance moves contaminants away

Efficient clearance reduces time available for microbes to bind respiratory epithelium.

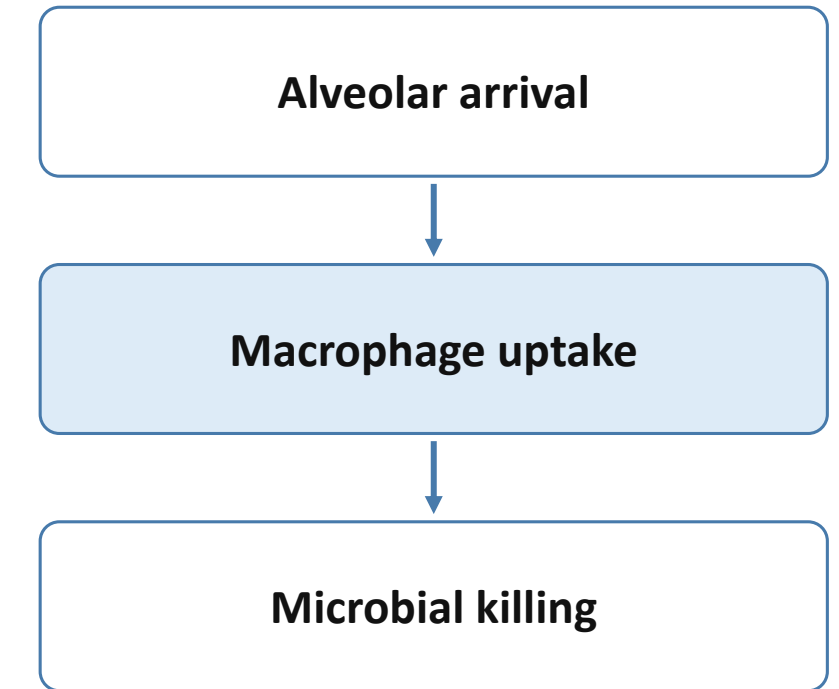


Causal sequence — schematic

Alveolar phagocytes defend the distal airway

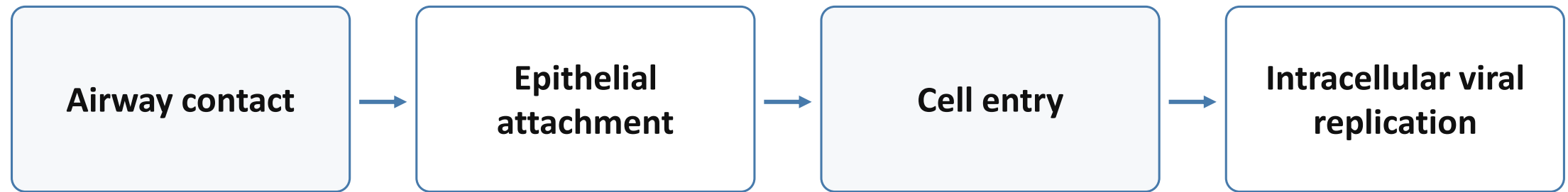
- Small inhaled particles reach alveolar compartments.
- Phagocytic leukocytes, especially alveolar macrophages, constitute a major local defense.
- An organism able to survive after phagocytosis may establish pulmonary infection.

NORMAL DEFENSE



Influenza uses respiratory epithelial cells

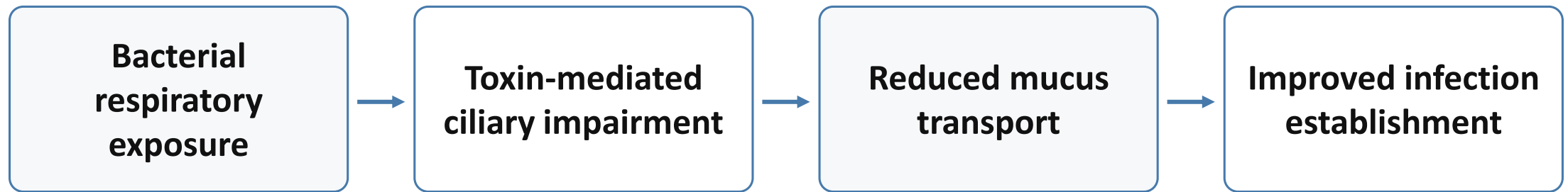
Attachment and intracellular multiplication allow respiratory viruses to establish infection.



Causal sequence — schematic

Bordetella pertussis interferes with cilia

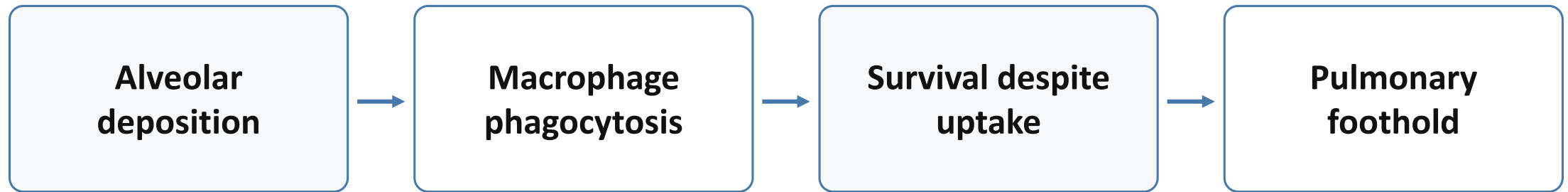
Loss of mechanical clearance allows pathogens more opportunity to persist.



Causal sequence — schematic

Mycobacterium tuberculosis resists phagocytic killing

Survival after macrophage uptake permits establishment in distal air spaces.



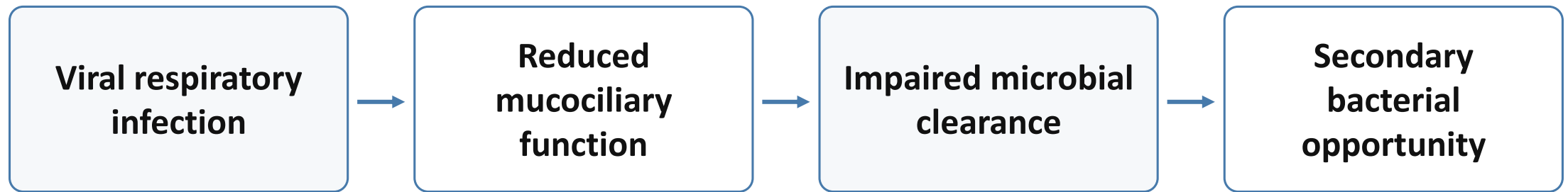
Causal sequence — schematic

Respiratory pathogens exploit distinct defenses

Protective process	Evading pathogen	Mechanism
Intact respiratory epithelium	Influenza virus	Attachment, entry and replication
Mucociliary activity	B. Pertussis	Ciliary impairment by toxins
Alveolar phagocytosis	M. Tuberculosis	Resistance to intracellular killing

Influenza can predispose to subsequent bacterial infection

An initial infection can alter host defenses and facilitate another infection.



Causal sequence — schematic

Smoking and ventilation impair airway defenses

Smoking

- Compromises mucociliary clearance
- Creates conditions favoring bacterial infection

Mechanical ventilation

- May disturb normal airway defenses
- Increases opportunity for pathogen establishment

A respiratory portal can become susceptible without a more virulent organism.

Cystic fibrosis is a clearance-vulnerability state

- Cystic fibrosis impairs respiratory mucociliary clearance.
- Reduced clearance creates a permissive environment for bacterial infection.
- Portal susceptibility reflects host physiology as well as exposure.

HOST FACTOR

Defective clearance



Airway retention



Bacterial susceptibility

Systemic immunodeficiency changes respiratory risk

Common defense evasion

- Influenza infects epithelial cells
- B. Pertussis interferes with ciliary function

Compromised systemic immunity

- Pneumocystis jirovecii infection
- Aspergillus species infection

Organisms with limited success in immunocompetent hosts may cause disease when systemic defenses fail.

Airway susceptibility: Identify the broken defense

Setting	Compromised defense	Interpretation
Influenza infection	Respiratory clearance	Creates bacterial susceptibility
Smoking / ventilation	Mucociliary function	Reduced removal of inhaled microbes
Cystic fibrosis	Mucociliary clearance	Persistence of inhaled organisms
Immunodeficiency	Systemic immune surveillance	Opportunistic respiratory infection

Clinical reasoning: Alveolar infection

An inhaled organism reaches the alveoli and survives within pulmonary macrophages.

Mechanistic question

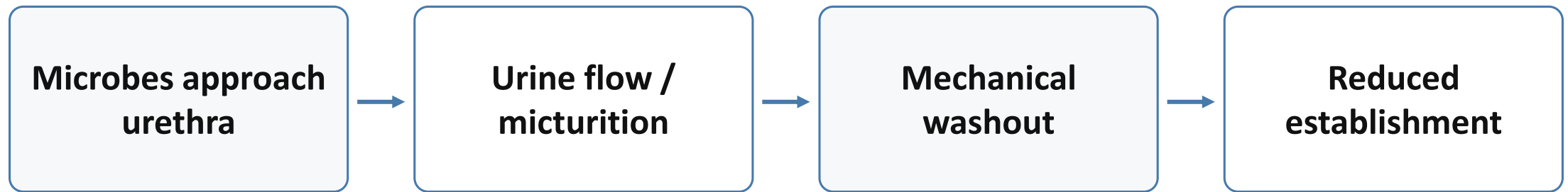
Which host defense was bypassed, and which organism illustrates it?

Macrophage-mediated intracellular killing; *Mycobacterium tuberculosis* illustrates this mechanism.

This is different from ciliary toxin-mediated escape in upper conducting airways.

Urinary flushing is a first-line defense

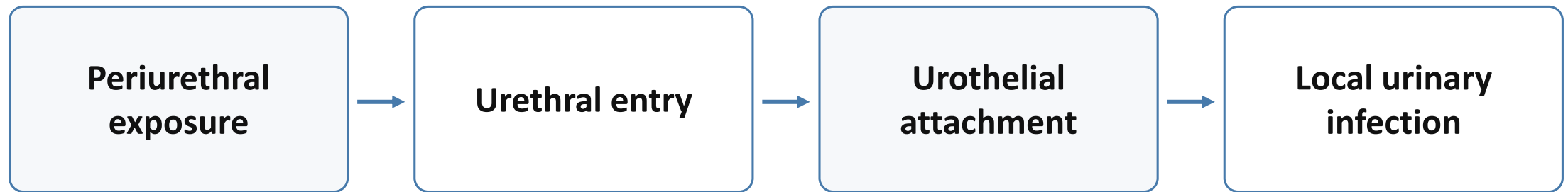
Regular urinary emptying limits persistence and local proliferation.



Causal sequence — schematic

Most urinary pathogens ascend through the urethra

Escherichia coli illustrates a pathogen adapted to ascending urinary entry.



Causal sequence — schematic

Urothelial adhesion counters washout

Without sustained adhesion

- Urination removes many organisms
- Local establishment is prevented

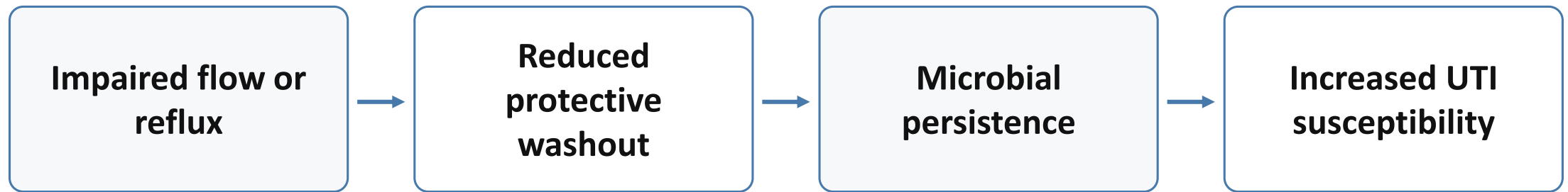
With microbial adhesion

- Organisms remain despite urinary flow
- Local proliferation becomes possible

Successful colonization requires persistence under mechanical clearance.

Obstruction and reflux raise UTI susceptibility

Normal urinary outflow is an important anti-infective mechanism.



Causal sequence — schematic

Shorter urethral anatomy influences UTI risk

- Shorter female urethral length contributes to higher susceptibility to ascending UTIs.
- A shorter access route facilitates movement of bacteria from the rectal region.
- Anatomical susceptibility is distinct from an intrinsic microbial virulence factor.

ANATOMIC CONTRIBUTION

Perineal bacteria



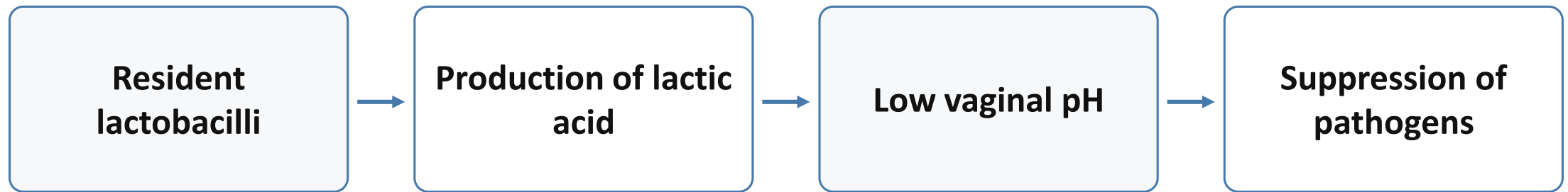
Short urethral access



Ascending exposure

Lactobacilli preserve an acidic vaginal milieu

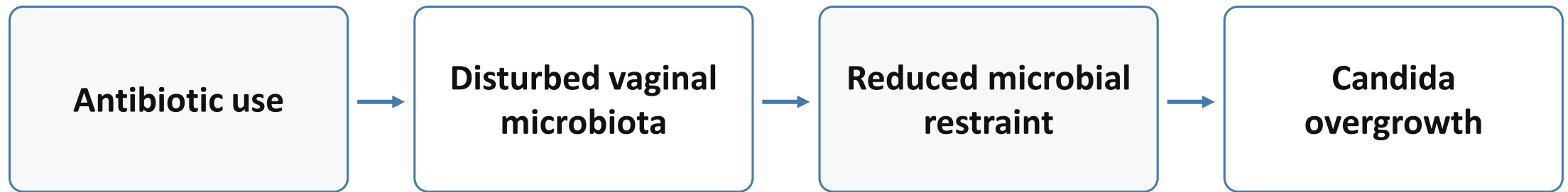
The protective environment is described between puberty and menopause.



Causal sequence — schematic

Antibiotics may undermine vaginal colonization resistance

Candida albicans can exploit disruption of normal vaginal microbiota.



Causal sequence — schematic

Gonococci can establish infection at intact mucosa

- An intact epithelial barrier is not sufficient against every genital pathogen.
- *Neisseria gonorrhoeae* can attach and proliferate locally.
- The success of infection reflects microbial adaptation to a mucosal niche.

MUCOSAL ENTRY

Mucosal contact



Attachment



Local proliferation

Genital pathogens may invade local tissue

Attachment and proliferation

- *Neisseria gonorrhoeae*
- Mucosal colonization despite an epithelial barrier

Direct local infection or invasion

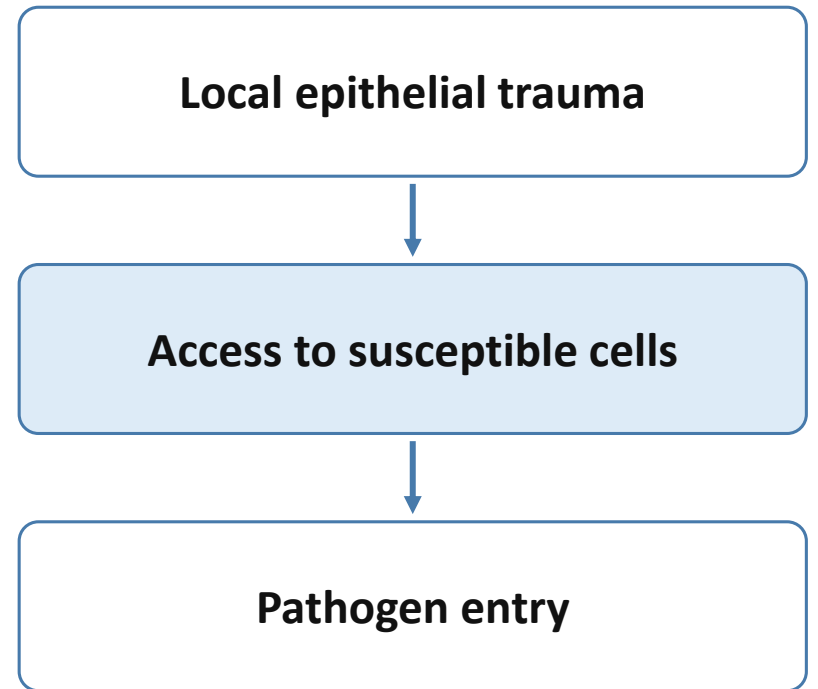
- Herpes viruses
- Syphilis

Mucosal attachment and invasion represent distinct strategies for local infection.

Local trauma can facilitate genital infection

- Disrupted genital epithelium may provide a portal for sexually transmitted infection.
- Human papillomavirus is listed as an example associated with local trauma.
- Physical breach and mucosal attachment are complementary routes.

BARRIER FAILURE



Urogenital defense mechanisms compared

Site / barrier	Failure mechanism	Example
Urinary tract: Flushing	Obstruction / reflux; Adhesion	E. Coli
Vagina: Protective microbiota	Antibiotic-associated disruption	C. Albicans
Genital mucosa: Epithelium	Attachment; Local proliferation	N. Gonorrhoeae
Genital epithelium: Integrity	Local trauma	HPV

Four portals: One unifying framework

Portal	Protective bottleneck	Typical solution for pathogen
Skin	Intact keratinized epidermis	Wound, bite, needle or penetration
Gastrointestinal	Acid, enzymes, motility, microbiota	Resistance, attachment, invasion
Respiratory	Ciliary clearance, macrophages	Epithelial infection, toxin, survival
Urogenital	Flushing, acidity, epithelium	Adhesion, altered flow, trauma

Local infection does not imply systemic dissemination

Localized disease

- Pathogen remains near entry site
- Clinical effects arise from local infection

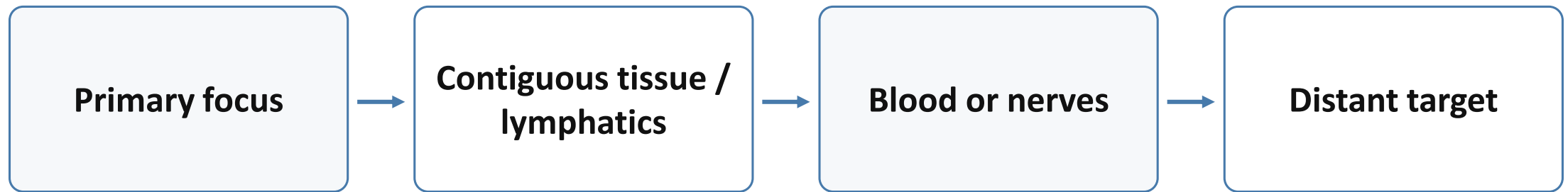
Disseminated disease

- Organism invades tissues or transport routes
- Remote organs may be seeded

Entry and subsequent spread are separable phases of pathogenesis.

Microbes disseminate by several anatomical routes

Bloodstream spread is described as the most efficient route to multiple organs.

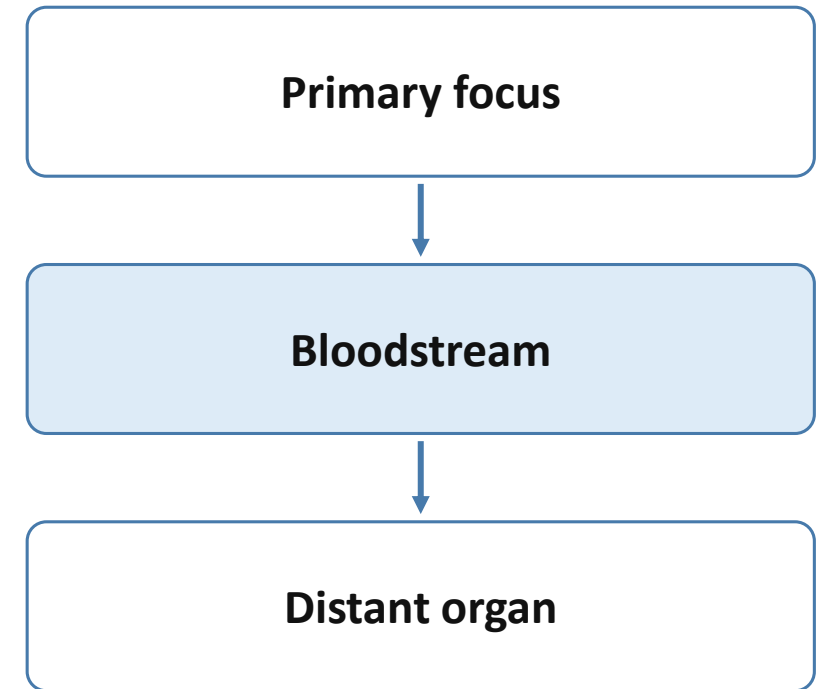


Causal sequence — schematic

Bloodstream dissemination can seed distant organs

- Hematogenous spread grants access to multiple organ systems.
- Seeding of tissues can become the dominant manifestation of disseminated infection.
- Widespread infection can trigger systemic illness and organ dysfunction.

HEMATOGENOUS SPREAD

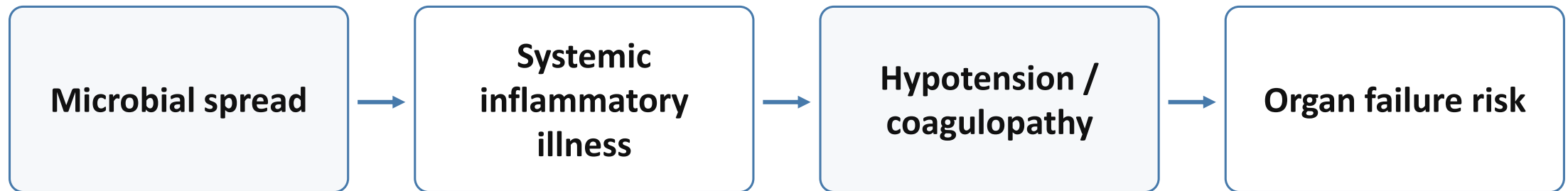


Lymphatic, contiguous and neural spread are distinct

Route	Transport mechanism	Distinctive feature
Contiguous	Direct tissue invasion	Progressive extension from focus
Lymphatic	Movement through lymphatics	May ultimately reach blood
Neural	Axonal transport	Access toward nervous system

Disseminated infection may produce sepsis

Widespread infection can produce fever, hypotension, coagulopathy and organ failure.



Causal sequence — schematic

Clinical reasoning: Portal versus dissemination

A patient develops infection at a skin break followed by evidence of infection at distant organs.

Mechanistic question

Which events must be explained separately?

First, breach of epidermal protection; Second, dissemination beyond the primary site, potentially through the bloodstream.

The initial portal does not specify the complete route taken to the distant site.

Apply the portal–barrier–bypass triad

Exposure clue	Defense to assess	Candidate bypass
Puncture / burn	Keratinized epidermis	Mechanical defect
Food / water	Gastric and intestinal defenses	Acid tolerance or epithelial entry
Inhaled aerosols	Mucociliary clearance / phagocytes	Epithelial invasion or intracellular survival
Ascending urinary bacteria	Urine washout / urothelium	Adhesion or obstruction

Compare susceptibility states at the four portals

Host setting	Local failure	Clinical implication
Damaged epidermis	Loss of physical barrier	Skin or soft-tissue infection
Broad-spectrum antibiotics	Loss of GI microbiota competition	C. Difficile overgrowth
Defective mucociliary clearance	Airway retention of organisms	Bacterial respiratory infection
Urine flow obstruction	Reduced urinary flushing	UTI susceptibility

Five questions locate the mechanistic entry defect

This sequence converts a list of pathogens into a testable explanation of pathogenesis.

1. Where did exposure occur?

2. Was epithelium intact or injured?

3. Which local defense normally protects the site?

4. How did the organism evade or bypass it?

5. Was infection local or disseminated?

Integrated assessment: Identify the portal

Match four clinical clues: (1) needle injury, (2) contaminated water, (3) inhaled particles reaching alveoli, (4) urinary obstruction.

Mechanistic question

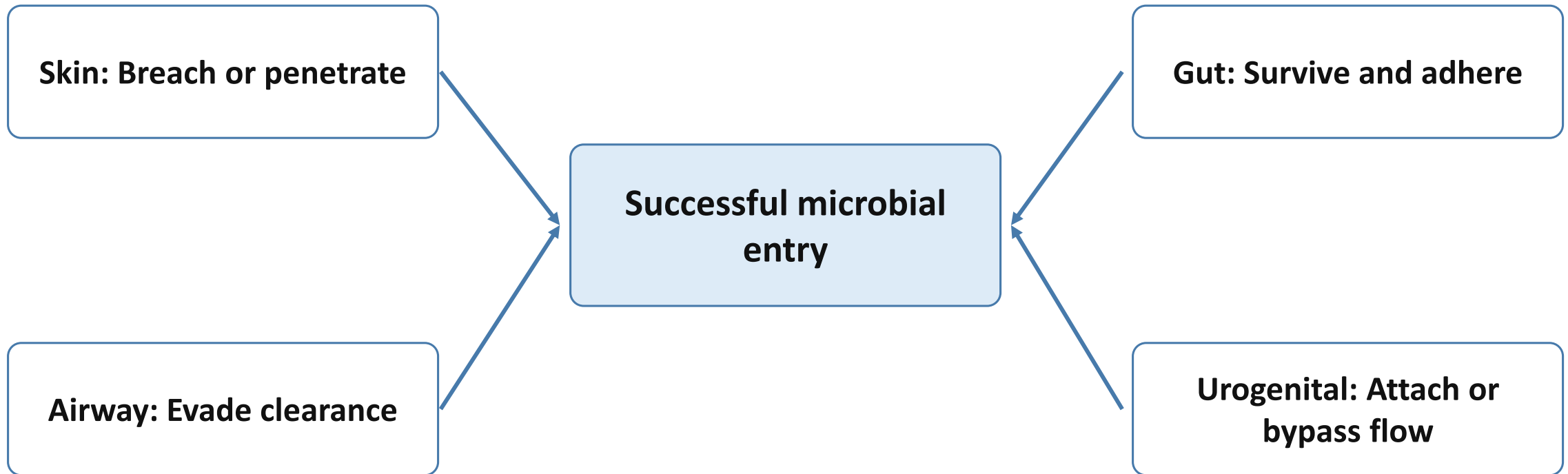
Which distinct entry or defense mechanism belongs to each?

(1) skin inoculation; (2) ingestion and enteric defenses; (3) alveolar phagocytic protection; (4) impaired urinary washout.

Different portals expose different host vulnerabilities.

Core conclusions: Entry is defense-specific

A framework for clinical and pathological interpretation



The same causal sequence recurs: Portal → local defense → pathogen adaptation or host defect → infection.

References and reading context

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 8, “Infectious Diseases,” pp. 304–305: “Routes of Entry of Microbes,” Table 8.1.
- Adjacent section: “Spread and Dissemination of Microbes Within the Body,” p. 305.