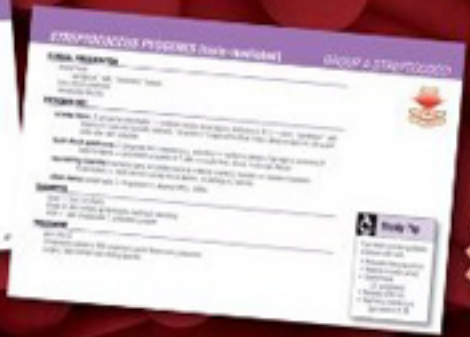
LIPPINCOTT'S MICROCARDS

MICROBIOLOGY FLASH CARDS

THIRD EDITION

SANJIV HARPAVAT SAHAR NISSIM



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MICROCARDS

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DEDICATION

In much of our world today, infectious disease is a leading cause of human suffering, economic loss, and death. Here, we aspire to accumulate in a concise and clear way the most current clinical information about the agents behind these problems. We dedicate this effort to all health care professionals and scientists working to understand, treat, and eradicate infectious disease both in the United States and around the world.

ACKNOWLEDGMENTS

These cards reflect the hard work of many editors and proofreaders, without whom this project would have never been completed. We would like to thank several people at Lippincott Williams & Wilkins for the support and guidance they gave us in the third edition of this card deck: Susan Rhyner, Stacey Sebring, and Joy Fisher-Williams. We would also like to thank Michael Brown for consultation and Harold Medina for assistance with artistic design.

Many fine physicians helped edit various sections to ensure that the information is concise, relevant, and accurate. We especially appreciate the help of Dr. Bill Rodriguez, Dr. Nilesh B. Dave, Dr. Manisha Harpavat, Dr. Yi Chen Lai, Dr. Joseph Mahoney, Dr. Lokesh Nagori, Dr. Andrew Norwalk, Dr. Adrienne L. Prestridge, and Dr. Tahniat Syed. Each provided critical comments on various parts of the manuscript.

We would also like to thank students around the world who have helped improve this product with their comments. These students include Nadia Caballero (Pritzker School of Medicine), Jessica Felt (University of Rochester), Stephen Massimi (Albert Einstein College of Medicine), Ashwin Narayana (American University of Antigua - College of Medicine), Drorit Or (Haifa, Israel), Jon Roggenkamp (Riverside Community College), Danial Mir (Weill Cornell Medical College in Qatar), and Isaac Shalom (Tel Aviv University).

We are very pleased to present the third edition of Lippincott's Microcards, a product designed for medical students to learn and review clinical microbiology. The project began with a simple idea: to create a concise yet comprehensive microbiology review tool. After years of work, what has emerged is a deck of cards that we believe will help medical students learn this material and sail through USMLE Part 1 examinations, will offer physicians a handy reference, and will inspire enthusiasm and interest in microbiology at all levels of the health care profession.

For this edition, we have also bundled this deck with free access to over 150 mobile flash cards that contain all the cards in the print deck in addition to a bonus 70 USMLE-style Q&A for iPhones and iPod touch devices.

This product contains two general types of cards:

CONCEPT CARDS

The deck begins with a series of CONCEPT CARDS. These cards organize the vast amount of information in microbiology into systems, diagramming the various microorganisms that cause disease in each organ system.

MICROORGANISM CARDS

These cards comprise the bulk of this product. Each card catalogues a medically important microorganism, detailing its clinical presentation, pathogenesis, diagnosis, treatment, and other interesting facts. In addition, each card offers some special features to facilitate understanding and recall of the information. These features include the following:

- **Title Bars:** on both sides, these list the microorganism's scientific name on the left and its common name on the right
- **Pictures:** on the front side, these highlight distinguishing structural features of the microorganism, schematize its life cycle, or illustrate its pathobiology

(continued over)

- **Flow Charts:** on the front side, these group the microorganisms based on structure or pathobiology, allowing you to categorize the microorganism at a glance
- **Clinical Cases:** these simulate the case-based questions found on the USMLE Part 1 exam; each case is placed on the front side to allow self-quizzing and review of the material
- **Pathogenesis Icons:** on the back side, these icons categorize a microorganism's mechanism of disease into intuitive groups (the first concept card summarizes all of these icons)
- **Study Tips:** on the back side, these are composed of quick lists for "high-yield," bullet-type review

We hope that you use these cards energetically and to their utmost—flip through them many times to reinforce material, study the pathogenesis sections to understand the mechanisms of disease, and test yourself with the clinical cases. Our experience is that the more you use the cards, the more you will discover and the more you will get out of them!

Great luck!

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P.S. As new information is discovered every day, the information on these cards will surely change. Please e-mail along any additions or corrections—we'll do our best to incorporate them and acknowledge your contribution in the next edition.

Pathogenesis Icon Guide

BACTERIA

Toxin: bacteria release toxin that causes illness
Example: C. tetani toxin causes tetanus (26)

Host immune response: response of host to bacteria causes illness
Example: excess cytokine release leads to toxic shock syndrome (12)
Example: granuloma formation contributes to tuberculosis (59)

Proliferation and invasion: growth and spread of bacteria significant in illness
Example: subcutaneous spread of *S. aureus* causes cellulitis (13)

VIRUSES

Cytopathic effect: viral infection disrupts normal cell physiology
Example: Rotavirus infects and lyses villus cells of small intestine, causing gastroenteritis (79)

Host immune response: response of host to virus causes illness
Example: inflammation in response to HBV infection leads to hepatitis (110)

Tumorigenesis: viral infection promotes uncontrolled proliferation of infected cells
Example: HPV proteins E6 and E7 transform infected basal cells, leading to benign warts that may progress to carcinomas (102)

FUNGI

Overgrowth: spread of fungal infection significant in illness
Example: C. albicans may overgrow in the mouth, leading to oral thrush (119)

Host immune response: response of host to fungus causes illness
Example: ringworm infections trigger a delayed-type hypersensitivity reaction that causes inflammation, itching, scaly skin, and pustules (114)

PROTOZOA

Displacement: tissue displacement/obstruction due to growth of protozoa causes illness
Example: growth of *E. histolytica* in liver abscess causes abdominal pain (124)

Cytopathic effect: intracellular protozoa infection disrupts normal cell physiology
Example: L. donovani divides in and damages cells of the reticuloendothelial system, leading to splenomegaly, thrombocytopenia, anemia, and leukopenia (129)

Host immune response: response of host to protozoa causes illness
Example: inflammation against *T. cruzi* in cardiac muscle can lead to CHF and myocarditis (130)

HELMINTHS

Displacement: tissue displacement/obstruction due to growth of helminth causes illness
Example: growth of *T. solium* cysts in the brain can cause neurological defects or blindness (137)

Parasite/Competition: helminth consumes host nutrition
Example: T. saginata in small intestine consumes food ingested by host, leading to malnutrition (136)

Host immune response: response of host to helminth causes illness
Example: inflammation and fibrosis around *W. bancrofti* worms obstruct lymphatic drainage, leading to elephantiasis (144)

Mechanisms of Major Bacterial Exotoxins

EXOTOXIN CAUSES ↑ [cAMP] OR [cGMP]		
V. cholerae (44)	cholera toxin	**AB_5:** B binds receptors on gut epithelium, A ADP-ribosylates Gs, keeping adenylate cyclase active and ↑ [cAMP]
E. coli (39)	LT toxin	
B. pertussis (53)	pertussis toxin	**AB:** B binds cell surface receptor, A ADP-ribosylates and inactivates Gi proteins, keeping adenylate cyclase active and ↑ [cAMP]
E. coli (39)	ST toxin	stimulates guanylate cyclase and ↑ [cGMP]
EXOTOXIN INHIBITS PROTEIN SYNTHESIS		
C. diphtheriae (31)	diphtheria toxin	**AB:** B binds cell surface receptor, A ADP-ribosylates EF-2 and inhibits protein synthesis
P. aeruginosa (45)	exotoxin A	
S. dysenteriae (42)	shiga toxin	binds 60S ribosome and inhibits protein synthesis
E. coli (39)	shiga-like toxin	
EXOTOXIN BLOCKS RELEASE OF NEUROTRANSMITTERS		
C. tetani (26)	tetanospasmin	cleaves synaptobrevin, blocking vesicle formation and release of inhibitory neurotransmitters GABA and glycine
C. botulinum (27)	botulinum toxin	cleaves synaptobrevin, blocking vesicle formation and release of acetylcholine
OTHER EXOTOXINS		
B. anthracis (25)	anthrax toxin	three proteins: PA, EF, LF cause dermal necrosis
S. aureus (12)	TSST-1	induces excess cytokine release (e.g., Il-1, TNF)
S. pyogenes (17)	erythrogenic toxin	

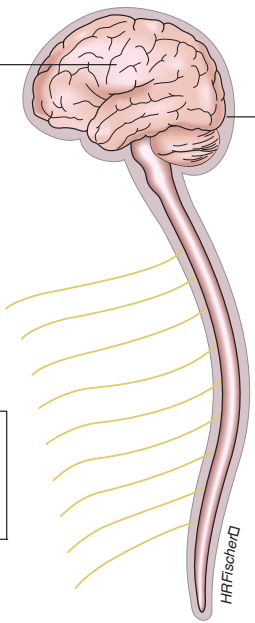
Nervous System Infections

Encephalitis

HSV-1 (105)	Viral
HSV-2 (106)	Viral
Rabies virus (98)	Viral
Japanese Encephalitis virus and other arboviruses (84)	Viral
T. gondii (128)	Protozoan
T. brucei (131)	Protozoan

Axon/Synapse Pathogenesis

C. tetani (26)
C. botulinum (27)
M. leprae (60)
Poliovirus (73)



Meningitis

Neonatal:	*S. agalactiae* (19)
	L. monocytogenes (30)
	E. coli (39)
6 mos.–6 yrs.:	*S. pneumoniae* (22)
	N. meningitidis (35)
	H. influenzae type B (51)
6 yrs.–60 yrs.:	*N. meningitidis* (35)
	Poliovirus (73)
	S. pneumoniae (22)
Aseptic:	Coxsackie virus (74)
	Echovirus (74)
	Mumps virus (96)
	Poliovirus (73)
Fungal:	*C. neoformans* (120)

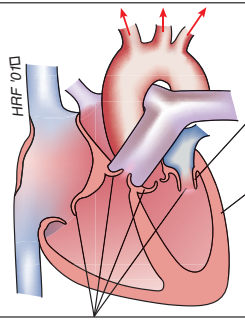
CSF Profiles in Meningitis

ETIOLOGY	PROTEIN	GLUCOSE	CELL INFILTRATION	PRESSURE
Bacterial	↑ ↑	↓ ↓	PMNs	↑
Viral	↑ or normal	normal	lymphocytes	normal
Fungal	↑	↓	lymphocytes	↑

Cardiovascular System Infections

Septic Shock

E. coli (39)	*P. mirabilis* (43)	*S. aureus* (12)	
K. pneumoniae (38)	*P. aeruginosa* (45)	*S. pyogenes* (17)	
Enterobacter (38)	*B. fragilis* (50)	*S. agalactiae* (19)	Neonatal



Rheumatic Heart Disease

S. pyogenes (18)

Myocarditis

Coxsackievirus type B (74)	Viral
T. cruzi (130)	Protozoan
S. aureus (13) and *E. faecalis* (20) (complication of endocarditis)	Bacterial
C. diphtheriae (31)	Bacterial
B. burgdorferi (62)	Bacterial

ENDOCARDITIS

Native Valve

Viridans streptococci (23)
S. bovis (21)
S. pyogenes (18)
E. faecalis (20)
S. aureus (13)
S. epidermidis (14)

IV Drug Users (often tricuspid)

S. aureus (13)	Bacterial
Streptococci	Bacterial
E. faecalis (20)	Bacterial
P. aeruginosa (45)	Bacterial
C. albicans (119)	Fungal

Prosthetic Valve

S. epidermidis (14)	Acute
S. aureus (13)	Acute
Gram – bacilli	Acute
C. albicans (119)	Acute
Streptococci	Subacute

Respiratory System Infections

Pharyngitis/Laryngitis

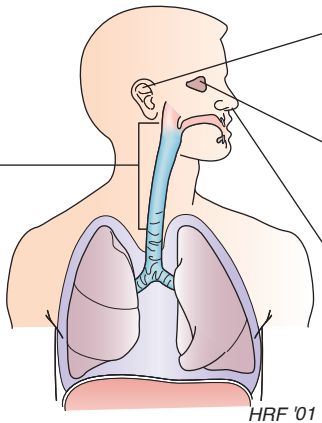
- *S. pyogenes* (16) — Bacterial
- *M. catarrhalis* — Bacterial
- *N. gonorrhoeae* (36) — Bacterial
- *C. diphtheriae* (31) — Bacterial
- Common cold viruses — Viral
- Adenovirus (104) — Viral
- RSV (95) — Viral

Epiglottitis

H. influenzae type B (51)

Croup

- *M. pneumoniae* (65) — Bacterial
- Parainfluenza virus (94) — Viral
- Influenza virus (93) — Viral
- RSV (95) — Viral



HRF '01

Otitis externa

P. aeruginosa (45)

Otitis media

- *S. pneumoniae* (22)
- *H. influenzae* type B (51)
- *M. catarrhalis*
- *S. agalactiae* (19) — neonatal

Sinusitis

- *S. pneumoniae* (22)
- *H. influenzae* type B (51)
- *M. catarrhalis*
- *S. aureus* (13)

Rhinitis (Common Cold)

Rhinovirus (76)
Coronavirus (89)
Influenza C virus (93)
Coxsackieviruses type A+B (74)
Parainfluenza virus (94)

Respiratory System Infections

Community-Acquired Pneumonia

- *M. pneumoniae* (65)
- *S. pneumoniae* (22)
- *H. influenzae* type B (51)
- *C. pneumoniae* (68)
- *L. pneumophila* (52)
- *M. catarrhalis*
- *S. aureus* (12)
- *Nocardia* (33)
- *M. tuberculosis* (59)
- *C. psittaci* (66)

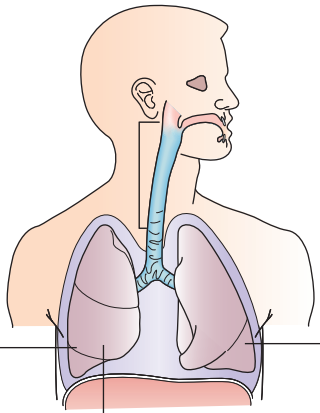
Bacterial

- Influenza virus (93)
- RSV (95)

Viral

- *C. immitis* (116)
- *H. capsulatum* (117)
- *B. dermatitidis* (118)

Fungal



HIV-associated Pneumonia

- *P. jiroveci* (121)
- *M. tuberculosis* (59)

Atypical Pneumonia

- *M. pneumoniae* (65)
- *L. pneumophila* (52)
- *C. pneumoniae* (68)
- *C. burnetti* (71)
- Viral causes of pneumonia

Gastrointestinal System Infections

Dental caries

S. mutans (23)

Hepatitis

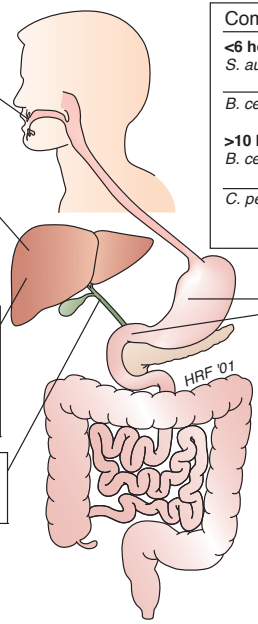
Hepatitis A virus (75)
Hepatitis B virus (110)
Hepatitis C virus (84)
Hepatitis D virus (88)
Hepatitis E virus (78)
Yellow fever virus (83)

Other Liver Infections

E. histolytica (124) – liver abscess
L. donovani (129) – visceral leishmaniasis
E. granulosus (139) – hydatid cysts
Schistosoma species (142) – liver flukes

Biliary Tract Infection

E. faecalis (20)



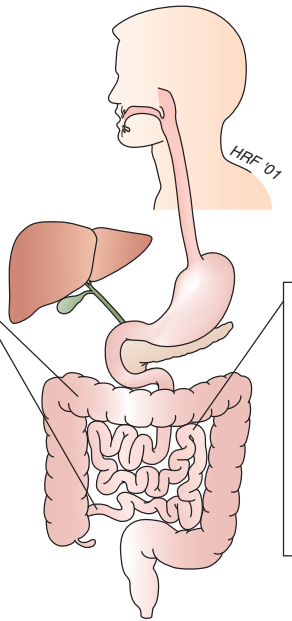
Common Causes of Food Poisoning

<6 hours incubation		
S. aureus (12)	toxin ingested	vomiting, nausea, diarrhea
B. cereus (24)	toxin ingested	vomiting, nausea (emetic syndrome)
>10 hours incubation		
B. cereus (24)	toxin ingested	diarrhea, cramps (diarrheal syndrome)
C. perfringens (29)	bacteria ingested, toxin released in GI tract	diarrhea, cramps

Ulcers

H. pylori (48)

Gastrointestinal System Infections



Large Intestine/Distal Small Intestine Infections: Inflammatory or Bloody Diarrhea

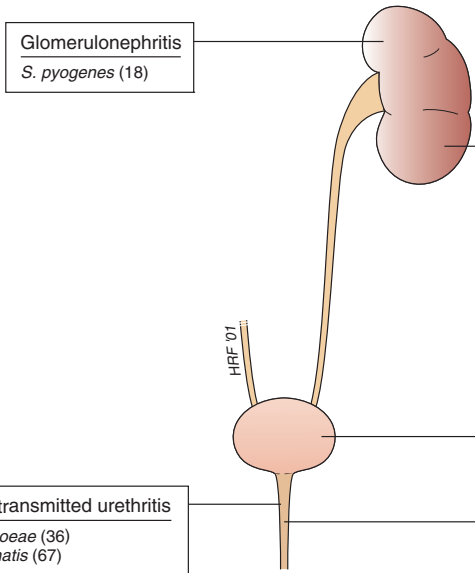
Shigella species (42)	Bacterial
* *S. typhi* (40)	
S. enteritidis (41)	
C. jejuni (49)	
Enterohemorrhagic *E. coli* (39)	
Enteroinvasive *E. coli* (39)	
* *Y. enterocolitica* (46)	
V. parahaemolyticus (44)	
C. difficile (28)	
E. histolytica (124)	Protozoan

* May penetrate small intestine and spread systemically

Small Intestine Infections: Noninflammatory or Watery Diarrhea

V. cholerae (44)	Bacterial
Enterotoxigenic *E. coli* (39)	
C. perfringens (29)	
B. cereus (24)	
S. aureus (12)	
Rotavirus (79)	Viral
Norwalk virus (77)	
Adenovirus (104)	
G. lamblia (125)	Protozoan
C. parvum (126)	

Urinary Tract Infections



Glomerulonephritis
S. pyogenes (18)

Pyelonephritis

Cystitis

Urethritis

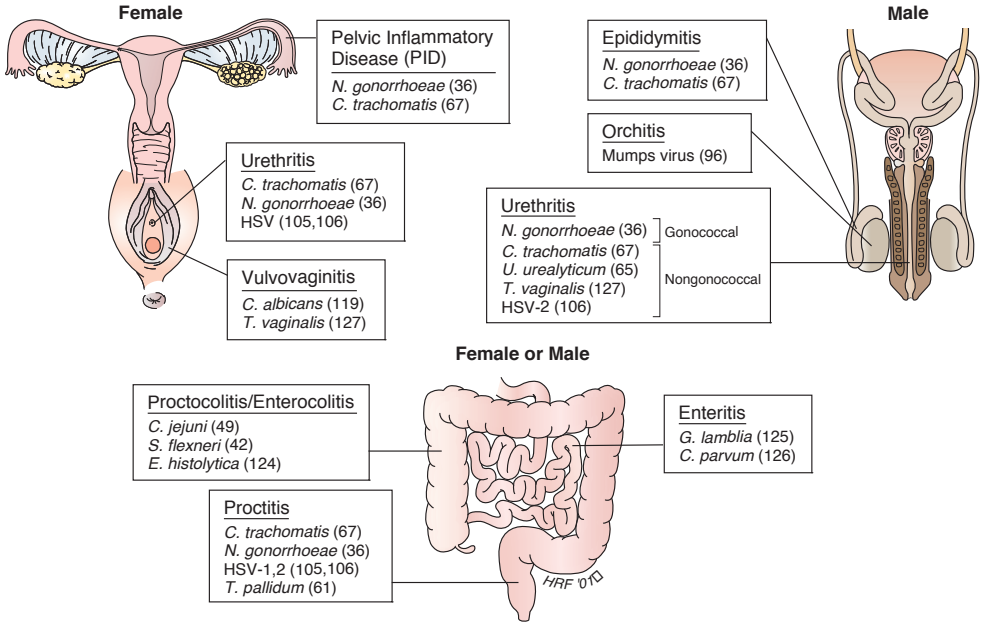
Sexually transmitted urethritis
N. gonorrhoeae (36)
C. trachomatis (67)

UTI

Uncomplicated
E. coli (39)
S. saprophyticus (15)

Complicated (catheter, calculi, obstruction)
E. coli (39)
E. faecalis (20)
P. aeruginosa (45)
K. pneumoniae (38)
P. mirabilis (43)

Genital System Infections



Genital System Infections

CUTANEOUS LESIONS OF THE GENITALIA:

Ulcerative lesions:	**Painful?**	**Type of Lesion**
HSV-1, HSV-2 (105, 106) – Herpes	✓	vesicles
T. pallidum (61) – Syphilis		indurated
H. ducreyi – Chancroid	✓	
C. trachomatis (67) – Lymphogranuloma venereum		solitary, nonindurated

Wart lesions:

HPV (102)
Molluscum contagiosum (112)

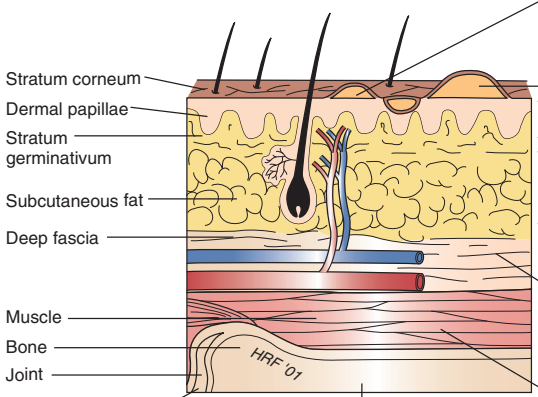
SEXUALLY TRANSMITTED PATHOGENS WITH SYSTEMIC EFFECTS:

HIV (86)
HTLV (87)
HBV (110)
CMV (108)
T. pallidum (61)

COMMON VAGINAL INFECTIONS:

		DISCHARGE		
	Itchiness?	**Color**	**Amount**	**Other Features**
C. albicans (119)	✓	white	small	clumped discharge
T. vaginalis (127)	✓	yellow	copious	
Gardnerella vaginalis		white/gray	moderate	malodorous

Skin/Muscle/Bone Infections



Vesicles

VZV (107)
Smallpox virus (111)
HSV-1,2 (105,106)
Coxsackievirus A (74)
Molluscum contagiosum virus (112)

Bullae

S. aureus (13)
S. pyogenes (16,17)
C. perfringens (29)

Erysipelas

S. pyogenes (16)

Cellulitis

S. pyogenes (16)
S. aureus (13)
P. aeruginosa (45)
P. multocida (56) - cat/dog bites

Necrotizing fasciitis

S. pyogenes (16)
C. perfringens (29)

Septic arthritis

N. gonorrhoeae (36)
S. aureus (13)
H. influenzae (51)

Osteomyelitis

S. aureus (13)
S. typhi (40) - sickle cell patients
P. multocida (56) - cat/dog bites

Myositis

C. perfringens (29)
S. aureus (13)
T. spiralis (138)
T. solium (137)
Coxsackievirus B (74)
Dengue Fever Virus (84)

Skin/Muscle/Bone Infections

MAJOR CAUSES OF RASH:

Viral		
VZV (107)	chickenpox	widespread vesicles with red base appearing as "dew on a rose petal," rash spreads centrifugally
HSV-1, HSV-2 (105, 106)	herpes	vesicular lesions in mouth/eye or genital/perianal region
Coxsackievirus A (74)	herpangina, hand-foot-and-mouth disease	red oropharynx vesicles, vesicles on hand/foot/mouth
Smallpox virus (111)	smallpox	macules form first in the head and later in the extremities, becoming pus-filled vesicles and then crusts
Molluscum contagiosum virus (111)	molluscum contagiosum	small pink skin tumors with a central dimple often on trunk and anogenital regions
Rubella virus (82)	rubella	maculopapular rash beginning in face and spreading to extremities
Measles virus (97)	measles	starts at head and progresses to feet, disappearing in the order it appears
HHV 6 (108)	roseola	in infants, rash on trunk
Parvovirus B19 (101)	erythema infectiosum	"slapped-cheek" appearance
Bacterial		
S. pyogenes (17)	scarlet fever	"sandpaper" rash begins on trunk and spreads outward
R. rickettsii (69)	Rocky Mountain spotted fever	maculopapular rash on palms and soles spreading proximally to trunk (centripetal spread)
R. prowazekii (70)	epidemic typhus	begins on trunk and spreads outward (centrifugal spread) but spares palms, soles, and face
Bacterial (*continued*)		
B. burgdorferi (62)	Lyme disease	erythema chronicum migrans: spreading annular red lesion surrounding clear bite mark
T. pallidum (61)	syphilis	maculopapular rash on palms and soles

OTHER INFECTIONS WITH CUTANEOUS SYMPTOMS:

Bacterial		
B. anthracis (25)	anthrax	ulcerous lesion with blackened necrotic eschar
F. tularensis (55)	tularemia	papule forms and develops into ulcer with black base
Y. pestis (47)	bubonic plague	cutaneous hemorrhagic necrosis with black color
M. leprae (60)	leprosy	anesthetized lesions vulnerable to secondary damage
A. israelii (32)	sinus tracts	sinus tracts form through skin, muscle, bone, and organs
Viral		
HPV (102)	warts	
Fungal		
S. schenckii (115)	sporotrichosis	ulcerating nodules
Ringworm (tinea) infections (114)	dermatophytoses	inflammation, itching, scaly skin, pustules
Protozoan		
Leishmania species (129)	cutaneous leishmaniasis	skin or mucosal ulcers

Hepatitis Virus Infections

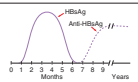
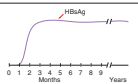
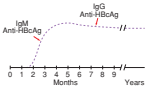
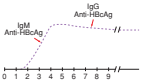
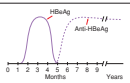
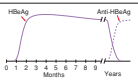
	Hepatitis A Virus (75)	Hepatitis B Virus (110)	Hepatitis C Virus (85)	Hepatitis D Virus (88)	Hepatitis E Virus (78)
Classification: Family	**Picornaviridae**	**Hepadnaviridae**	**Flaviviridae**	**—**	**Caliciviridae**
Nucleic acid	RNA (positive, single stranded)	DNA (partially double stranded)	RNA (positive, single stranded)	RNA (negative, single stranded, circular)	RNA (positive, single stranded)
Lipid envelope (renders susceptible to bile acids)		✓	✓	✓	
Clinical Presentation: Transmission					
oral–fecal route	✓				✓
blood, sexual contact		✓	✓	✓	
Incubation time					
short (2–8 weeks)	✓				✓
long (2–24 weeks)		✓	✓	✓	
Length of infection					
acute	✓	✓	✓	✓	✓
chronic		✓	✓	✓	
Important sequelae	—	cirrhosis, hepatocellular carcinoma	cirrhosis, hepatocellular carcinoma	cirrhosis, hepatocellular carcinoma	—
Diagnosis/Therapy: Diagnosis	anti-HAV IgM, IgG (confers immunity)	see opposite side	anti-HCV (does not confer immunity)	anti-HDV (does not confer immunity)	anti-HEV IgM, IgG (confers immunity)
Therapy	None	Interferon	Interferon	None	None
Vaccine	Yes	Yes (HBsAg)	No (because viral antigens vary over time)	No (but vaccination against HBV is effective)	No

*Hepatitis G virus, a flavivirus, is being studied as another viral cause of hepatitis.

Hepatitis Virus Infections

SEROLOGY COURSE OF HEPATITIS B INFECTION:

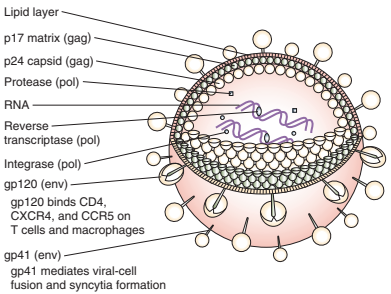
Viral particles shed three proteins from their icosahedral capsid, all of which are important for hepatitis B diagnosis:

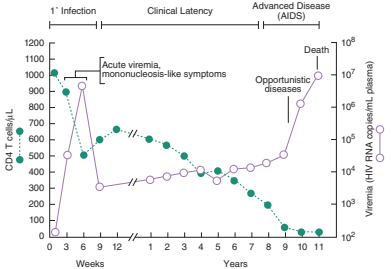
	Acute	Chronic
1) Hepatitis B surface antigen (HBsAg) • presence of HBsAg signifies a live infection • Anti-HBsAg antibodies protect against infection		
2) Hepatitis B core antigen (HBcAg) • Anti-HBcAg antibodies reveal length of infection: acute—IgM anti-HBcAg chronic—IgG anti-HBcAg • Anti-HBcAg antibodies are simply markers; they do not protect against infection		
3) Hepatitis B e antigen (HBeAg) • presence of HBeAg signifies increased viral replication and spread (highly contagious state) • Anti-HBeAg antibodies reduce infectivity but do not eliminate infection altogether		

Adapted from Harrison's, p. 1680.

SEROLOGY PROFILE OF HBV INFECTIONS:

	s		c		e	
	HBsAg	**Anti-HBsAg**	**Anti-HBcAg IgM**	**Anti-HBcAb IgG**	**HBeAg**	**Anti-HBeAg**
Acute infection	✓		✓		✓	
Chronic infection						
less contagious	✓			✓		✓
more contagious	✓			✓	✓	
Convalescence		✓		✓		✓
Immunized		✓				





VIRAL LIFE CYCLE:

viral gp120 binds CD4 on cell surface → viral gp120 conformational change → altered viral gp120 binds coreceptor CXCR4 (for T cell infection only) or CCR5 (for T cell or macrophage infection) → viral gp41 brought close to cell membrane → viral gp41 mediates virus–cell fusion

viral genome uncoated → reverse transcriptase converts viral RNA genome to dsDNA → integrase inserts randomly several copies of dsDNA into host genome → integrated provirus remains latent

when host cell activated (e.g., via chemokines), provirus genes expressed:

- *gag* encodes polyprotein of virion core
- *pol* encodes polyprotein of reverse transcriptase, integrase, and protease
- *env* encodes envelope glycoproteins
- six other genes encode for regulators of gene expression

viral protease cleaves polyproteins → infectious particles assemble at cell membrane and bud off cell membrane

COURSE OF CD4+ T CELL COUNT AND VIREMIA:

1° Infection Stage (first months): acute viremia → contained by vigorous host immune response → mononucleosis-like symptoms → equilibrium established between viral production and host containment

Clinical Latency Stage (7–10 years): virus replicates, especially in lymphoid organs → host responds to contain infection, mutations allow virus to evade → no or low-level symptoms

viral load gradually increases, CD4+ count gradually drops

CD4+ cells depleted by various mechanisms, including:

- —immune attack on infected cells by CTLs
- —cell lysis from extensive viral budding
- —syncytium formation between infected and uninfected cells (via gp120–CD4 interactions)

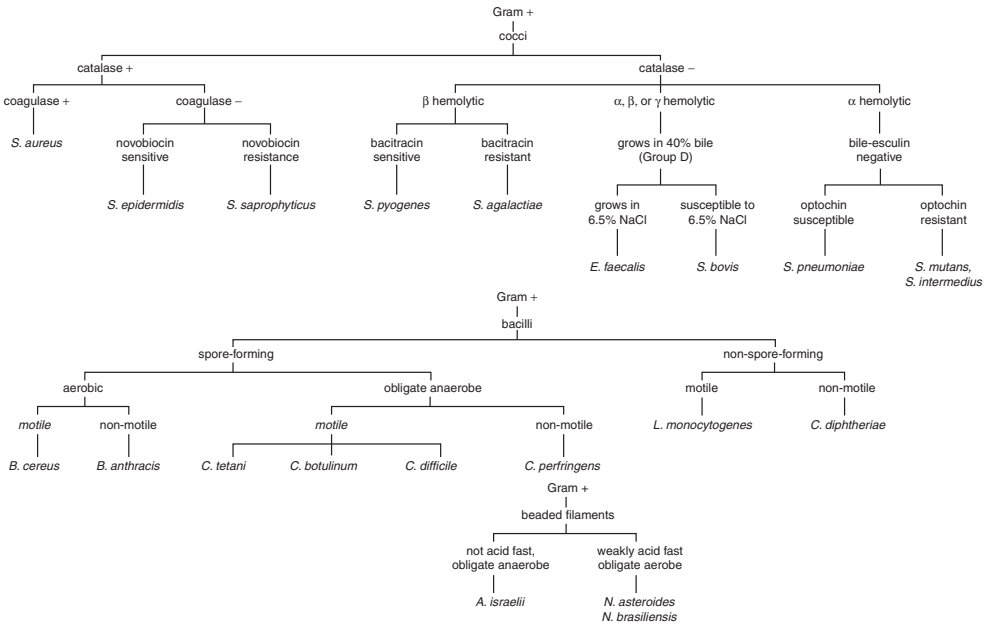
Advanced Disease (AIDS): CD4+ T cell count, <200 cells/μL → common opportunistic infections/neoplasms causing death (see card 86 for more details)

COMMON OPPORTUNISTIC INFECTIONS IN HIV+ PATIENTS

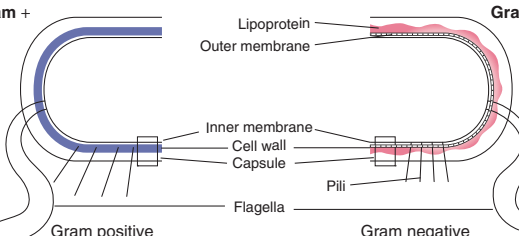
450–200 CD4+ T_h cells/μL		200–50 CD4+ T_h cells/μL		50–0 CD4+ T_h cells/μL	
H. influenzae (51)	pneumonia, sinusitis	*C. neoformans* (120)	meningitis	*M. avium-intracellulare* (59)	lung, liver, bone infection
S. pneumoniae (22)	pneumonia, sinusitis	*C. immitis* (116)	pneumonia, systemic infection		
S. aureus (13)	catheter-related sepsis			CMV (108)	retinitis, esophagitis, colitis
S. epidermidis (14)	catheter-related sepsis				
Salmonella species (40)	dysentery				
Shigella species (42)	dysentery	*P. jirovecii* (121)	pneumonia		
Campylobacter species (49)	dysentery	*C. parvum* (126)	diarrhea	*H. capsulatum* (117)	pneumonia, systemic infection
M. tuberculosis (59)	tuberculosis	*T. gondii* (128)	encephalitis		
EBV (109)	oral hairy leukoplakia				
VZV (107)	shingles				
HSV-1, HSV-2 (105, 106)	recurring oral and/or genital ulcers				
C. albicans (119)	thrush, vaginitis				
Tinea infections (114)	athlete's foot and other common fungal infections				

AIDS: <200 CD4+ cells/μL in an HIV+ individual

Gram + Bacteria



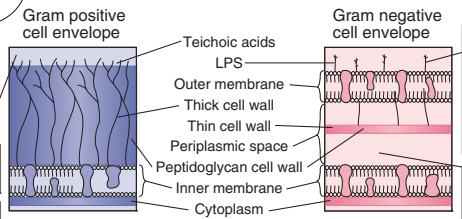
Important Features of Gram + and Gram – Bacteria



	G +	G –
LPS		✓
Outer membrane		✓
Teichoic acids	✓	
Periplasmic space		✓
Cell wall	thick	thin

Capsule:

- protects against phagocytosis
- polysaccharide (exception: *B. anthracis* has D-glutamic acid)
- glycocalyx is capsule slime that allows some bacteria to adhere to surfaces (e.g., *S. epidermidis* to catheters)
- capsule polysaccharide often used for vaccine (e.g., Pneumovax for *S. pneumoniae*)
- quellung reaction is a diagnostic test in which specific antiserum causes the capsule to swell (e.g., *S. pneumoniae*, *H. influenzae* type B)



LPS (lipopolysaccharide):

lipid A + polysaccharide

- lipid A → endotoxin component of LPS that causes fever, shock
- polysaccharide → important surface antigen (O antigen) in Gram – bacteria

Teichoic Acid

- important surface antigen in Gram+ bacteria

Spores:

- important for *Clostridium & Bacillus* species
- form when nutrients are absent and can remain dormant for years
- resistant to heat & chemicals – require autoclaving to kill

Peptidoglycan Cell Wall:

- penicillins & cephalosporins inhibit cell wall synthesis
- cell wall protects bacteria from osmotic pressure
- lysozyme in human secretions (tears, saliva) cleaves peptidoglycans — this is part of natural immunity to infections

Periplasmic Space:

- site of β-lactamases, enzymes that cleave β-lactam drugs such as penicillins

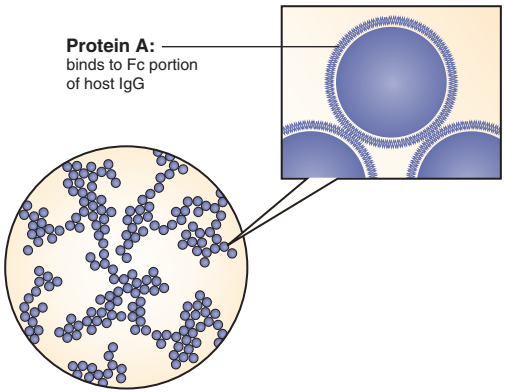
Flagella:

- for motility/ chemotaxis

Pili:

- shorter than flagella
- help bacteria to attach to surfaces or cells

Staphylococcus aureus (toxin-mediated)



Gram + bacteria

cocci

catalase +

coagulase +

S. aureus

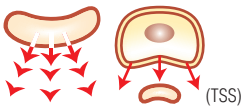
CLINICAL CASE

A young woman develops a 102°F fever 2 days after menses. She reports using tampons. After several days, the fever is accompanied by dizziness, hypotension, myalgias, and a diffuse rash on the chest. With a penicillinase-resistant penicillin and IV fluids, the symptoms resolve within 2 weeks. A desquamation of the palms is observed throughout the convalescence.

Staphylococcus aureus (toxin-mediated)

CLINICAL PRESENTATION

Toxic Shock Syndrome (TSS)
Scalded Skin Syndrome
    Ritter's disease in newborn
food poisoning


(TSS)

PATHOBIOLOGY

Toxic Shock Syndrome: tampon use, trauma/surgery introduce bacteria → bacteria colonize → toxic shock syndrome toxin-1 (TSST-1) released and diffuses systemically → TSST-1 is a superantigen → promotes excess cytokines released (e.g., IL-1, TNF) → acute fever, rash, desquamation on palms and soles, hypotensive shock → organ hypoperfusion and dysfunction → possible death

Scalded Skin Syndrome: skin wound or cutting umbilicus in neonates promotes local epidermal infection→ exfoliative toxins (e.g., ET-A,B) released and diffuse systemically → epidermis separates and skin sloughs off → fluid loss and potential secondary infection → possible death

food poisoning: bacteria release toxin in food such as custards → heat-stable toxins (e.g., Enterotoxin SE-A) ingested → gastroenteritis → self-limited, 8- to 24-hour nausea, vomiting, diarrhea, and abdominal pain

DIAGNOSIS

detection of toxin production by *in vitro* culture (blood cultures negative because organism does not invade bloodstream)

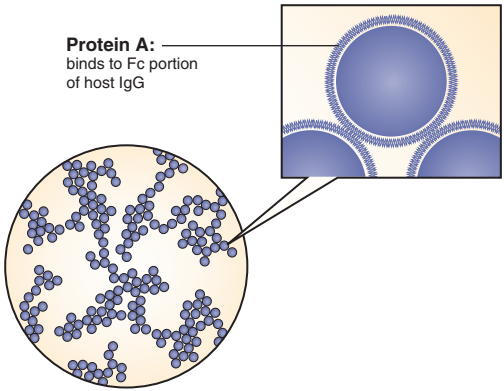
TREATMENT

removal of foreign bodies, drainage of purulent collections; fluid replacement; penicillinase-resistant penicillins hasten recovery; (future) blocking effects of IL-1 and TNF with antibodies

QUICK FACTS

Antibiotics are not curative—they kill bacteria but do not remove already-released exotoxin.
Scalded skin syndrome has a 50% mortality rate among adults due to complications from hypovolemia and secondary infection.
Ritter's syndrome is the most severe form of scalded skin syndrome in neonates. It occurs after *S. aureus* colonizes the cut umbilicus and releases ET-A,B systemically.

Staphylococcus aureus (infections)



Gram + bacteria

cocci

catalase +

coagulase +

S. aureus

CLINICAL CASE

An IV-drug user presents with a high fever and signs of heart failure. A notable heart murmur prompts an echocardiogram that reveals tricuspid valve vegetations. The patient is immediately begun on IV penicillinase-resistant penicillin that proves to be effective.

Staphylococcus aureus (infections)

CLINICAL PRESENTATION

Local
- skin/subcutaneous: *impetigo, cellulitis, folliculitis, furuncles, carbuncles*
- respiratory: *pneumonia with cavitations*

Systemic
- *acute endocarditis, meningitis, osteomyelitis, septic arthritis*

PATHOBIOLOGY

bacteria colonize skin (following breach) or nasopharynx (following intubation, viral respiratory infection) ⟶ overgrow and evade host defenses using:
- protein A (binds Fc portion of IgG)
- coagulase (forms fibrin coat around organism)
- hemolysins, leukocidins (destroy RBCs and WBCs)

neutrophils localize to infection site ⟶ purulent abscesses form ⟶ skin/subcutaneous infections or pneumonia

bacteria may more deeply invade and reach bloodstream using:
- hyaluronidase (breaks down connective tissue)
- staphylokinase (lyses formed clots)
- lipase (breaks down fat)

hematogenous spread to visceral organs ⟶ systemic infection

DIAGNOSIS

blood culture positive: Gram + clusters, catalase +, coagulase +

TREATMENT

antibiotic treatment:
- MSSA (methicillin-sensitive *S. aureus*): penicillinase-resistant penicillins
- MRSA (methicillin-resistant *S. aureus*): vancomycin

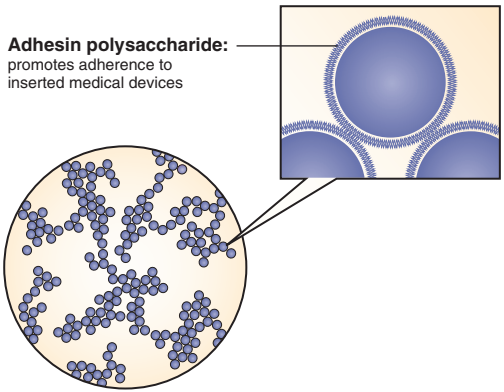
QUICK FACTS

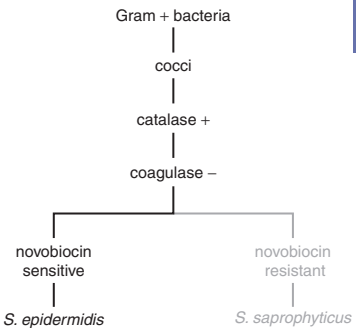
Tricuspid valve endocarditis frequently affects IV drug users.

Patients with chronic granulomatous disease (impaired neutrophil function) are vulnerable.

S. aureus is a leading cause of osteomyelitis in children and adults.

Staphylococcus epidermidis





CLINICAL CASE

Ten days after undergoing chemotherapy for non-Hodgkin's lymphoma, a middle-aged man develops a fever. On exam, he has erythema and tenderness at the insertion site of the IV catheter. Blood cultures are positive. The original catheter is removed and the patient is started on vancomycin.

Staphylococcus epidermidis

CLINICAL PRESENTATION

infection on indwelling medical devices (e.g., prosthetic valve, prosthetic joint, Foley catheter, IV line)

PATHOBIOLOGY

bacteria normal flora of skin → polysaccharide capsule allows adherence to inserted medical device (catheter, valve, prosthetic) → indwelling device inoculates bacteria to internal site → bacteria colonize, inflammation at site of device

DIAGNOSIS

Gram + clusters, catalase +, coagulase −, novobiocin sensitive

TREATMENT

vancomycin (most strains resistant to penicillins and cephalosporins)
removal of foreign body

QUICK FACTS

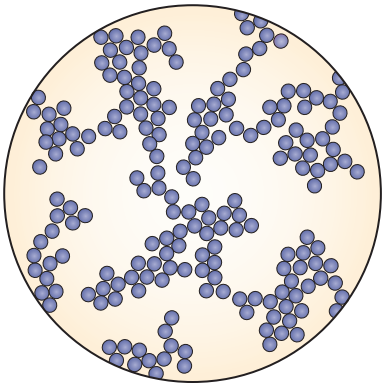
Skin flora often contaminates blood cultures (be cautious of false-positive *S. epidermidis* blood cultures).
Neutropenic patients are most susceptible, and infection can lead to bacteremia.

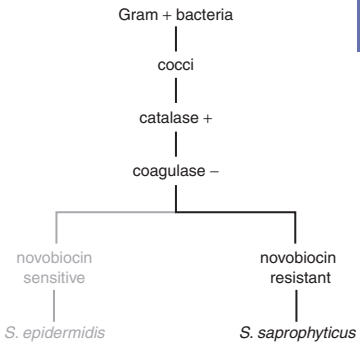
Study Tip

When you see endocarditis with a prosthetic heart valve, think:

- *S. epidermidis* within 60 days of a valve replacement
- Viridans Streptococci after 60 days of valve replacement

Staphylococcus saprophyticus





CLINICAL CASE

A sexually active young woman develops dysuria, pyuria, and fever suggestive of urinary tract infection. Urine cultures show Gram + bacteria in clusters that are catalase +, coagulase −. The patient is started on TMP-SMX.

Staphylococcus saprophyticus

CLINICAL PRESENTATION

urinary tract infection, cystitis

PATHOBIOLOGY

bacteria enter urinary tract by sexual activity ⟶ infection and inflammation in urinary tract ⟶ may spread to bladder, resulting in cystitis

DIAGNOSIS

Gram + clusters, catalase +, coagulase −, novobiocin resistant

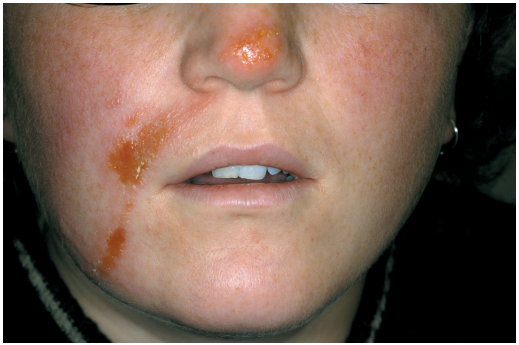
TREATMENT

TMP-SMX

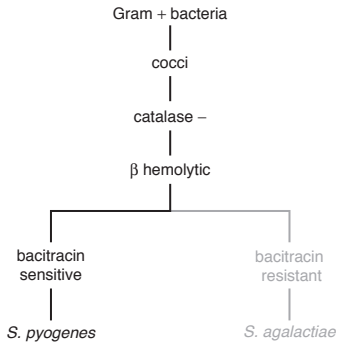
Study Tip

Most common causes of cystitis among sexually active young women:

1. *E. coli*
2. *S. saprophyticus*



Impetigo



CLINICAL CASE

A young child presents with fever and a skin rash localized around the lips and on his arms. The rash appears pustular with yellow crusts. Cultures from the impetigo show Gram + cocci in chains that are β-hemolytic. The doctor administers penicillin G and warns the parents that the child may develop transient smoky-colored urine soon.

Streptococcus pyogenes (infections)

CLINICAL PRESENTATION

pharyngitis
impetigo, erysipelas, cellulitis

PATHOBIOLOGY

may be normal flora of skin, oropharynx

pharyngitis: transmitted human-to-human via respiratory droplets or food → adhere to pharyngeal epithelium via pili and colonize → inflammation → sore throat, enlarged cervical lymph nodes → spontaneous recovery or may lead to:

- bacterial spread → bacteremia, meningitis, otitis
- toxin release → scarlet fever, TSS
- anti-streptococcal Ab reactions → glomerulonephritis, Rheumatic fever

skin infections: trauma inoculates bacteria in skin → bacteria colonize → inflammation → pustular lesions and honeycomb-like crusts (impetigo) at site of inoculation→ deeper infection results in erysipelas, cellulitis → spontaneous recovery or may lead to:
anti-streptococcal Ab reactions → glomerulonephritis (not Rheumatic fever)

virulence factors promoting spread and inflammation:

- streptokinase: converts plasminogen to plasmin → fibrinolysis
- M protein: resists phagocytosis
- hyaluronidase: breaks down connective tissue
- DNase: digests DNA

DIAGNOSIS

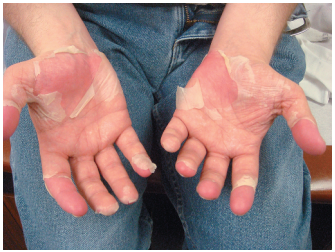
Gram + cocci in chains; throat or skin culture: β-hemolytic, bacitracin sensitive; ASO +: anti-streptolysin O antibodies present

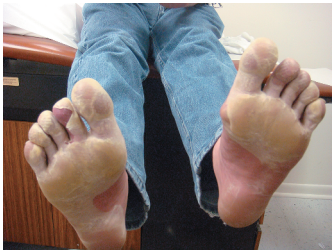
TREATMENT

penicillin G

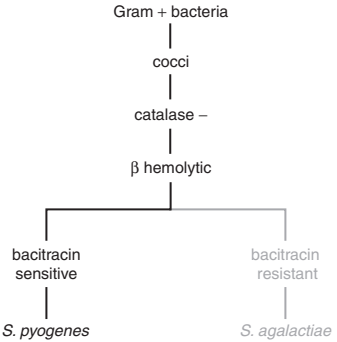
QUICK FACTS

While "strep throat" (Strep A pharyngitis) is usually self-limited, treatment is mandatory to prevent complications such as Rheumatic fever and glomerulonephritis.





Desquamation seen with Scarlet Fever



CLINICAL CASE

A young girl is brought to her doctor because of a rough-appearing rash on her trunk and neck that has spread to her arms. Physical exam reveals that her axilla is most affected, but her palms and soles are spared. Her parents say that she has been suffering from a fever and sore throat. Lab studies reveal her serum is ASO +, and she is administered with penicillin. In a few days, her rash subsides and her palms and soles desquamate.

Streptococcus pyogenes (toxin-mediated)

CLINICAL PRESENTATION

Scarlet Fever
"sandpaper" rash, "strawberry" tongue
Toxic Shock Syndrome
necrotizing fasciitis

PATHOBIOLOGY

Scarlet Fever: *S. pyogenes* pharyngitis → systemic release of pyrogenic exotoxins A, B, C → fever, "sandpaper" rash (begins on trunk and spreads outward), "strawberry" tongue within first 2 days, desquamation of palms and soles after rash subsides

Toxic Shock Syndrome: *S. pyogenes* skin infection (e.g., cellulitis) → systemic release of pyrogenic exotoxins A (superantigen) → polyclonal activation of T cells → acute fever, shock, multiorgan failure

necrotizing fasciitis: trauma/surgery inoculates bacteria in fascia investing muscles → release of exotoxin B (protease) → rapid necrosis along fascial planes, no damage to muscles

other toxins: streptolysin O, streptolysin S: destroy RBCs, WBCs

DIAGNOSIS

Gram + cocci in chains
throat or skin culture: β-hemolytic, bacitracin sensitive
ASO +: anti-streptolysin O antibodies present

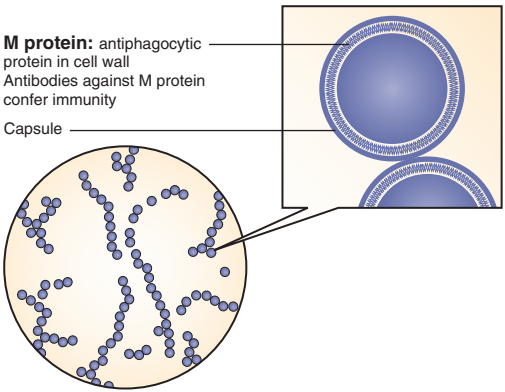
TREATMENT

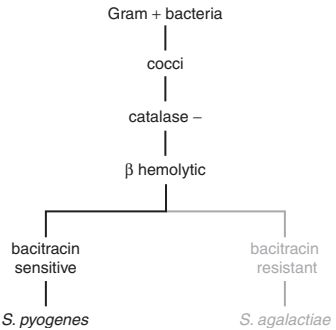
penicillin G
clindamycin added in TSS to prevent Scarlet fever toxin production
surgery, debridement for necrotizing fasciitis

Study Tip

Five most common pediatric diseases with rash:

- Measles (measles virus)
- Rubella (rubella virus)
- Scarlet fever (*S. pyogenes*)
- Roseola (HHV-6)
- Erythema infectiosum (parvovirus B19)





CLINICAL CASE

An adolescent presents to the clinic complaining of brownish urine that started the day before. Two weeks earlier, he had a sore throat that resolved. Physical exam reveals high BP and slight swelling around his eyes. Serum studies are significant for elevated BUN and Cr, ASO +, and diminished levels of C3 (complement protein). In addition, urinalysis indicates protein and RBC casts. Although a kidney biopsy was not performed, if it were, EM studies would likely reveal subepithelial humps ("lumpy-bumpy pattern") in the glomerulus.

Streptococcus pyogenes (immune-mediated)

CLINICAL PRESENTATION

Glomerulonephritis
hematuria, periorbital edema, hypertension
Rheumatic fever
carditis, chorea, migratory polyarthritis, erythema marginatum, subcutaneous nodules

PATHOBIOLOGY

Glomerulonephritis: *S. pyogenes* skin infection or pharyngitis → anti-streptococcal antibodies generated → immune complexes form → deposit on glomerular basement membrane → glomerular inflammation → 2–3 weeks after infection, develop hematuria, hypertension, periorbital edema → complete recovery likely

Rheumatic fever: *S. pyogenes* pharyngitis left untreated → autoimmune cross-reaction of anti-streptococcal antibodies with antigen of joints and heart tissue → 2 weeks after pharyngitis, develop inflammatory response at various tissues (e.g., mitral valve) → permanent endocardial damage → years later may present as murmurs

DIAGNOSIS

ASO +: anti-streptolysin O antibodies present
renal or cardiac studies
"Jones criteria" for Rheumatic fever

TREATMENT

symptomatic treatment
prophylaxis: penicillin to patients with history of Rheumatic fever prevents further valve damage

QUICK FACTS

Valves damaged by Rheumatic fever are susceptible to colonization by Enterococci or Viridans Streptococci, causing endocarditis.

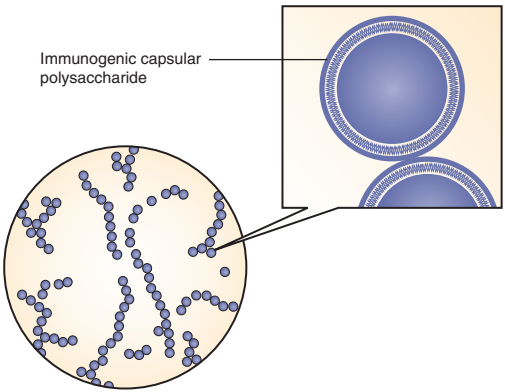
Study Tip

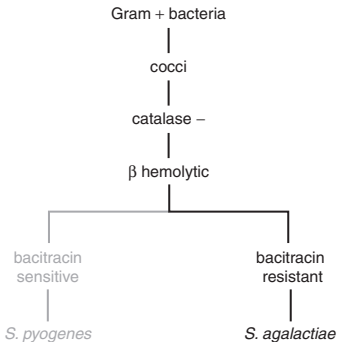
Jones criteria for diagnosis requires two major or one major + two minor criteria, and evidence of prior infection. Major criteria:

- Carditis (endocarditis, myocarditis, or pericarditis)
- Polyarthritis
- Sydenham's chorea
- Erythema marginatum rash
- Subcutaneous nodules

Minor criteria:

- Fever
- Arthralgia
- Elevated ESR or CRP
- Prolonged PR interval
- + Streptococcal antibody





CLINICAL CASE

Soon after birth, an infant develops seizures, a marked irritability, poor feeding, and fever. The infant's birth records note a prolonged labor with premature rupture of membranes. An LP was done and the infant was started on antibiotics.

Streptococcus agalactiae — Group B Streptococci

CLINICAL PRESENTATION

neonatal meningitis, neonatal pneumonia, neonatal sepsis

PATHOBIOLOGY

bacteria carried in maternal genital tract → colonize neonate, especially following obstetric complications, causing:

- meningitis: seizures, irritability develop weeks after birth → survivors may have neurological impairment
- pneumonia: respiratory distress, lethargy, hypotension develop within a day after birth

DIAGNOSIS

Gram stain of CSF, urine, blood
Gram +, β-hemolytic, bacitracin resistant

TREATMENT

penicillin G
Prophylaxis: ampicillin to pregnant women testing positive for *S. agalactiae*
Future: polysaccharide-protein conjugate vaccines, especially in pregnancy

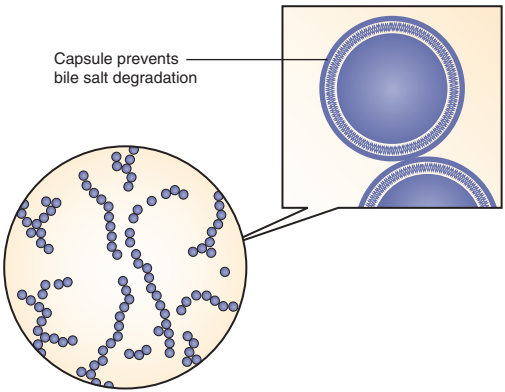
QUICK FACTS

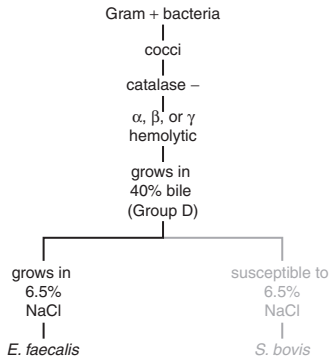
Most common cause of meningitis in newborns.

Study Tip

Most common causes of neonatal meningitis:

Group B Strep
E. coli
Listeria





CLINICAL CASE

An old man develops a UTI 5 days after admission to the hospital. His record indicates that he is receiving antibiotic treatment including cephalosporins for an unrelated infection. In treating the patient, physicians check for resistance to vancomycin.

Enterococcus faecalis

CLINICAL PRESENTATION

Local
- *UTIs, biliary tract infections*

Systemic
- *Subacute Bacterial Endocarditis (SBE)*

PATHOBIOLOGY

normally inhabits intestines, biliary tract, genitourinary tract ⟶ overgrows locally when normal flora is suppressed by cephalosporins ⟶ UTI, biliary tract infection

may enter bloodstream when mucosal or epithelial barrier disrupted (e.g., bedsores, IVDU) ⟶ systemic infection ⟶ colonize heart valves, endocarditis

DIAGNOSIS

Gram +, catalase −

culture in 40% bile and 6.5% NaCl (vs. Nonenterococci), α- or β- or γ-hemolytic

TREATMENT

ampicillin or vancomycin + aminoglycosides (synergistic)

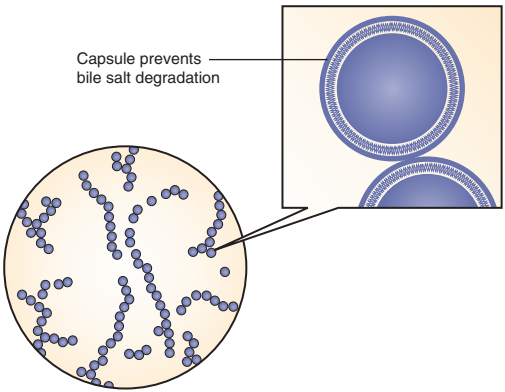
VRE (vancomycin-resistant enterococci): linezolid, daptomycin

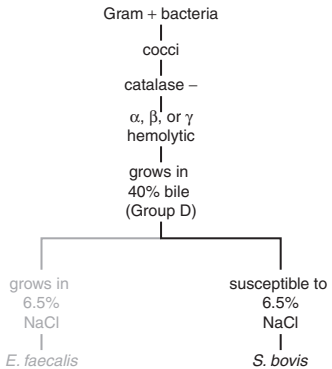
QUICK FACTS

Second most common cause of nosocomial infections in the U.S. due to high resistance: all strains resistant to cephalosporins, and some strains also resistant to vancomycin.

SBE: Enterococci as well as Viridans Streptococci colonize valves previously damaged by group A Streptococci (Rheumatic fever).

Infection is frequent complication of biliary/hepatic surgery.





CLINICAL CASE

An elderly man develops low-grade fever and signs of endocarditis over a period of 2 weeks. Following blood culture, his doctor also becomes concerned about possible colon cancer.

CLINICAL PRESENTATION

Subacute Bacterial Endocarditis (SBE)

PATHOBIOLOGY

normally inhabits lower GI tract → penetrates epithelium via lesions in colon (e.g., colon cancer) → enters lymphatics → travels in bloodstream → localizes to aortic valve, adhering to platelet-fibrin aggregates → endocarditis

DIAGNOSIS

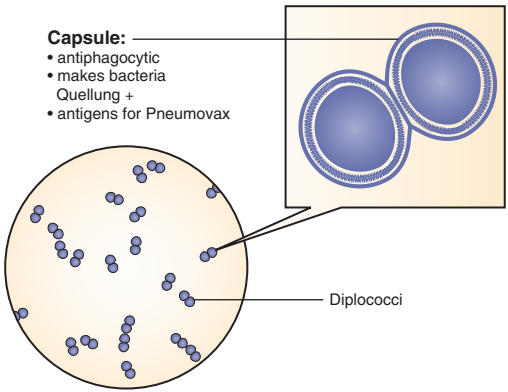
Gram +, catalase −
culture in 40% bile but not in 6.5% NaCl (vs. Enterococci), α- or β- or γ-hemolytic

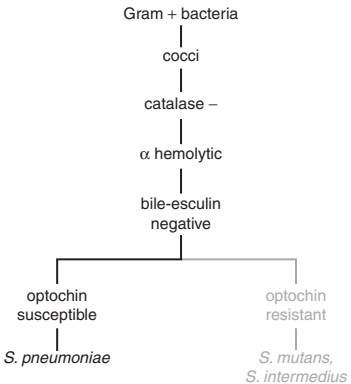
TREATMENT

penicillin

QUICK FACTS

Because it invades through GI lesions, *S. bovis* bacteremia oftentimes signals colonic carcinomas or inflammatory bowel disease.

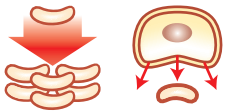




CLINICAL CASE

An elderly woman presents with a cough producing rusty-colored sputum. She complains of sharp right-sided chest pains, chills, and fevers. Physical exam reveals increased fremitus, dullness to percussion, and bronchial breath sounds on the lower right side. CXR shows right lower lobe consolidation, and Gram stain of sputum shows Gram + diplococci. Physicians begin treatment with cephalosporins.

Streptococcus pneumoniae — Pneumococci



CLINICAL PRESENTATION

Local
lobar pneumonia, otitis media
Systemic
meningitis

PATHOBIOLOGY

spread by respiratory droplets → colonizes nasopharynx epithelium (especially if clearance hindered by viral infection, allergy, and smoking) → evades host defenses by:
- capsule (escapes phagocytosis)
- IgA proteases

may travel to anatomically connected structures (e.g., middle ear, sinuses) and stimulate inflammation → otitis media, sinusitis
may travel to alveoli and stimulate inflammation → disseminates throughout lobe via pores of Kohn → lobar pneumonia
if host lacks anti-capsular IgG → invasive strains enter lung lymphatics → enter bloodstream → seed target organs (e.g., meninges) and stimulate inflammation

DIAGNOSIS

Gram + diplococci, α-hemolytic, catalase −, susceptible to optochin
Quellung reaction

TREATMENT

penicillin or cephalosporins, except vancomycin for meningitis
Pneumovax: vaccine with capsular polysaccharides

QUICK FACTS

Major cause of community-acquired pneumonia.
Other systemic infections caused by *S. pneumoniae* include osteomyelitis, septic arthritis, and endocarditis.
Asplenic patients are especially susceptible because unable to remove Ab-coated organisms (give Pneumovax).

Study Tip

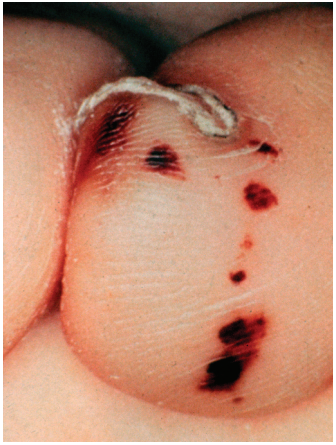
Common causes of pneumonia in:

adults (40–65 yrs)
S. pneumoniae
H. influenzae
Legionella

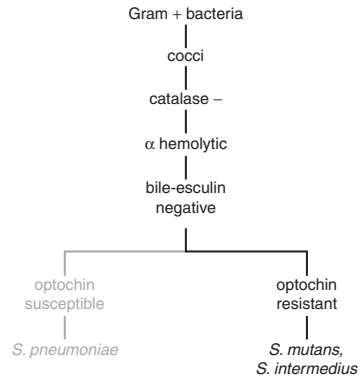
elderly (>65 yrs)
S. pneumoniae
Gram − rods
H. influenzae

Most common causes of meningitis in 60+ yrs:
S. pneumoniae
Gram − rods
Listeria

Streptococcus mutans, Streptococcus intermedius



Painful Osler's nodes on the sole, from immune complexes causing vasculitis



CLINICAL CASE

A middle-aged woman presents with low-grade fever and general malaise. Physical exam reveals Janeway lesions, Osler's nodes, Roth's spots, and splinter hemorrhages under her fingernails. Echocardiogram indicates vegetations on the mitral valve. In the doctor's office, she recounts a dentist appointment a few weeks ago and several bouts of sore throat as a child.

Streptococcus mutans, Streptococcus intermedius

CLINICAL PRESENTATION

Local
- *dental caries (S. mutans)*
- *brain or abdominal abscesses (S. intermedius)*

Systemic
- *Subacute Bacterial Endocarditis (SBE)*

PATHOBIOLOGY

normally inhabits oropharynx epithelium → seeds bloodstream during aggressive activity such as flossing → localizes to previously damaged valves (e.g., Rheumatic fever), adhering to platelet-fibrin aggregates → SBE

S. mutans binds to pellicle of teeth → bacteria ferments sugars into lactic acid → lactic acid demineralizes tooth enamel → dental caries

S. intermedius normally inhabits GI tract → microaerophilic bacteria thrive in low-oxygen environment of brain/liver abscesses

DIAGNOSIS

Gram + cocci, α-hemolytic (most), optochin-resistant

Quellung reaction

TREATMENT

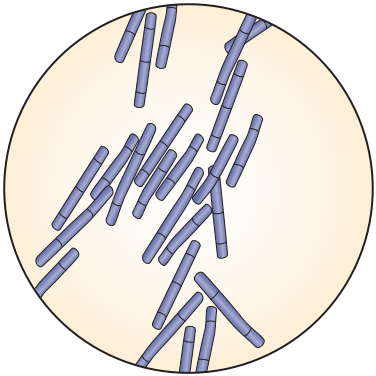
penicillin G

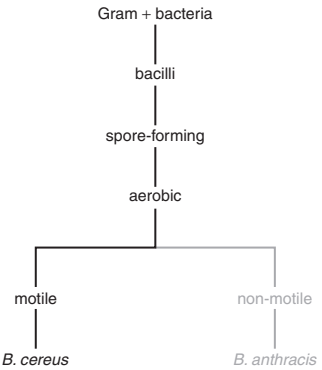
QUICK FACTS

SBE: Viridans Streptococci as well as Enterococci colonize valves previously damaged by group A Streptococci (Rheumatic fever).

Blood cultures of *S. intermedius* often indicate the presence of abscesses.

Bacillus cereus





CLINICAL CASE

A young man enters the emergency room dehydrated, afebrile, and complaining of nausea and vomiting. Since he began vomiting 1 hour ago, he has been "hugging the toilet" nearly every 10 minutes. He remembers eating a dish with fried rice at an Asian restaurant several hours ago.

Bacillus cereus

CLINICAL PRESENTATION

food poisoning
- *emetic* syndrome (~1–5 hours after ingestion)
  - or
- *diarrheal* syndrome (~15–20 hours after ingestion)

PATHOBIOLOGY

bacteria contaminate uncooked food (e.g., rice) → during high-temperature cooking, form protective spores later, when food rewarmed, spores germinate → secrete one of two major toxins into food → contaminated food ingested

toxin determines syndrome:
- heat-stable enterotoxin (like *Staphylococcus* enterotoxin) → vomiting, nausea (emetic syndrome)
- heat-labile enterotoxin (AB_5 toxin like *E. coli* LT) → ↑ [cAMP] →↓ reabsorption of NaCl → diarrhea (diarrheal syndrome)

DIAGNOSIS

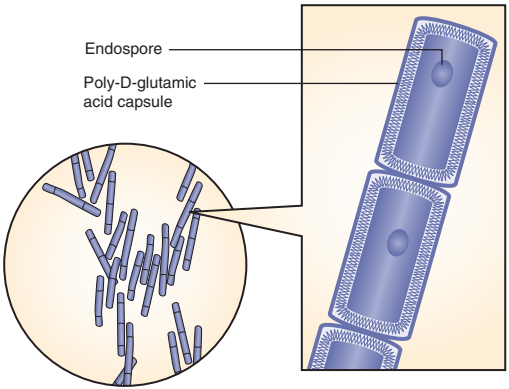
usually not performed
Gram + rod, forms spores, motile

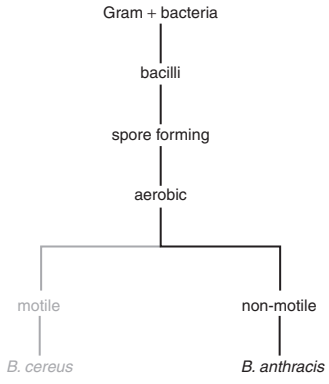
TREATMENT

rehydration
prevention: good food handling and storage (e.g., avoid reheating rice)

QUICK FACTS

B. cereus food poisoning caused by foods other than reheated rice is probably much more prevalent than appreciated.





CLINICAL CASE

A 33-year-old woman presents with an ulcerous lesion on the neck. The ulcer has a blackened necrotic eschar surrounded by edema. The woman first noticed the lesion 2 weeks ago as a painful, small red macule that gradually developed into an ulcer and, over the last few days, became painless. On the occupational history, the patient reveals that she works in the imported wool and hides industry.

Bacillus anthracis — Anthrax

CLINICAL PRESENTATION

Local
- *Cutaneous Anthrax* (most common)
  - malignant pustules
- *GI Anthrax*
  - dysentery

Systemic
- *inhalation anthrax/woolsorter's disease*

PATHOBIOLOGY

spores from goat, cow, or other herbivore products ⟶ spores enter human via:
- cutaneous abrasion ⟶ spores germinate and multiply locally ⟶ anthrax toxin secreted locally ⟶ causes tissue hemorrhage and necrosis ⟶ malignant pustules
- ingestion ⟶ spores germinate and multiply locally in oropharynx or intestines ⟶ anthrax toxin secreted locally causes lesions in throat, intestines ⟶ dysentery
- inhalation ⟶ spores germinate and multiply in respiratory tract ⟶ bacteria enter bloodstream and divide ⟶ anthrax toxin secreted systemically ⟶ may cause fever, dyspnea, nonproductive cough ⟶ 100% mortality

anthrax toxin consists of protective antigen (PA) and either edema factor (EF) or lethal factor (LF)
- PA: binds cell membrane and mediates endocytic entry of EF or LF
- EF: adenylate cyclase activity ⟶↑ [cAMP] ⟶ edema and inhibition of polymorphonuclear leukocytes
- LF: cell death

DIAGNOSIS

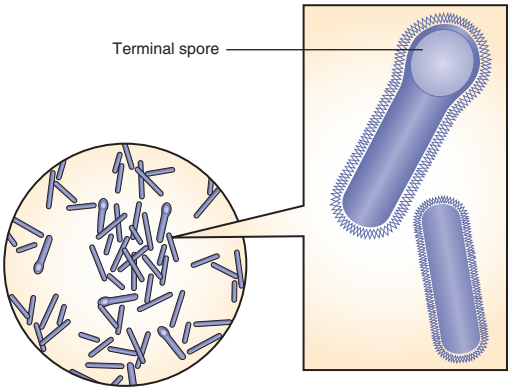
Gram + rod in chains, protein capsule, aerobic, nonmotile serology

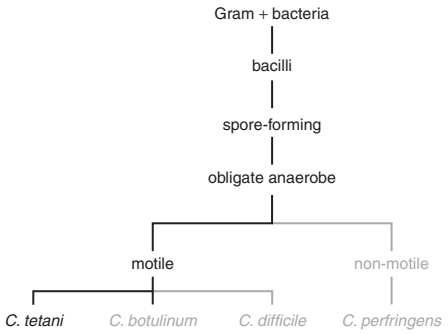
TREATMENT

parenteral penicillin G
anti-PA vaccine

QUICK FACTS

Spores are destroyed by boiling but can survive for years in dry earth or goat skin.
Only medically important bacteria with *protein* rather than polysaccharide capsule.
Sought by several nations as a biological weapon.





CLINICAL CASE

A teenage girl enters the emergency room suffering from painful muscle spasms. Throughout her examination, she sustains a facial sneer, a stiff arched back, and clamped palms. Her father is anxious about the fact that she has also experienced difficulty eating, probably due to a stiff jaw. The father affirms that his daughter is usually quite active and boasts how, a week ago, she continued a soccer game even after falling on a nail in the field.

Clostridium tetani — Tetanus, Lockjaw

CLINICAL PRESENTATION

spastic paralysis
lockjaw, risus sardonicus

PATHOBIOLOGY

spores survive in soil, feces for years → spores enter skin injuries → bacteria germinate → bacteria release toxin
tetanospasmin → tetanospasmin travels retrogradely on axons of peripheral motor neurons, as well as through bloodstream → blocks release of inhibitory neurotransmitters GABA and glycine from Renshaw cell interneurons of spinal cord → motor nerves become hyperexcited → spastic paralysis, sustained muscle contraction (tetanus)
tetanus progresses from head to trunk to extremities (order determined by length of neurons) → masseter muscle most sensitive, giving lockjaw

DIAGNOSIS

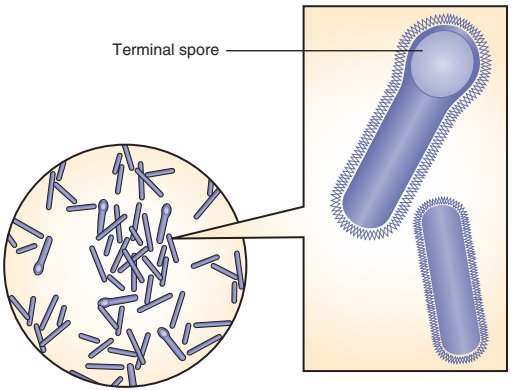
Gram + rod with large terminal spore (shaped like a tennis racket), anaerobic, motile

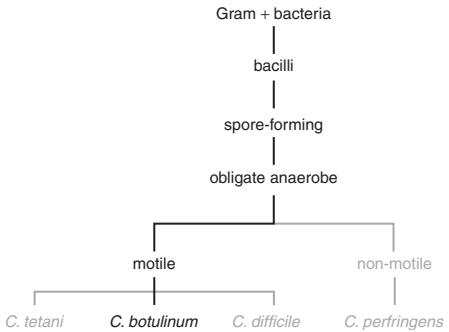
TREATMENT

prophylaxis:
DTaP vaccine: tetanus toxoid, boosters required
treatment:
clean wound
antitoxin (human anti-tetanospasmin immunoglobulin)
DTaP vaccine booster
penicillin, metronidazole
diazepam (a GABA agonist)

QUICK FACTS

DTaP vaccines are administered at 2, 4, 6, and 18 months, again before starting school, and every 10 years thereafter.
Spores can affect neonates through cut umbilical cord, especially when the mother is not immunized.





CLINICAL CASE

A woman straggles into the emergency room with a marked paralysis of her upper body. She describes the paralysis as a weakness that began in her neck and spread to her arms. She also complains of blurred double vision and requests water to soothe her dry throat. Although she has no fever, she appears quite dizzy and her eyelids are drooping. The day before, she returned from a camping trip where she insists she maintained good hygiene, limiting her diet to canned foods only.

CLINICAL PRESENTATION

Adult botulism (food poisoning)
Infant botulism (floppy baby syndrome)

PATHOBIOLOGY

adult botulism: heat-labile toxin released in anaerobic environment, especially in canned foods → ingestion of contaminated food → neurotoxin quickly enters vascular system and spreads to peripheral cholinergic nerve terminals (12–36 hrs) → blocks acetylcholine release at:

- cranial nerves → diplopia, dysarthria, dysphagia
- neuromuscular junctions → symmetric descending paralysis spreading from head to extremities
- postganglionic parasympathetic nerve endings, peripheral ganglia → dizziness, dry throat, ptosis

infant botulism: spores often in honey → infant eats contaminated honey → spores germinate in large intestine → release toxin → toxin slowly absorbed (over days) → blocks acetylcholine release → constipation, flaccid paralysis (floppy baby syndrome) → good prognosis with supportive therapy

in both cases, no fever because bacteria do not invade

DIAGNOSIS

Gram + rod, anaerobic
check for toxin in uneaten food
mouse test: inject patient serum into mouse and check for paralysis/death

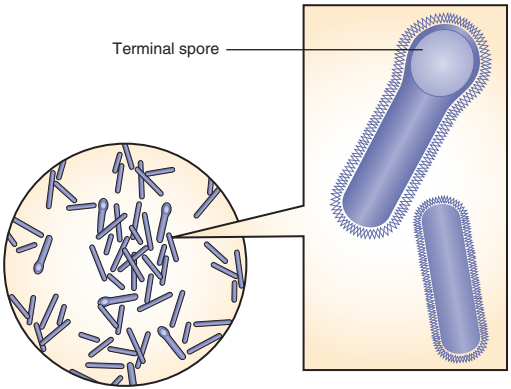
TREATMENT

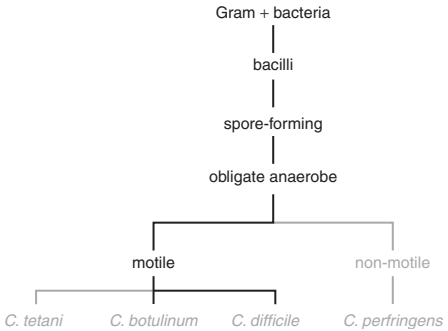
antitoxin
respiratory support

QUICK FACTS

Wound botulism can occur when spores germinate and release toxin in wounds.
Swollen food cans warn of poor sterilization and contamination since *C. botulinum* enzymes generate gas.
Botulinum toxin has been applied successfully to treat a number of conditions, including strabismus, muscle spasticity, and facial wrinkles.

Clostridium difficile





CLINICAL CASE

An old woman comes to the doctor with a fever and loose bowels. Her diarrhea occurs in tremendous volumes, she complains, although she does not remember ever seeing blood. She has an unremarkable recent past medical history, except for an infection a few weeks earlier that was treated with clindamycin. Sigmoidoscopy of her colon reveals yellow-white plaques, which the doctor predicted after analyzing her stools for toxins.

Clostridium difficile

CLINICAL PRESENTATION

Pseudomembrane Colitis (PMC), diarrhea

PATHOBIOLOGY

normal flora of GI tract ⟶ antibiotic treatment disrupts normal flora but *C. difficile* survives by forming spores ⟶ spores germinate following antibiotic treatment ⟶ grow rapidly (fewer competing microorganisms) ⟶ secrete two toxins:

- toxin A ⟶ alters fluid secretion ⟶ watery diarrhea
- toxin B ⟶ cytotoxic to epithelial cells ⟶ pseudomembrane

DIAGNOSIS

Gram + rod, strict anaerobe
stool specimen: toxin B present in feces
colonoscopy: pseudomembranes (yellow-white plaques) present

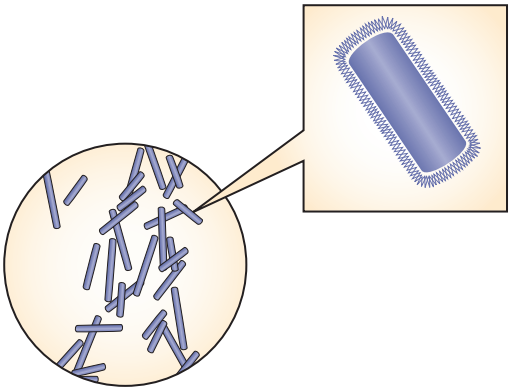
TREATMENT

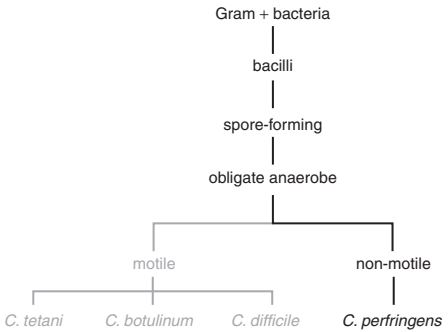
oral metronidazole or oral vancomycin (not absorbed, act on intestinal bacteria)
withdraw causative antibiotic (often clindamycin)

QUICK FACTS

Major cause of hospital-acquired diarrhea, often transmitted by the hands of hospital personnel.
Inflammation by toxin A can sometimes cause hypoalbuminemia.

Clostridium perfringens





CLINICAL CASE

A man enters the emergency room claiming to have been stabbed 2 days earlier. Muscles in his arm hurt, and on palpation, small air bubbles are felt below the skin. The wound area exudes a blackish, ill-smelling fluid and generates a crackling sound when touched. The patient has a fever, a low blood pressure, marked tachycardia, and has urinated very little since his injury. The doctors decide to amputate the arm, as well as monitor the patient for shock and renal failure.

Clostridium perfringens

CLINICAL PRESENTATION

cellulitis
gas gangrene (myonecrosis with crepitus)
food poisoning

PATHOBIOLOGY

cellulitis: normally found in soil, GI tract → bacteria infect anaerobic environment of necrotic skin wound → release degradative enzymes (e.g., collagenase, hyaluronidase) → slow, painless infection and gas production → forms collections of gas under skin that crackle when touched (crepitus)

gas gangrene: spores in soil → introduced via deep muscle laceration (esp. military wounds, automobile accidents, crude abortions) → grows in anaerobic environment → releases:

- alpha toxin (lecithinase) → muscle cell necrosis
- degradative enzymes → subcutaneous gas bubbles → crepitus

gangrenous muscles → black fluid exudate leaking from skin → shock may follow

food poisoning: spores in meat/poultry foods → survive cooking and germinate → contaminated food ingested → bacteria release heat-labile enterotoxin in GI tract → enterotoxin inhibits glucose transport, damages epithelium → diarrhea, gastric pain, nausea (no fever or vomiting)

DIAGNOSIS

Gram + rod, strict anaerobes, nonmotile

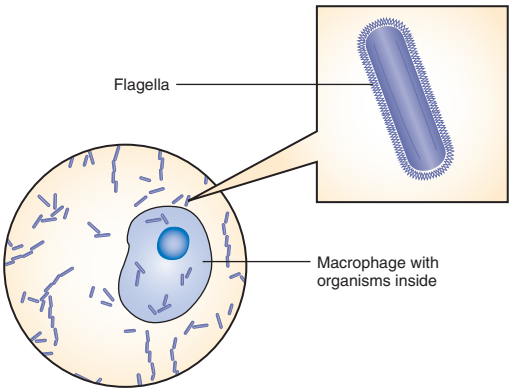
TREATMENT

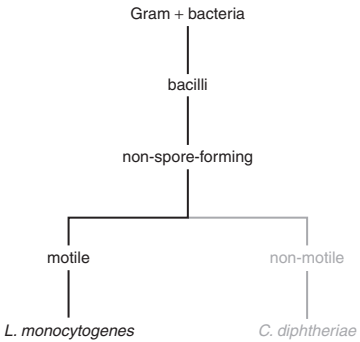
surgical removal of infected areas
hyperbaric oxygen to kill anaerobic organisms
penicillin, clindamycin (effective only in local, weak infections)

QUICK FACTS

C. perfringens is the only nonmotile *Clostridium* member.
Enteritis necroticans: necrosis of small intestine caused by β-toxin release, common in New Guinea following large ingestion of pork (excess protein overwhelms trypsin digestion of β-toxin), 40% mortality.

Listeria monocytogenes





CLINICAL CASE

A mother brings her 2-month-old infant to the hospital because he exhibits fever, convulsions, irritability, and poor eating. The pediatrician-in-training notes a widespread rash and a stiff neck on physical exam. She orders a spinal tap that reveals low glucose, ↑ PMNs, ↑ protein, and Gram + rods with "tumbling" motility in cultures. Upon further questioning, the pediatrician discovers that the mother does not breast-feed and feeds her baby with fresh cow's milk.

Listeria monocytogenes

CLINICAL PRESENTATION

listeriosis (meningitis and sepsis in neonates, immunocompromised)

PATHOBIOLOGY

heat-resistant organism survives in poorly pasteurized milk → consumed by host → penetrates GI mucosa and invades phagocytes → grows intracellularly (intracellular infection)
spreads through blood → tropism for neural tissue → meningitis
in fetus, neonates: organism normally colonizes vaginal tract → transmitted to fetus across placenta or during birth → spreads through blood → disseminated abscesses, meningitis

DIAGNOSIS

Gram + rod, tumbling motility

TREATMENT

ampicillin ± gentamicin
TMP-SMX

QUICK FACTS

People deficient in cell-mediated immunity (pregnant women, neonates, AIDS patients) have ineffective phagocytosis and are most susceptible.

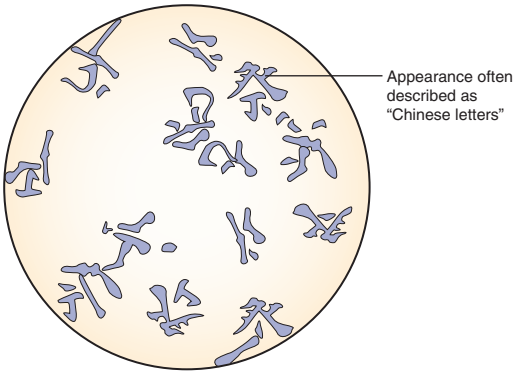
L. monocytogenes has unique growth properties. It can survive both intracellularly (in macrophages, neutrophils) and extracellularly. It can also grow at refrigerated temperatures.

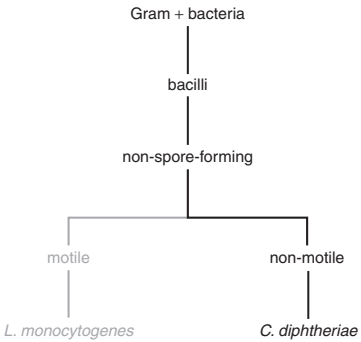
L. monocytogenes and β-hemolytic Streptococci appear similar on blood agar plates; however, *L. monocytogenes* can be distinguished because it is catalase +.

L. monocytogenes inherits a second membrane upon invading a host cell. It can digest away this membrane with the listeriolysin O bacterial toxin.

Study Tip

Listeria: only Gram + with endotoxin
Bacteroides: only Gram – without typical endotoxin

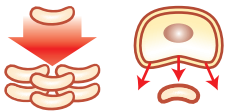




CLINICAL CASE

A young immigrant girl goes to the doctor complaining of a sore throat and difficulties in breathing and swallowing. Her voice is unusually nasal and a large gray mucous film is noticed on the oropharynx. The patient also exhibits ST-T wave changes on an electrocardiogram and a slight paralysis of her tongue. Her blood pressure is low, her lungs edematous, and her neurological examination shows cranial nerve problems. Her physician begins immediate treatment and orders a potassium tellurite culture to confirm his worst suspicions.

Corynebacterium diphtheriae — Diphtheria



CLINICAL PRESENTATION

Local
- *pseudomembrane, airway obstruction*

Systemic
- *myocarditis, polyneuritis*

PATHOBIOLOGY

enters nasopharynx via respiratory droplets → creates gray fibrinous exudate (pseudomembrane) composed of bacteria, WBCs, and necrotic mucosa → may block airways

secretes diphtheria toxin (*AB toxin* that ADP ribosylates EF-2 and prevents protein synthesis in all cells) → toxin effects:
- cardiac: arrhythmia, myocarditis
- nervous: cranial and peripheral nerve palsy

DIAGNOSIS

Gram + rod, aerobic, "Chinese letter" appearance
black colonies on potassium tellurite

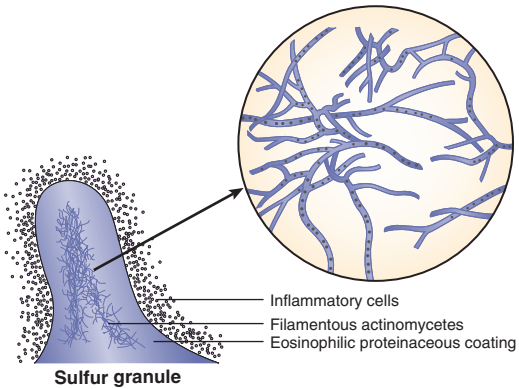
TREATMENT

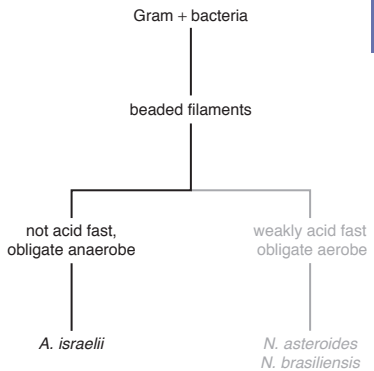
prophylaxis:
- DTaP vaccine: Diphtheria toxoid, with boosters

treatment:
- antitoxin
- penicillin or erythromycin for local colonization
- DTaP booster

QUICK FACTS

One should avoid trying to scrape the pseudomembrane because bleeding and toxin spread may result.
DTaP vaccines are administered at 2, 4, 6, and 18 months, again before starting school, and every 10 years thereafter.
Diphtheria toxin is carried by a phage, so only lysogenic organisms cause systemic disease.





CLINICAL CASE

A 45-year-old man presents with multiple sinuses on the left side of his face. The sinuses discharge pus and are painless. His past medical history is insignificant except for a dental surgery done a few weeks ago for a dental infection. His doctor examines the pus under the microscope and finds filamentous organisms. The doctor rules out *Nocardia* by lack of acid-fast staining and makes the diagnosis by noting sulfur granules.

Actinomyces israelii — Actinomycosis

CLINICAL PRESENTATION

abscesses in mouth, lungs, GI tract, and GU tract
draining sinus tracts

PATHOBIOLOGY

normal flora of oral cavity, GI tract, female GU tract → trauma/surgery disrupts mucosal barrier → local infection and inflammation → yellow sulfur granules develop (filamentous bacteria lined by proteinaceous coat) surrounded by PMNs → forms pus-filled abscess, often in mouth, lungs, GI tract, and GU tract

slow expansion to contiguous tissue without respect to tissue planes → sinus tracts form through skin, muscle, bone, and organs → possible hematogenous spread to other sites

DIAGNOSIS

Gram +, anaerobic
beaded filaments, yellow sulfur granules

TREATMENT

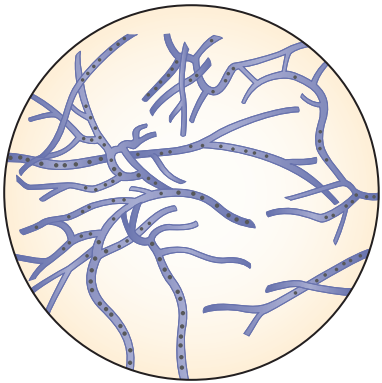
penicillin G
surgical drainage of abscesses

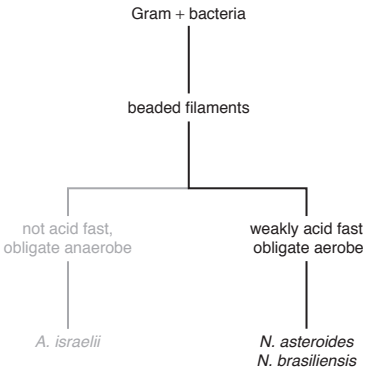
QUICK FACTS

A. israelii are true bacteria that form long, branching filaments resembling hyphae or fungi.
Called the "most misdiagnosed disease" because it is often confused with neoplasms.
Males are three times more likely to develop actinomycosis; for women, intrauterine devices are a risk factor.
Because of their yellow-orange color, colonies of these filamentous bacteria appear as sulfur granules. However, no sulfur is actually present.

Study Tip

A. israelii and *Nocardia* are both bacteria-resembling fungi, but only *A. israelii* forms sulfur granules and only *Nocardia* is acid-fast.

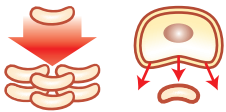




CLINICAL CASE

A heart transplant patient on immunosuppressants develops slight fever, weight loss, and a cough, producing a viscous, purulent sputum. The patient explains that these symptoms come and go over weeks and generally do not bother him enough for a checkup. The doctor decides to take a CXR, which reveals small abscesses with sinus tracts in the lung. A biopsy of the lung tissue reveals a filamentous, acid-fast, Gram + microorganism. The doctor prescribes sulfonamides and follows the patient for 6 months until a cure is certain.

Nocardia asteroides, Nocardia brasiliensis — Nocardiosis



CLINICAL PRESENTATION

pneumonia
abscesses in kidney, brain

PATHOBIOLOGY

frequently found in soil → inhaled → phagocytosed → mycolic acid cell wall allows intracellular survival and proliferation → caseous granulomas wall off infectious particles → pneumonia, cavitations
may spread via blood to adjacent tissue → abscesses in kidney, brain
infections are most common in immunocompromised patients

DIAGNOSIS

Gram +, aerobic
beaded filaments
weakly acid-fast

TREATMENT

TMP-SMX
surgical drainage of abscesses

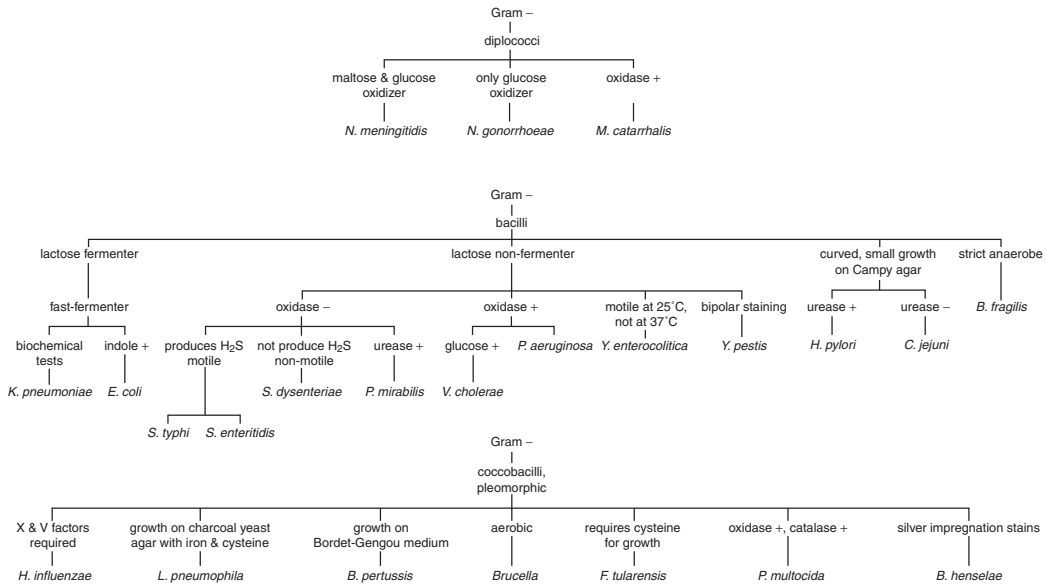
QUICK FACTS

Resembles TB in clinical presentation and in acid-fast stain, but distinguished by beaded, filamentous growth.
Some *Nocardia* species, as well as some fungi, cause a local foot infection called mycetoma. If untreated, chronic infection may lead to draining sinuses through tissue and bone.

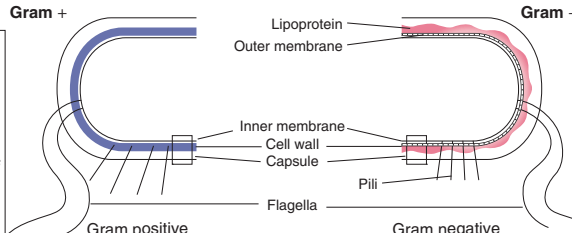
Study Tip

Nocardia and *Mycobacteria* are the two clinically important bacteria that have acid-fast positive staining.
Nocardia and *A. israelii* are both bacteria-resembling fungi, but only *A. israelii* forms sulfur granules and only *Nocardia* is acid-fast.

Gram – Bacteria



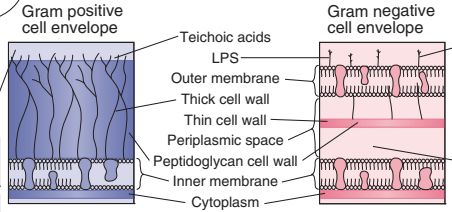
Important Features of Gram + and Gram – Bacteria



	G +	G –
LPS		✓
Outer membrane		✓
Teichoic acids	✓	
Periplasmic space		✓
Cell wall	thick	thin

Capsule:

- protects against phagocytosis
- polysaccharide (exception: *B. anthracis* has D-glutamic acid)
- glycocalyx is capsule slime that allows some bacteria to adhere to surfaces (e.g., *S. epidermidis* to catheters)
- capsule polysaccharide often used for vaccine (e.g., Pneumovax for *S. pneumoniae*)
- quellung reaction is a diagnostic test in which specific antiserum causes the capsule to swell (e.g., *S. pneumoniae, H. influenzae* type B)



LPS (lipopolysaccharide):

lipid A + polysaccharide

- lipid A → endotoxin component of LPS that causes fever, shock
- polysaccharide → important surface antigen (O antigen) in Gram – bacteria

Teichoic Acid

- important surface antigen in Gram+ bacteria

Spores:

- important for *Clostridium & Bacillus* species
- form when nutrients are absent and can remain dormant for years
- resistant to heat & chemicals – require autoclaving to kill

Peptidoglycan Cell Wall:

- penicillins & cephalosporins inhibit cell wall synthesis
- cell wall protects bacteria from osmotic pressure
- lysozyme in human secretions (tears, saliva) cleaves peptidoglycans — this is part of natural immunity to infections

Periplasmic Space:

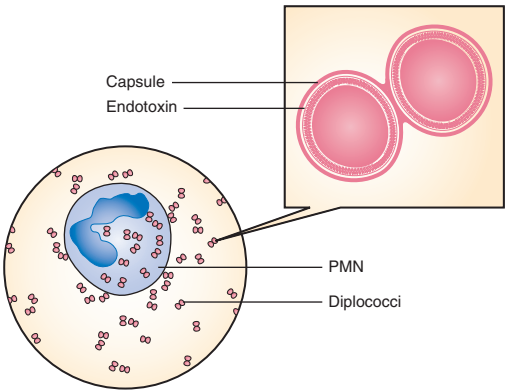
- site of β-lactamases, enzymes that cleave β-lactam drugs such as penicillins

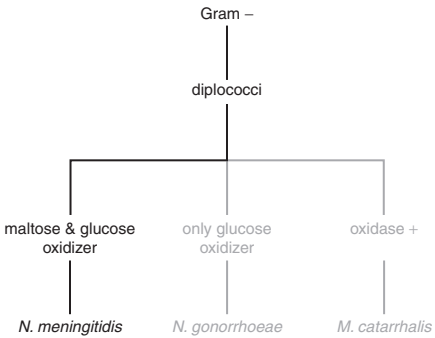
Flagella:

- for motility/ chemotaxis

Pili:

- shorter than flagella
- help bacteria to attach to surfaces or cells

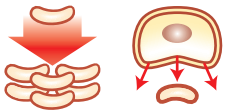




CLINICAL CASE

Early one evening, a young soldier in an army base enters the emergency room with a petechial rash, fever, and headache. Physical exam reveals + Kernig's sign, nuchal rigidity, and impaired mental status. An LP is performed showing ↑ PMNs, ↑ protein, ↓ glucose, as well as intracellular kidney bean-shaped diplococci.

Neisseria meningitidis



CLINICAL PRESENTATION

meningococcemia with petechial rash
(when fulminant, Waterhouse-Friderichsen syndrome)
meningitis

PATHOBIOLOGY

carried by humans → colonizes nasopharynx epithelium → evades IgA antibodies with IgA protease → crosses mucosa via phagocytic vacuoles of non-ciliated cells → enters and multiplies in bloodstream (meningococcemia) → endotoxin released → vascular necrosis and hemorrhage in skin (petechial rash)
in fulminant cases: vascular necrosis and hemorrhage in adrenal glands → adrenal insufficiency (Waterhouse-Friderichsen syndrome) along with shock, DIC → multiorgan failure → possible death
organisms in bloodstream may have tropism for meninges → stimulate inflammation → meningitis

DIAGNOSIS

Gram − diplococci within PMNs
metabolizes maltose and glucose (meningitidis) vs. *N. gonorrhoeae*
selectively grows on Thayer-Martin media

TREATMENT

penicillin G, ceftriaxone
rifampin for close contacts as prophylaxis
vaccines with capsule polysaccharides

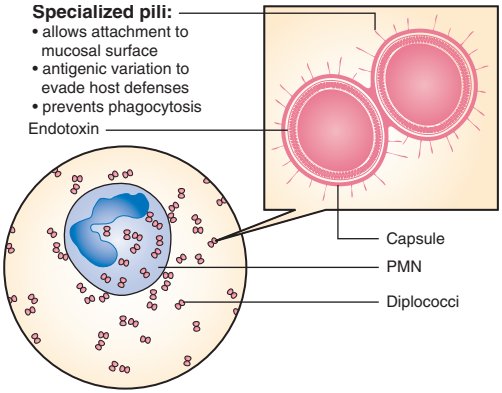
QUICK FACTS

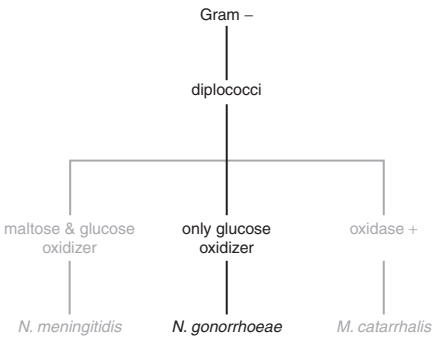
Major cause of meningitis, especially in close quarters (e.g., army bases).
Neonates are protected by maternal antibodies until 6 months.
"Meningitis belt" of sub-Saharan Africa may result from dust interference with IgA secretion in nasopharynx.

Study Tip

Most common causes of meningitis 6–60 yrs:

N. meningitidis
Enterovirus
S. pneumoniae





CLINICAL CASE

A teenager complains of pain during sexual intercourse and irregular intermenstrual bleeding. She has also begun to experience lower abdominal pain. A pelvic exam reveals a yellow mucopurulent discharge; during the exam, the cervix begins to bleed. Gram stain of discharge reveals Gram – intracellular diplococci. The teenager reports that she has been sexually active with several partners over the last year. One of her partners, a male, comes to the same clinic complaining of dysuria and profuse yellow urethral discharge.

Neisseria gonorrhoeae — Gonococci, Gonorrhea

CLINICAL PRESENTATION

Local (genital tract or anorectal infections)
- *asymptomatic, urethritis, dysuria (in men), cervicitis (in women), ophthalmia neonatorum*

Systemic
- *septic arthritis*

Complications
- *Pelvic Inflammatory Disease, ectopic pregnancy, sterility, Fitz-Hugh-Curtis Syndrome*

PATHOBIOLOGY

bacteria survive only in humans → attach via pili to mucosal cells of urethra and vagina → evades IgA antibodies with IgA protease → endocytosed by cells → kill ciliated cells → inflammatory response leading to urethritis (in men), cervicitis (in women)
- in women, infection may progress to uterus, fallopian tubes, ovaries (PID) → increased risk for ectopic pregnancies → from fallopian tubes, bacteria may spill into peritoneal cavity (peritonitis) → may infect liver capsule (Fitz-Hugh-Curtis Syndrome)
- can invade submucosa and enter bloodstream → may collect in synovial fluid → septic arthritis

in neonates, inoculates conjunctiva during passage through birth canal → ophthalmia neonatorum → risk for blindness

DIAGNOSIS

Gram − diplococci within PMNs
metabolizes glucose but not maltose (gonorrhea) vs. *N. meningitidis*
selectively grows on Thayer-Martin media

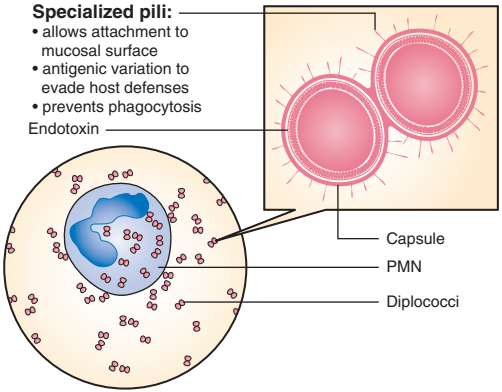
TREATMENT

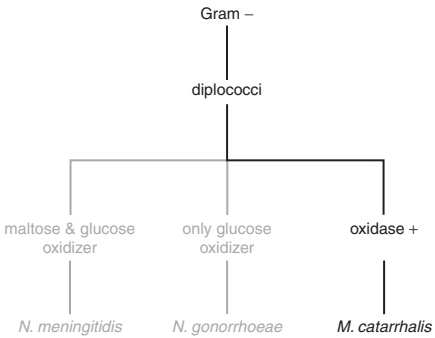
ceftriaxone (+ doxycycline for probable concurrent *Chlamydia* infection)
prophylactic erythromycin eye drops for neonates
vaccine development difficult because of pili antigen variations

QUICK FACTS

Higher incidence of infection with menstruation or IUD.
Most common cause of septic arthritis in sexually active people.
Antigenic variation prevents immunity allowing recurrent infections.

Moraxella catarrhalis





CLINICAL CASE

A 2-year-old girl returns to her pediatrician with fevers, recurrent ear pain, and new onset yellow discharge from the right ear. She had been diagnosed earlier in the week with right otitis media and treated with amoxicillin. The pediatrician correctly suspects that a beta-lactamase–producing organism is causing the infection, and had he gram stained the ear discharge, he would have found gram-negative diplococci.

Moraxella catarrhalis

CLINICAL PRESENTATION

otitis media, sinusitis, pneumonia

PATHOBIOLOGY

normally colonizes nasopharynx → spreads to contiguous mucosal surfaces → releases endotoxin → stimulates inflammatory response

DIAGNOSIS

hydrolyzes tributyrin
produces DNAse, reduces nitrite/nitrate
does not use sucrose, glucose, maltose, and lactose (unlike some *Neisseria* species)

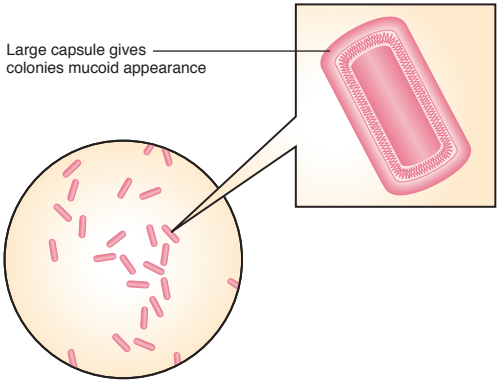
TREATMENT

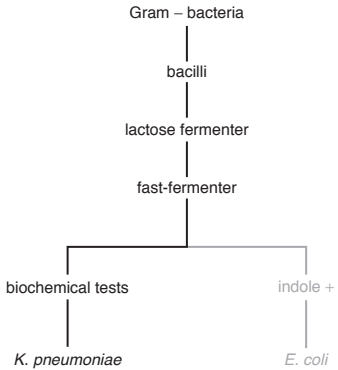
amoxicillin-clavulanate (95% produce beta-lactamase)
second- and third-generation cephalosporins
TMP-SMX

QUICK FACTS

Second most common cause of bacterial pneumonia in patients with chronic obstructive lung disease, behind nontypeable *H. influenzae.*

Klebsiella pneumoniae





CLINICAL CASE

An alcoholic presents with a fever, pleuritic chest pain, dyspnea, and cyanosis. His cough produces a bloody "currant-jelly" sputum. CXR shows inflammation involving the right upper lobe with possible cavities.

Klebsiella pneumoniae

CLINICAL PRESENTATION

pneumonia
nosocomial UTI

PATHOBIOLOGY

pneumonia: most frequently colonizes right upper lobe → avoids host defenses with antiphagocytic capsule → stimulates inflammation throughout the lobe → necrotizes tissue, forms cavities → produces bloody "currant-jelly" sputum

UTI: establishes infection when (1) all competing bacteria are killed (e.g., hospital-administered antibiotics) and (2) urinary tract is "complicated" or blocked (e.g., by a catheter or stone) → organisms colonize tract → inflammation, UTI

DIAGNOSIS

Gram − rods, capsule
mucoid-appearing colonies
lactose fermenting

TREATMENT

third-generation cephalosporin

QUICK FACTS

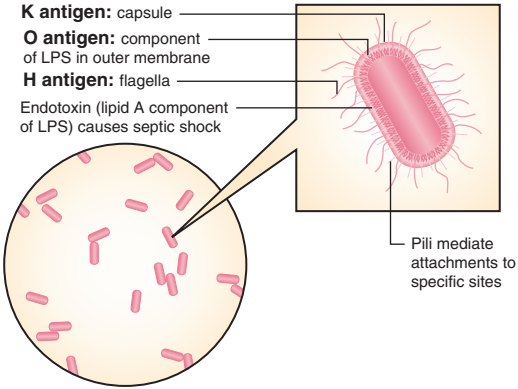
Frequent cause of serious pneumonia in alcoholics.
Klebsiella are among the most drug-resistant microbes causing nosocomial infections.

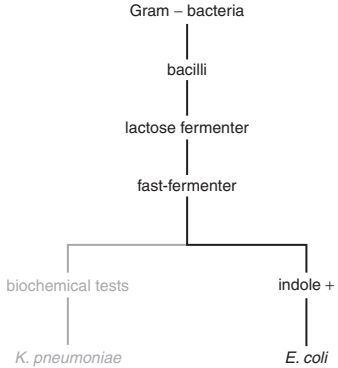
Study Tip

Similar nosocomial infections caused by:

Klebsiella
Serratia marcescens
Enterobacter

Escherichia coli



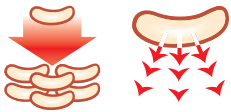


CLINICAL CASE

A series of patients in a small town visit the hospital complaining of bloody diarrhea, fatigue, and confusion. Physical exams reveal neurological deficits, and laboratory tests show anemia, thrombocytopenia, and uremia. Peripheral blood smears show fragmented RBCs, but subsequent Coombs tests are negative. After careful questioning, the doctors discover that each patient frequents the same fast-food burger joint. The physicians identify the causative agent with serological testing and stool cultures appearing metallic green.

Escherichia coli

CLINICAL PRESENTATION



enteritis (*watery diarrhea or dysentery,* depending on the strain); *UTI; pneumonia; neonatal meningitis*
septic shock, complications: *Hemolytic Uremic Syndrome (HUS)*

PATHOBIOLOGY

Enteritis: normal GI flora of humans, animals → virulent strains transmitted via fecal–oral route → use pili to adhere

- ETEC: adhere to jejunum, ileum epithelium but do not invade → produce heat-labile toxin (LT) and heat-stabile toxin (ST) → watery diarrhea (traveler's diarrhea)
- EPEC, EAEC: adhere to ileal epithelium but do not invade → induces structural changes in mucosal cells → flattening of intestinal villi (effacement) and malabsorption → diarrhea, most often in children (infant's diarrhea)
- EHEC: adhere to colonic epithelium but do not invade → secretes cytotoxic Shiga-like toxins (SLT 1 and 2) → inflammation, bleeding → dysentery (hemorrhagic colitis); SLTs and endotoxin may enter bloodstream → spread to and damage kidneys (HUS)
- EIEC: adhere to colonic epithelium → invade mucosal layer and secrete SLT 1 and 2 → fever, inflammation, bleeding → dysentery with leukocytes in stool (similar to shigellosis)

Other infections: UTI: adhere by strain-specific pili to urethra (urethritis) → may ascend to bladder (cystitis) and kidneys (pyelonephritis); Septic shock (endotoxin release); neonatal meningitis; pneumonia

E. coli toxins:

LT (similar to cholera toxin): AB_5 toxin → ADP ribosylates Gs → activates adenylate cyclase → ↑ cAMP → crypt cells secrete more Cl^-, villous cells absorb less Na^+ → osmotic loss of water to lumen → watery diarrhea

ST (similar to *Y. enterocolitica* toxin): activates guanylate cyclase → ↑ cGMP → ↓cotransport of NaCl into cells → water remains in lumen → watery diarrhea

SLT (also called verotoxin): inactivates 60S ribosome unit → blocks protein synthesis → cell death

DIAGNOSIS

Gram − rod; ferments lactose (green metallic sheen on EMB, light purple on MacConkey); serology (O and H antigens)

TREATMENT

rehydration (diarrhea); TMP-SMX, penicillin (UTI); third-generation cephalosporin (meningitis, sepsis)

QUICK FACTS

E. coli is the most common cause of UTI and Gram − sepsis.
EHEC (O157:H7) outbreaks, sometimes with serious complications such as HUS, result from poorly cooked hamburger meat.
HUS: fever, hemolytic anemia, thrombocytopenia, acute renal failure

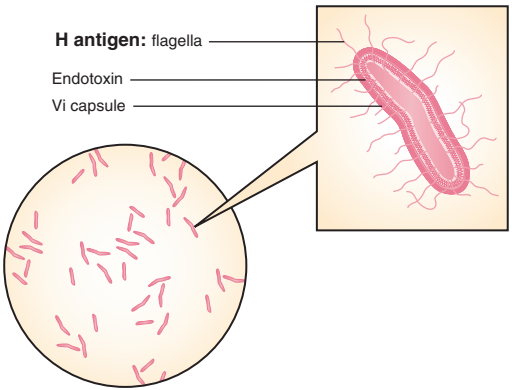
Study Tip

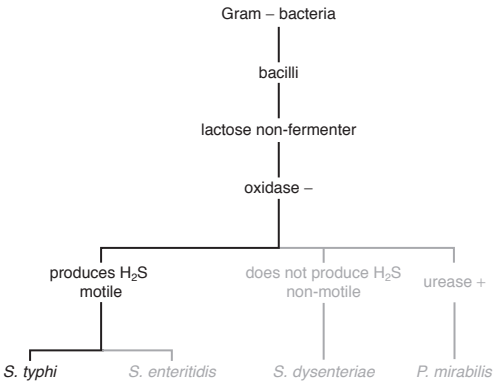
Most common causes of neonatal meningitis:

Group B Strep
E. coli
Listeria

Most common causes of neonatal pneumonia:

Group B Strep
E. coli

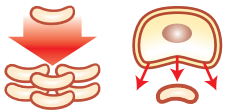




CLINICAL CASE

A woman who recently returned from a trip to South America complains of a persistent high fever, malaise, and constipation that has lasted for over a week. She recalls that the fever began slowly and climbed its way up to the current 41°C. A physical exam reveals that she has an enlarged spleen and a generally tender abdomen with red macules. The physician asks for a stool sample to complete the diagnosis.

Salmonella typhi — Typhoid fever



CLINICAL PRESENTATION

asymptomatic carriers
Typhoid Fever (Enteric Fever)
osteomyelitis in sickle cell patients

PATHOBIOLOGY

survives only in humans → fecal–oral transmission → large inoculum overcomes gastric acid defense → bacteria penetrates mucosal barrier in distal ileum or colon → transient asymptomatic bacteremia
capsular Vi polysaccharide allows survival in phagocytes of Peyer's patches → spread via phagocytes to gallbladder, liver, spleen → releases endotoxin → rose spots on abdomen, fever, diarrhea, and abdominal pain (typhoid fever) → may progress to carrier state or self-resolves
carrier state:
stored in gallbladder, especially in gallstones → may reenter bowel lumen → generates organisms to be spread via feces

DIAGNOSIS

Gram – rod cultured in blood
motile by flagella (vs. nonmotile *Shigella*)
H_2S-producing (vs. *Shigella*)
does not ferment lactose (vs. *E. coli*)

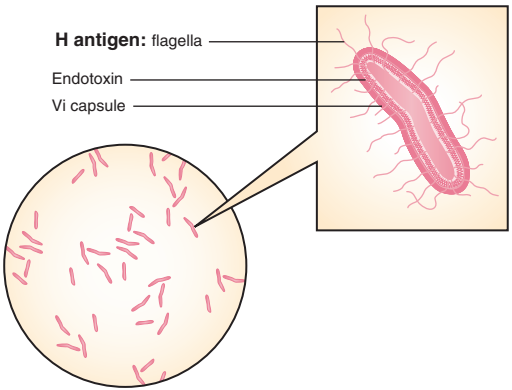
TREATMENT

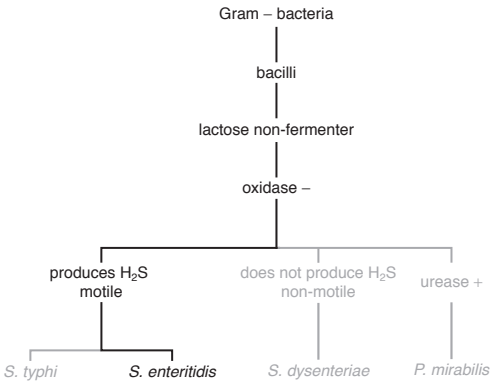
ceftriaxone for resistant strains
ciprofloxacin, ampicillin for carriers
cholecystectomy may be necessary for carriers
two oral vaccines (killed or live-attenuated) available for travelers

QUICK FACTS

Sickle cell patients are functionally asplenic and have trouble clearing Vi-encapsulated *Salmonella*.
Patients with impaired gastric acid secretion (e.g., antacid use or pernicious anemia) are more susceptible.
Because *S. typhi* are stored well by gallstones, carriers may present with *S. typhi*-induced necrotizing cholecystitis.
Treating an *S. typhi* infection increases the chance of relapse, because the host's defense system is not allowed to develop a suitable response.
A carrier is a major health risk—in the early 1900s, Typhoid Mary, a cook, was jailed in Boston after a *Salmonella* outbreak was traced to her kitchen.

Salmonella enteritidis





CLINICAL CASE

A veterinary school student complains to the doctor of diarrhea and abdominal tenderness. He is certain that these symptoms followed nausea and vomiting the day before. He admits that he may have caused himself this misery by excessively playing with his turtle.

Salmonella enteritidis

CLINICAL PRESENTATION

gastroenteritis

PATHOBIOLOGY

carried in animals and humans → fecal–oral transmission → large inoculum overcomes gastric acid defense → penetrates mucosal barrier in distal ileum or colon → inflammation, fever, diarrhea

DIAGNOSIS

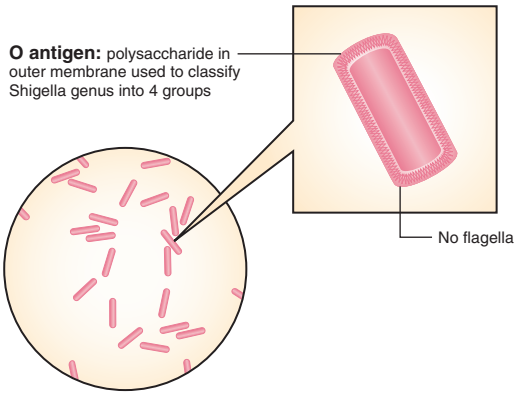
Gram − rod cultured in stool or urine
motile by flagella (vs. nonmotile *Shigella*)
H_2S-producing (vs. *Shigella*)
does not ferment lactose (vs. *E. coli*)

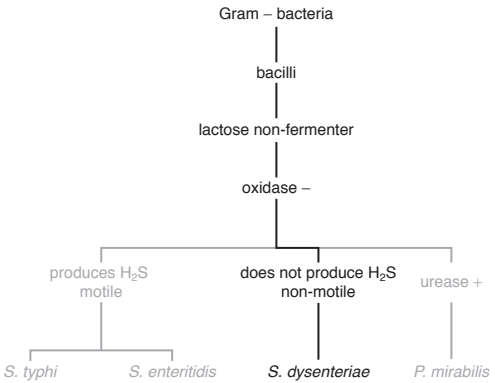
TREATMENT

fluid and electrolytes

QUICK FACTS

Because antibiotic treatment may prolong carrier state, it is reserved for patients with risk of invasive disease or neonates.
Patients with impaired gastric acid secretion (e.g., antacid use or pernicious anemia) are more susceptible.
Turtles or uncooked chicken are common sources of *Salmonella* gastroenteritis.

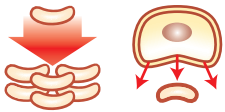




CLINICAL CASE

A photographer for National Geographic returning from Thailand develops a fever and abdominal cramps on the plane. By the time the plane lands, he suffers from bloody diarrhea. His fever peaks at 40°C. The doctor decides to do an endoscopy exam and makes a diagnosis based on the hemorrhagic mucosa and ulcerations observed in the distal colon.

Shigella dysenteriae — Dysentery



CLINICAL PRESENTATION

dysentery (bloody diarrhea)

PATHOBIOLOGY

carried only in humans → fecal–oral transmission → small inoculum (~100 organisms) can overcome gastric acid defense → endocytosed by colonic epithelium → escapes endocytic vesicle → replicates intracellularly and spreads cell-to-cell → causes mucosal ulcers and bleeding → damage to large intestine prevents fluid reabsorption → dysentery

releases Shiga toxin, which inactivates 60S ribosomes → further damages mucosa but not vital for disease

DIAGNOSIS

Gram − rod in stool culture
nonmotile (vs. motile *Salmonella*)
does not produce H_2S (vs. *Salmonella*)
does not ferment lactose (vs. *E. coli*)

TREATMENT

oral rehydration for moderate cases
fluoroquinolones for severe cases

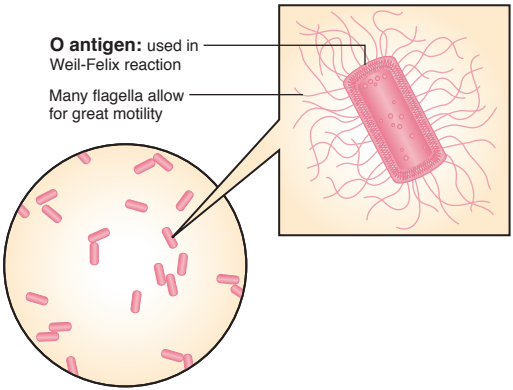
QUICK FACTS

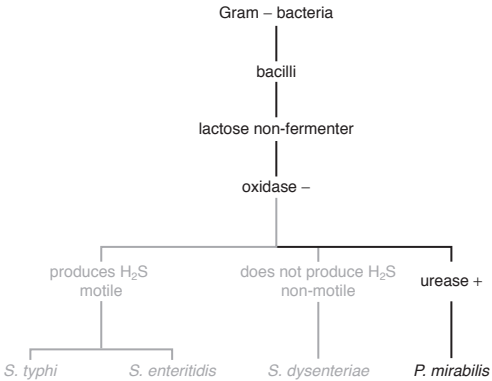
Because of the small inoculum needed, hypochlorhydric patients are not at increased risk.
Shiga toxin, similar to Shiga-like toxins produced by EHEC, can cause HUS.
Other species, in decreasing virulence, include *S. flexneri, S. boydii,* and *S. sonnei*. The decreasing virulence reflects the lack of toxin produced in these strains.

Study Tip

four Fs for transmission: fingers, flies, food, feces

Proteus mirabilis





CLINICAL CASE

A woman returns to the doctor because of an annoying and persistent urinary tract infection. The woman's complaint of dysuria motivates more diagnostic tests, revealing the presence of large radiopaque stones in the urinary tract. The woman also provides several urine samples, which are consistently high in pH.

Proteus mirabilis

CLINICAL PRESENTATION

"struvite" stones
UTI
nosocomial infections

PATHOBIOLOGY

part of normal GI flora, also found in sewage and soil ⟶ microorganism enters human through urinary tract ⟶ urease splits urea to form ammonium hydroxide, which ↑ pH ⟶↑ pH precipitates ammonium magnesium phosphate, leading to struvite calculi formation ⟶ urinary stones may backlog urine and damage kidney or may serve as sites of new/persistent infection (UTI)

bacteria may spread to blood following a surgical procedure ⟶ septic shock

DIAGNOSIS

Gram − rod, "swarming" growth, urease +
alkaline urine

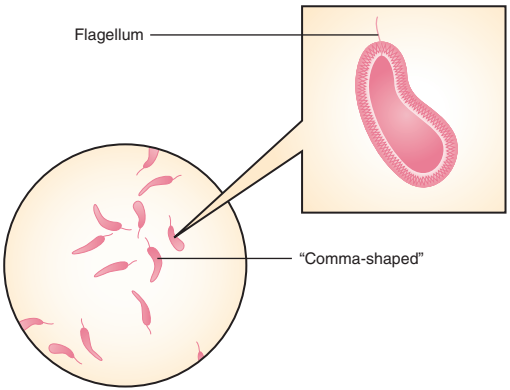
TREATMENT

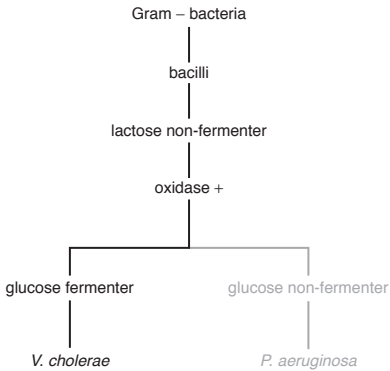
TMP-SMX
ampicillin

QUICK FACTS

The Weil-Felix reaction uses *Proteus vulgaris* antigens to diagnose *Rickettsia*. The *Proteus* antigens cross-react with a patient's serum antibodies against *Rickettsia*.

Providencia, once classified with *Proteus*, is the most common cause of UTI in nursing home patients with indwelling catheters.





CLINICAL CASE

A man visiting India arrives in the emergency room with signs of severe dehydration: He is thirsty, has decreased skin turgor, tachycardia, and somnolence. He abruptly began to suffer from diarrhea this morning and complains about the magnanimous watery volumes he is excreting. He has no fever, and the doctor treats with fluid and electrolytes.

Vibrio cholerae — Cholera

CLINICAL PRESENTATION

"rice-water" diarrhea
dehydration

PATHOBIOLOGY

carried in water, food, and shellfish → large inoculums necessary to overcome gastric acid defense → produces mucinase to digest protective mucous coat around intestinal cells → attaches to proximal small intestine (little competition from other bacteria here)
secretes cholera toxin (AB_5 toxin) → toxin ribosylates Gs, keeping adenylate cyclase active and increasing [cAMP] → crypt cells secrete more Cl^-, villous cells absorb less Na^+ → osmotic loss of water to lumen → watery diarrhea and dehydration → if no care, hypovolemic shock and death

DIAGNOSIS

comma-shaped Gram − rods with single flagella in stool cultures
flat yellow colonies on TCBS agar

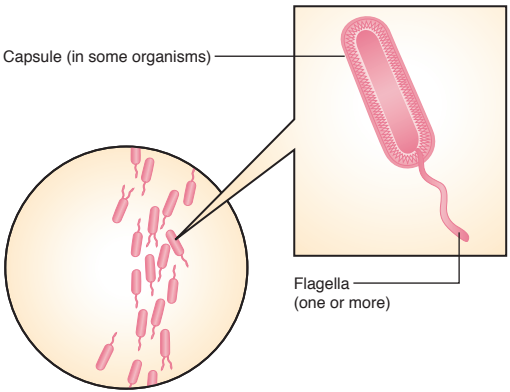
TREATMENT

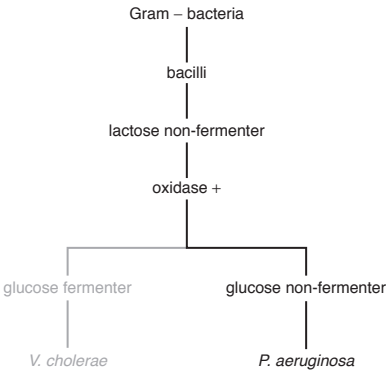
oral/IV rehydration therapy
tetracycline
killed-cell vaccines available (not very effective)

QUICK FACTS

Oral rehydration therapy (glucose + Na) capitalizes on Na-glucose cotransporters in the small intestine.
Cholera toxin is carried on bacteriophage.
Blood group O patients are more vulnerable.
Vibrio parahaemolyticus presents similarly but is associated with raw seafood consumption, most often in Japan.
Differences: grows in 8% NaCl unlike *V. cholera* (remember, it is from the sea); more invasive than *V. cholera* and thus can cause fever.

Pseudomonas aeruginosa





CLINICAL CASE

An elderly diabetic woman, who recently began swimming to control her weight, complains of painful discharge from her left ear. Physical exam shows extreme tenderness of the left tragus. A swab culture of the ear reveals blue-green colonies emitting a fruity odor. Fearing that the infection could eventually spread to the mastoid bone, her doctor prescribes antibiotic therapy.

Pseudomonas aeruginosa

CLINICAL PRESENTATION

pneumonia (CF patients); *UTI* (hospital patients); *burn wound infection, septicemia; endocarditis* (IV drug users); *osteomyelitis* (diabetics, IV drug users); *malignant external otitis* (diabetics); *folliculitis* (hot tub infection); many other infections in hosts with weakened immunity

PATHOBIOLOGY

inhabits many environments: soil, water, large intestine → infection arises by breach of host defense barriers (burns, catheters, endotracheal intubation) or immunocompromise (chemotherapy patients, infants, or elderly, AIDS) → attach to host surfaces by pili → secretes toxins → bacteria may remain local, spread to nearby tissue, or spread systemically in bloodstream → inflammation at sites of infection, contained by neutrophils

toxins important for nutrition and dissemination:

- exotoxin A → ADP ribosylates host EF2 → paralyzes host cell protein machinery (similar to diphtheria toxin)
- phospholipase C → cleaves phosphates from phospholipids → damages host cell membrane → liberated phosphates feed microorganism
- elastase → cleaves elastin, collagen, complement components, and immunoglobulins → allows microorganism to disseminate to better nutrient sources
- endotoxin → shock

DIAGNOSIS

Gram − rods, blue-green colonies (pyocyanin pigment) with fruity odor

TREATMENT

anti-pseudomonal penicillin + aminoglycoside (e.g., piperacillin + gentamicin, mezlocillin + gentamicin)
fluoroquinolones
other antibiotic combinations may be necessary because resistance arises quickly

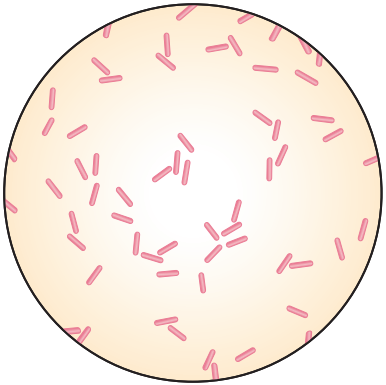
QUICK FACTS

P. aeruginosa is associated with moisture and can be introduced in hospitals through water in respiratory equipment, visitor's flowers, or endoscopes.

P. aeruginosa causes chronic pneumonia in CF patients but does not invade: In the CF setting, the bacteria produce an antiphagocytic capsule instead of invasive toxins.

P. pseudomallei causes melioidosis, a disease endemic to Southeast Asia that affected Vietnam veterans. It is characterized by fever, bloody sputum, and pneumonia, and treatment is ceftazidime.

Yersinia enterocolitica



Gram – bacteria

bacilli

lactose non-fermenter

motile at 25°C,
not at 37°C

Y. enterocolitica

CLINICAL CASE

A man and his two sons just returned from a vacation on their relative's farm. All three arrive complaining of bloody diarrhea. The youngest son becomes well spontaneously. The older son complains of right flank pain, while the father starts to notice tenderness in his joints. One surgeon, worried about appendicitis in the older son, performs the initial incisions and discovers a normal appendix but an inflamed colon. After also observing swollen mesenteric lymph nodes during surgery, he makes a diagnosis explaining the symptoms in all three patients.

Yersinia enterocolitica

CLINICAL PRESENTATION

enterocolitis (bloody diarrhea)
mesenteric adenitis

PATHOBIOLOGY

transmitted in raw milk or fecal–oral route → localizes in terminal ileum → secretes heat-stable enterotoxin (similar to *E. coli* ST toxin) to give diarrhea
invades and causes local inflammation → inflammation spreads to colon → ulcerates colon and produces dysentery-like symptoms
bacteria carried to mesenteric lymph nodes by lymphatics → replicates in nodes → swelling of mesenteric lymph nodes (mesenteric adenitis)
rarely progresses to septicemia

DIAGNOSIS

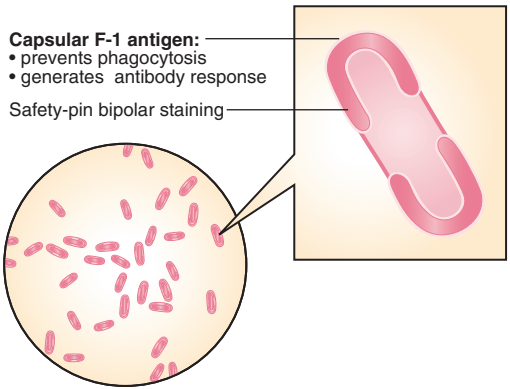
stool cultures: Gram − rod, motile

TREATMENT

self-limiting
gentamicin or chloramphenicol for septicemia

QUICK FACTS

Most common complication is arthritis, associated with HLA-B27.
In contrast to *Campylobacter jejuni* enterocolitis, *Y. enterocolitis* manifests differently in different ages:
<5 yrs: bloody diarrhea
>5 yrs: bloody diarrhea + appendicitis-like pain
adults: bloody diarrhea + arthritis



Gram – bacteria

bacilli

lactose non-fermenter

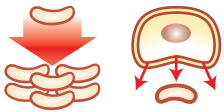
bipolar staining

Y. pestis

CLINICAL CASE

A traveler returning from New Mexico presents to the EW with fever, dark black skin patches, and enlarged, painful lymph nodes in his groin. He maintains an awkward pose with extremities extended, which he says lessens his pain. Doctors begin treatment immediately and inquire about possible flea bites. They then call local authorities in New Mexico and ask about any similar recent cases.

Yersinia pestis — The Plague, Black Death



CLINICAL PRESENTATION

Bubonic Plague

PATHOBIOLOGY

transmitted from rodents to humans by flea vector → phagocytosed → transported to regional lymph nodes → multiplies and stimulates inflammation → regional lymphadenitis (buboes) often in groin

within macrophages capsular F1 antigen prevents phagocytosis → intracellular replication, spread → invades liver, spleen, skin, and lungs → endotoxin causes DIC → cutaneous hemorrhagic necrosis causing black color ("Black Death")

DIAGNOSIS

culture of bubo fluid: Gram − rod, bipolar staining resembling safety pin

TREATMENT

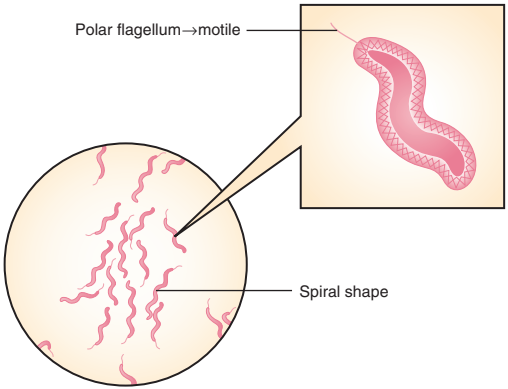
streptomycin, tetracycline

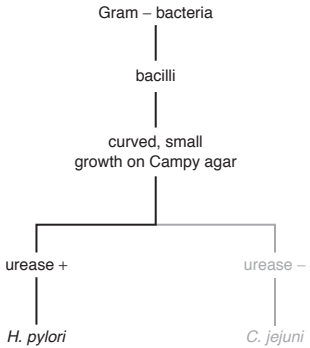
vaccine: killed and attenuated vaccines available, generate antibodies against F1 antigen

QUICK FACTS

With septicemia, *Y. pestis* can seed alveoli and cause pneumonia. This allows aerosol transmission of *Y. pestis* (Pneumonic Plague).

Helicobacter pylori

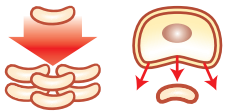




CLINICAL CASE

An aged man comes to the hospital complaining of upper abdominal pains, which become worse after a meal. Knowing the patient's history, the doctor is about to prescribe an H2 blocker and send the patient on his way, just as he has done for many patients before this one. However, biopsy of the stomach mucosa and urease + breath test lead the doctor to prescribe antibiotics in addition to treatment for peptic ulcer.

Helicobacter pylori



CLINICAL PRESENTATION

- acute
  - *gastritis*
- chronic
  - *antral gastritis*
  - *pangastritis*
  - *peptic ulcers (duodenal or gastric ulcers)*

PATHOBIOLOGY

- bacteria ingested → organism colonizes gastric antrum region but does not invade → bacteria produce ammonia (via urease) to protect from gastric acid → host inflammatory response leads to mucosal damage and loss of mucus-secreting cells → acute gastritis
- if gastritis limited to antrum (antral gastritis) → somatostatin secretion by antral D cells decreased → acid hypersecretion → risk of duodenal ulcers
- if gastritis extends throughout stomach (pangastritis) → acid hyposecretion → chronic infection and inflammation → risk of gastric ulcers, gastric carcinoma

DIAGNOSIS

- ^{14}C-labeled urea breath test: labeled urea ingested, and labeled CO_2 exhaled if bacteria urease present
- biopsy showing Gram − rods
- IgG titer in serum

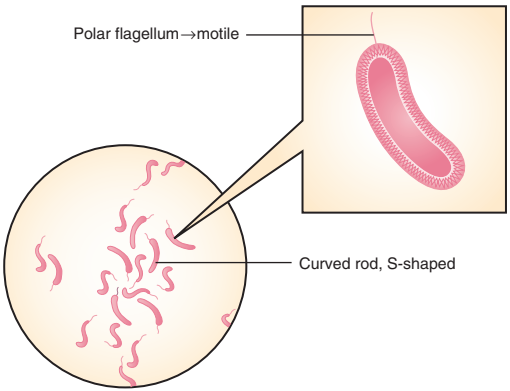
TREATMENT

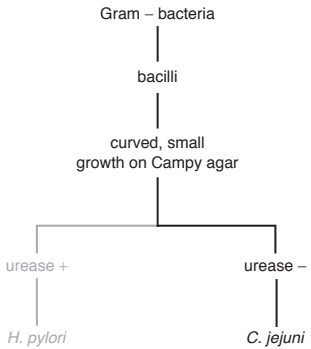
- PPI + amoxicillin + clarithromycin, or PPI + BMT (bismuth therapy, metronidazole, tetracycline)

QUICK FACTS

- 100% duodenal ulcers vs. 70% gastric ulcers associated with *H. pylori* infection.
- Ulcers associated with infection have a "punched-out" appearance and smooth borders, while ulcers associated with malignancies have heaped borders.
- Epidemiologically, *H. pylori* causes antral gastritis in the U.S. and pangastritis in developing countries.
- Chronic *H. pylori* gastritis is associated with gastric adenocarcinoma and MALT lymphoma.

Campylobacter jejuni





CLINICAL CASE

A man with fever, muscle pains, and headache feels no need to go to the doctor until about 1 day later, when he develops diarrhea and abdominal pain as well. The abdominal pain is so severe that his physician fears appendicitis until learning that the man may have had unpasteurized milk in the past week. A definitive diagnosis is made by growth on stool culture at 42°C, microaerophilic conditions.

Campylobacter jejuni

CLINICAL PRESENTATION

bloody diarrhea, secretory diarrhea

PATHOBIOLOGY

carried by poultry, cattle, dogs, and other domestic animals → transmitted by the fecal–oral route or unpasteurized milk
→ colonizes terminal ileum/colon and often invades → may release enterotoxin (cholera-like) and cytotoxin
→ watery, ill-smelling diarrhea preceding bloody stools

DIAGNOSIS

Gram – rod, S-shaped
grow best at 42°C, microaerophilic (grow best at lower oxygen than atmospheric)

TREATMENT

erythromycin, ciprofloxacin

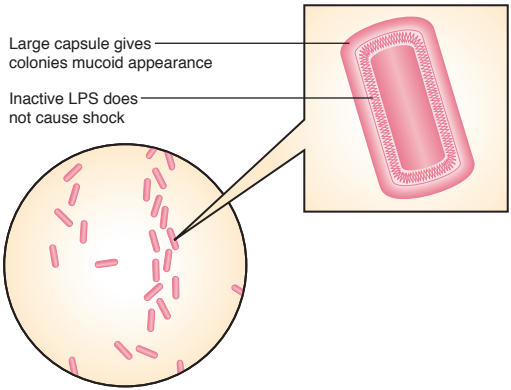
QUICK FACTS

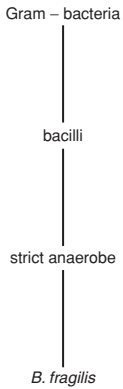
May be confused with Crohn's disease or ulcerative colitis because *Campylobacter* is difficult to detect.
Campylobacter intestinalis causes bacteremia. Unlike *C. jejuni*, it does not grow well at 42°C.
Many cases of Guillain-Barré Syndrome are thought to be complications of *Campylobacter* infections.

Study Tip

Along with rotavirus and ETEC, *C. jejuni* is one of the most common causes of diarrhea in the world.

Bacteroides fragilis





CLINICAL CASE

A patient whose appendix was removed is put on gentamicin to suppress Gram – aerobes causing the initial infection. The patient's fever declines, only to spike some hours later. Imaging of the patient's abdomen detects an abscess that has formed. The area near the abscess is also noted to have a reduced blood supply. The patient is given an additional antibiotic to combat anaerobic bacteria, and, as a result, her abscess rescinds and her fever disappears.

Bacteroides fragilis

CLINICAL PRESENTATION

peritonitis
GI or pelvic abscesses ("below the diaphragm")

PATHOBIOLOGY

normal GI flora → ruptured intestinal mucosa (trauma, surgery, perforation) → spills into peritoneum along with GI facultative anaerobes → survives oxygen environment via catalase and superoxide dismutase
facultative anaerobes eventually deplete all oxygen → organism thrives and becomes numerically dominant → local inflammation, purulent abscess formation → abscess serves as reservoir for organisms, which may spread causing shock (but not DIC because *B. fragilis* lacks typical Gram − endotoxin)

DIAGNOSIS

Gram − rod, strict anaerobe

TREATMENT

drain abscess + repair lesions + antibiotics (e.g., metronidazole, clindamycin)

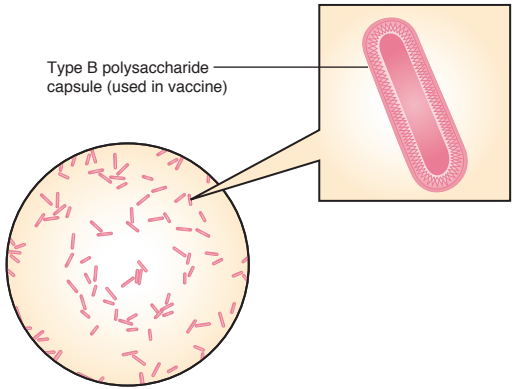
QUICK FACTS

Bacteroides species are the most common among normal GI flora.
Normally makes vitamin K for host.
B. fragilis may also cause pelvic abscesses following septic abortions or use of intrauterine devices.
Prevotella melaninogenica (previously known as *Bacteriodes melaninogenicus*) and *Fusobacterium nucleatum*, both also gram-negative rod anaerobes, are found in the upper airways ("above the diaphragm") and can cause pulmonary abscesses that can be treated with penicillin G.
Lemierre's syndrome is a suppurative thrombophlebitis of the jugular vein caused by gram-negative rod anaerobes of the *Fusobacterium* species. It typically occurs in young patients by progression from pharyngitis or dental infections and can be treated with ampicillin-sulbactam.

Study Tip

Bacteroides: only Gram − without typical endotoxin
Listeria: only Gram + with endotoxin

Haemophilus influenzae type B



Gram – bacteria

coccobacilli, pleomorphic

X & V factors required

H. influenzae

CLINICAL CASE

A 1-year-old infant develops a fever but really begins to alarm her parents when she seems unusually drowsy. The parents bring her to the hospital and the doctor notices neck rigidity and occasional seizures. The doctor identifies an organism in the infant's cerebrospinal fluid that requires both hemin and NAD to grow. The infant recovers after ceftriaxone is administered but seems to have acquired a partial hearing loss.

Haemophilus influenzae type B

CLINICAL PRESENTATION

Local
- *epiglottitis; otitis media; pneumonia*

Systemic
- *meningitis; septic arthritis; cellulitis*

PATHOBIOLOGY

only human carriers → inhaled in aerosol → protected from secretory IgA by IgA protease → colonizes upper respiratory tract → inflammation → epiglottitis, otitis media
avoids phagocytosis with capsule → invades submucosa and spreads by bloodstream → can seed CNS, large joints, or soft tissue (especially facial) → meningitis, septic arthritis, cellulitis

DIAGNOSIS

Gram −, requires hemin (X factor) and NAD (V factor) on chocolate agar
immunofluorescence
+ Quellung test

TREATMENT

third-generation cephalosporin (e.g., ceftriaxone)
Hib vaccine: capsular polysaccharide of type B strain conjugated to diphtheria toxoid
rifampin prophylaxis for close contacts

QUICK FACTS

Encapsulated organisms such as *H. influenzae* type B (Hib) frequently are invasive, whereas non-encapsulated organisms such as "non-typeable" *H. influenzae* colonize locally.

Hib poses a great risk to asplenic patients (e.g., sickle cell patients) because the spleen is the primary organ to eliminate opsonized bacteria.

Hib causes meningitis most commonly in children after maternal Ab protection has declined and before they have developed their own Abs.

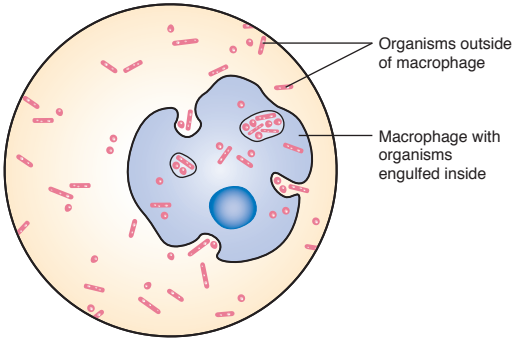
"Non-typeable" *H. influenzae* pneumonia occurs most often in adults with COPD or recent influenza viral infection.

HACEK organisms (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species) are gram-negative bacilli that are part of normal oral flora and can infect heart valves. They are the most common gram-negative cause of endocarditis in non-IV drug users.

Study Tip

Most common causes of meningitis in children 6 mos–6 yrs:
- *S. pneumoniae*
- *N. meningitidis*
- *H. influenzae* type B (↓ incidence with Hib vaccine)

Legionella pneumophila



Gram – bacteria

coccobacilli, pleomorphic

growth on charcoal yeast agar with iron & cysteine

L. pneumophila

CLINICAL CASE

A 67-year-old man with a history of heavy smoking comes to the doctor complaining of "the flu." He has a fever, loss of appetite, headache, chest pain, and a mild cough producing little sputum. The doctor believes that the watery diarrhea that the man also suffers from is related. Sputum sample reveals many neutrophils but no bacteria. CXR reveals nodular infiltrates. Serum tests are negative for cold agglutinins.

Legionella pneumophila

CLINICAL PRESENTATION

Pontiac fever
Legionnaire's disease (atypical pneumonia)

PATHOBIOLOGY

naturally inhabits water reservoirs → inhaled in aerosols from respiratory devices, air conditioners → adheres to respiratory epithelium via pili → phagocytosed by alveolar macrophages → survives and proliferates inside nutrient-rich phagosome → weakens macrophage's respiratory burst and prevents phagosome from fusing to lysosome → infected macrophages secrete neutrophil chemoattractants → may lead to:

- Pontiac fever: acute flulike illness lasting 2–5 days
- Legionnaire's disease: neutrophils arrive and form microabscesses (can be seen on X-ray) → severe atypical pneumonia

DIAGNOSIS

Gram stains poorly, visualize with silver stain
culture on charcoal yeast extract with iron and cysteine
urinary antigen detected by radioimmunoassay
serology

TREATMENT

erythromycin

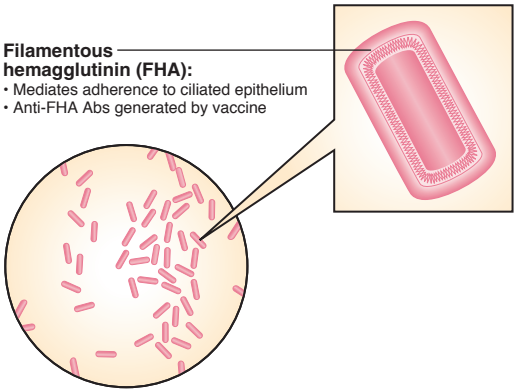
QUICK FACTS

Genus named after famous outbreak of pneumonia in American Legion convention in Philadelphia, 1976.
Legionellae are fastidious, a requirement satisfied by the rich intracellular environment of the macrophage.
Although often misdiagnosed, *Legionella* is an important cause of community-acquired pneumonia in elderly smokers.

Study Tip

Common causes of atypical pneumonia:

Mycoplasma
Legionella
Chlamydia
Viruses



Gram – bacteria

↓

coccobacilli, pleomorphic

↓

growth on Bordet-Gengou medium

↓

B. pertussis

CLINICAL CASE

An infant born in a rural area is brought to the EW with severe bouts of coughing throughout the day. During the visit, the baby appears cyanotic and suffers an attack of many coughs on a single expiration followed by a deep inspiration. The coughs produce copious greenish phlegm. Further history reveals that the infant has not been vaccinated. The physician fears that erythromycin therapy will not be helpful at this stage of the illness.

Bordetella pertussis — Whooping cough

CLINICAL PRESENTATION

whooping cough

PATHOBIOLOGY

only human carriers → airborne transmission → adheres to cilia of respiratory epithelium via filamentous hemagglutinin (FHA) → release exotoxins to generate disease:

- pertussis toxin → AB toxin → ADP-ribosylates and inactivates Gi proteins → uninhibited adenylate cyclase →↑ cAMP →lymphocytosis, ↓ phagocytosis
- secreted adenylate cyclase → taken up by phagocytes →↑ cAMP → inhibits bactericidal activity
- tracheal cytotoxin → kills ciliated epithelial cells → impairs mucous clearance

violent whooping cough develops (mechanism unknown) → promotes spread of bacteria

three stages:

catarrhal stage (1–2 weeks): flulike symptoms, highly contagious

paroxysmal stage (3rd week–2 months): intermittent bouts of many coughs on a single expiration followed by whooping inspiration

recovery stage (2–3 months): coughing subsides

DIAGNOSIS

Gram −, coccobacilli

Bordet-Gengou medium

TREATMENT

prophylaxis: DTaP vaccine: acellular Pertussis antigens

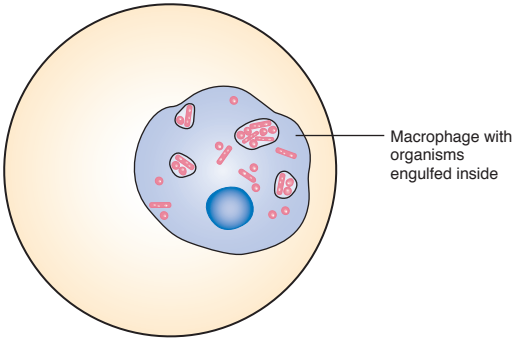
treatment: erythromycin (only before paroxysmal phase), supportive care

QUICK FACTS

DTaP vaccines are administered at 2, 4, 6, and 18 months, again before starting school, and every 10 years thereafter.

Because anti-FHA antibody production declines 15 years after vaccination, most mothers cannot transfer protective antibodies to their infants. Hence, infants are most susceptible.

Can be life threatening for children with cardiac or pulmonary problems, and neurological sequelae (from hypoxia) usually follow.



Gram – bacteria

coccobacilli,
pleomorphic

aerobic

Brucella

CLINICAL CASE

A doctor is struggling to diagnose a woman's flulike illness. She complains of a fever that rises during the day and peaks after dinner, fatigue, spinal tenderness, and loss of appetite. Her lymph nodes are enlarged in physical exam. The doctor has trouble narrowing down the possible etiologies until he hears that the woman tasted goat cheese at a local French village a month before the onset of her symptoms.

CLINICAL PRESENTATION

undulating fever

PATHOBIOLOGY

enter human body by ingestion of contaminated animal products (e.g., goat cheese) or direct skin contact → phagocytosed → localize to reticuloendothelial system → caseating granulomas and abscess formation

undulant fever: some patients experience rising fever that climbs during the day and declines at night, lasting for months

DIAGNOSIS

bone marrow or blood culture: Gram −, coccobacilli, facultative intracellular

+ brucellergin skin test (DTH response) indicates current or previous exposure

TREATMENT

doxycycline + gentamicin

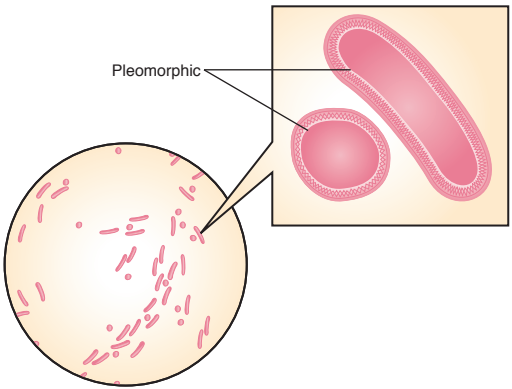
prevention: pasteurize milk

QUICK FACTS

Osteomyelitis is the most common complication.

Brucellosis in the U.S. most commonly occurs from ingestion of imported goat cheese that is poorly pasteurized.

B. melitensis is found in goats and sheep, *B. abortus* in cattle, *B. suis* in hogs, and *B. canis* in dogs. Infection often causes abortions in animals.



Gram – bacteria

coccobacilli,
pleomorphic

requires cysteine for growth

F. tularensis

CLINICAL CASE

A woman from Arkansas presents to the doctor with a small but persistent black ulcer on her arm. The area near the ulcer is erythematous and tender. Her axillary lymph nodes on the same side are enlarged. She believes the ulcer may be related to a tick bite that occurred on her arm while tending to her rabbit farm.

Francisella tularensis — Tularemia

CLINICAL PRESENTATION

tularemias (site-specific infection + lymphadenopathy):
- *ulceroglandular tularemia*
- *oculoglandular tularemia*
- *pulmonary tularemia*
- *typhoidal tularemia*

PATHOBIOLOGY

carried primarily in rabbits → incidental transmission to human by ticks, lice, or mites, or contact with infected animal at skin → bacteria multiply locally → papule forms → develops into ulcer with black base (ulceroglandular tularemia)

bacteria phagocytosed → localize to reticuloendothelial system → caseating granulomas → regional lymphadenopathy, long-lasting fever

less common sites of infection:
- conjunctiva (oculoglandular tularemia)
- inhalation (pulmonary tularemia)
- GI (typhoidal tularemia)

DIAGNOSIS

skin test (DTH response)
serology
cultures rarely performed because organism highly infectious

TREATMENT

streptomycin
live-attenuated vaccine for high-risk individuals

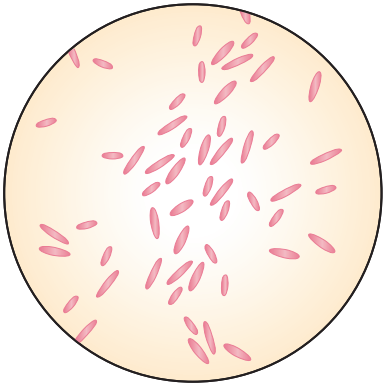
QUICK FACTS

Most cases occur in Arkansas, Oklahoma, and Missouri.

Study Tip

F. tularensis and BCG (for TB) vaccines are only live-attenuated vaccines for bacteria.

Pasteurella multocida



Gram – bacteria

coccobacilli
pleomorphic

oxidase +, catalase +

P. multocida

CLINICAL CASE

A young girl, bitten by a cat earlier in the day, develops redness, heat, induration, and tenderness at the site of the bite. Her physician also notes local lymphadenopathy. Culture of wound site shows Gram – coccobacilli with bipolar staining. The doctor cleans the wound and makes sure not to suture it.

Pasteurella multocida

CLINICAL PRESENTATION

cellulitis, osteomyelitis following cat/dog bites

PATHOBIOLOGY

normally inhabits oral cavity of animals → enters human skin via bite → at inoculation site, elicits inflammatory response → spreads locally to soft tissue (cellulitis) and bone (osteomyelitis) → may progress to septicemia

DIAGNOSIS

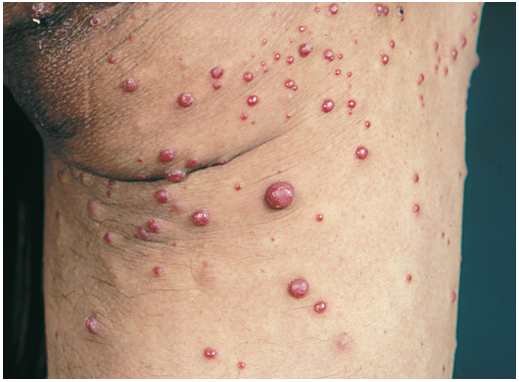
Gram − coccobacilli, bipolar staining

TREATMENT

penicillin G
clean and drain wound

QUICK FACTS

Suturing wound may worsen infection by creating a closed anaerobic environment.
A cat's sharp teeth can directly implant bacteria into bone and cause osteomyelitis.



Bacillary angiomatosis

Gram –

coccobacilli,
pleomorphic

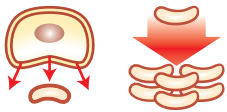
silver impregnation stains

B. henselae

CLINICAL CASE

A 54-year-old homeless HIV+ man is evaluated in a shelter clinic. He is found to have the rash shown above. He resides in an alley with his two cats but decided to seek medical attention after developing fevers. Biopsies of the skin lesions are taken, and pathology shows granulomatous inflammation with clusters of bacilli.

Bartonella henselae — Cat Scratch Disease



CLINICAL PRESENTATION

regional lymphadenopathy
fever of unknown origin
ocular involvement
hepatosplenomegaly
bacillary angiomatosis
organ-specific symptoms (see below)

PATHOBIOLOGY

cats serve as natural reservoir → inoculate human via cat scratch, bite, or saliva → primary cutaneous lesion → local infection causes regional lymphadenopathy
disseminated infection (especially in HIV patients, immunocompromised) results in symptoms depending on organs involved:
ocular: Parinaud's oculoglandular syndrome, granulomatous conjunctivitis, periauricular lymphadenopathy, optic neuritis
skin: bacillary angiomatosis
CNS: encephalitis, transverse myelitis, cerebellar ataxia
musculoskeletal: myalgias, arthralgias, arthritis, osteomyelitis
liver/spleen: necrotizing granulomas causing hepatosplenomegaly, peliosis hepatis (blood-filled cavities throughout liver)

DIAGNOSIS

serology
blood cultures
PCR
biopsy showing granulomatous inflammation

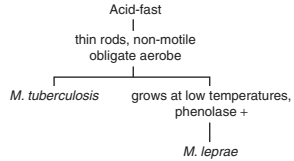
TREATMENT

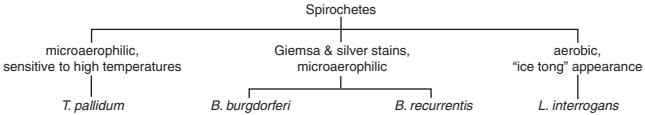
azithromycin or doxycycline

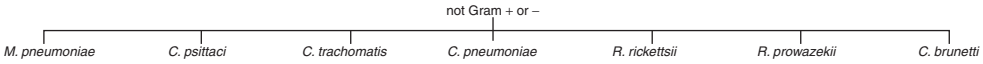
QUICK FACTS

Cat fleas have been implicated in transmission between cats, and flea feces has been implicated in transmission to humans.
The related *Bartonella quintana*, historically the cause of "trench fever," is now typically associated with bacillary angiomatosis, endocarditis, and fevers. It is transmitted by lice and typically occurs in homeless patients.

Other Bacteria: Acid-Fast Bacteria, Spirochetes, and Not Gram + or Gram − Bacteria







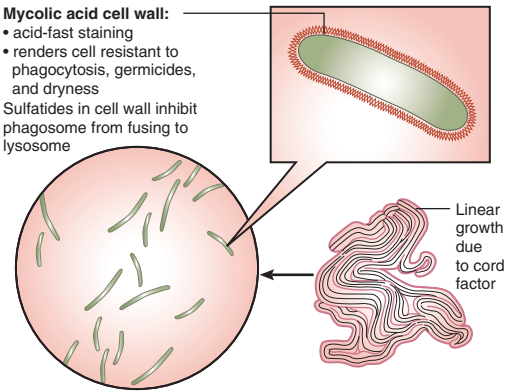
Important Features of Other Bacteria: Acid-Fast Bacteria, Spirochetes, and Not Gram + or Gram − Bacteria

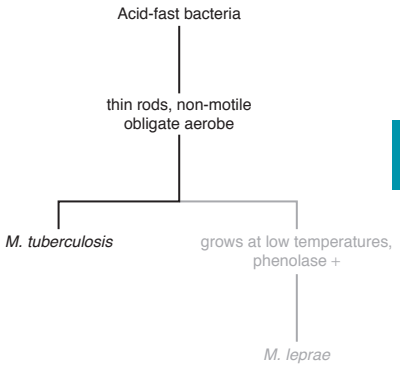
Acid-Fast Bacteria
- similar to Gram +
- differ in that cell wall has high amounts of mycolic acid (a lipid)
- mycolic acid makes cell wall hydrophobic, which Gram stains poorly
- however, once stained, retains stain ("acid-fast" because it does not decolorize with acid-alcohol wash)

Spirochetes
- similar to Gram − bacteria, but too thin to visualize by light microscopy (hence require dark-field microscopy)
- flexible, thin cell wall allows corkscrew-shape
- periplasmic flagella (between outer membrane and cell wall) allow corkscrew motility

***Mycoplasma* Species**
- smallest living organisms
- amorphous/pleomorphic because they have no cell wall

***Chlamydia* and *Rickettsia* Species**
- obligate intracellular bacteria
- *C. brunetti* is also a *Rickettsia* bacteria





CLINICAL CASE

A homeless man enters the hospital with wasting and fever. He has had a chronic cough for several months producing bloody sputum as well as night sweats. CXR reveals cavitations with air-fluid levels in the apex of his left lung. Diagnosis is confirmed by an acid-fast stain of sputum.

Mycobacterium tuberculosis — "Consumption"

CLINICAL PRESENTATION

tuberculosis

PATHOBIOLOGY

overview: 1° TB may progress to 2° TB, most often by reactivation of a dormant phase.

1° TB: transmitted in aerosol droplets → deposits in lower lobes of lung → ingested by macrophages → mycolic acid cell wall allows intracellular survival and proliferation

T cells, uninfected macrophages wall off and destroy infected macrophages → form caseous granulomas → leave fibrotic, calcified scars (tubercles) with few dormant organisms → can detect Ghon complex (calcified pulmonary tubercles + hilar lymph nodes) → may spread to other sites by lymphatics and blood, forming extrapulmonary tubercles

T-cell immunity manifests as PPD+

2° TB: weakened T-cell response → reactivation of pulmonary tubercles in apex (high oxygen favors aerobic growth) → macrophages respond, form large caseous granulomas → creates cavitations in lungs with air-fluid levels on CXR → may disseminate to other sites through lymphatics and blood (miliary TB)

other sites affected (by reactivation of extrapulmonary tubercles or dissemination from lung): CNS, vertebral bodies (Pott's disease), kidneys, GI, pericarditis, lymph nodes (scrofula)

DIAGNOSIS

acid-fast stain of sputum, PCR

purified protein derivative (PPD) test: + DTH reaction in active or previous infection

Ghon complex on CXR

measure IFN-gamma released by lymphocytes exposed to *M. tuberculosis* antigens (e. g., Quantiferon Gold assay)

TREATMENT

treat with RIPES (multiple drugs to avoid resistance): rifampin, isoniazid (INH), pyrazinamide, ethambutol, streptomycin prophylaxis (for PPD+): INH

BCG (Bacille Calmette-Guerin) vaccine: live attenuated vaccine for cell-mediated immunity, renders patient PPD+

QUICK FACTS

Mycobacterium avium complex (MAC) is comprised of two species that are difficult to distinguish, *M. avium* and *M. intracellulare*, collectively called *Mycobacterium avium-intracellulare* (MAI). MAI infections are clinically indistinguishable from pulmonary and systemic tuberculosis infections. They are a major opportunistic pathogen in AIDS patients with low CD4 counts and are resistant to multiple drugs. Treatment is with a macrolide (azithromycin or clarithromycin) + ethambutol + rifamycin (rifampin or rifabutin).

M. bovis is found in unpasteurized milk and can lead to GI tuberculosis. Alternatively, it can lead to pulmonary tuberculosis if inhaled.

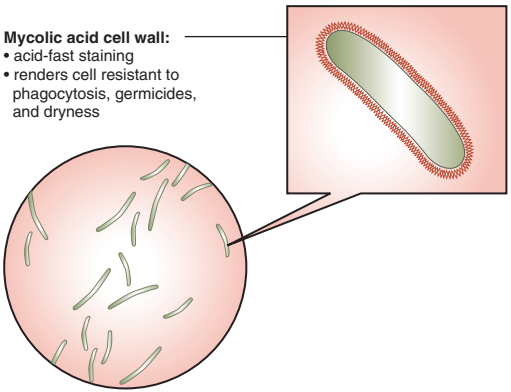
+ PPD test: >10 mm induration (or >5 mm induration if immunocompromised, in AIDS often false-negative).

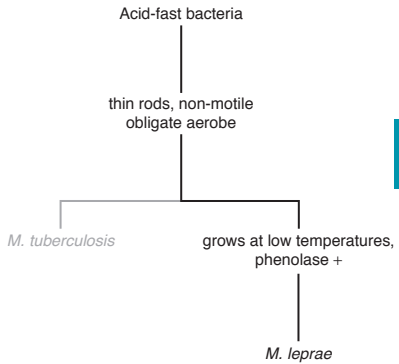
Study Tip

Mycobacteria and *Nocardia* are the two clinically important bacteria that have acid-fast positive staining.

BCG and *F. tularensis* vaccines are the only live-attenuated vaccines for bacteria.

Mycolic acid cell wall:
- acid-fast staining
- renders cell resistant to phagocytosis, germicides, and dryness





CLINICAL CASE

A Mexican immigrant presents with thickened cheeks and a deformed nose. Physical exam shows sensory losses in hands and legs as well as testicular atrophy. Posterior tibial and ulnar nerves are palpable. Soon after treatment begins, the patient develops nodular rashes and apparent worsening of symptoms. However, his doctor continues the same treatment regimen with the addition of thalidomide.

Mycobacterium leprae — Leprosy, Hansen's Disease

CLINICAL PRESENTATION

tuberculoid leprosy
lepromatous leprosy

PATHOBIOLOGY

bacteria transmitted from nasal discharge → grows in low temperature areas such as skin and appendages → infects cells of nerve sheaths → course depends on host immune response:

- tuberculoid leprosy (strong immune response): granuloma formation limits spread of microorganism → localized damage to superficial nerves and skin → results in thickened nerves (palpable) and one or two anesthetized lesions that are hypopigmented and hairless
- lepromatous leprosy (weak immune response): host defenses unable to contain microorganism → inflammatory damage, especially at cooler skin, nerves, testes → causes sensory loss at face, extremities → anesthetized host vulnerable to secondary insults → loss of eyebrows, saddle-nose deformity (thick nose), leonine facies (thick cheeks), infertility

DIAGNOSIS

skin/nerve biopsy: granulomas (tuberculoid) or acid-fast bacteria (lepromatous)
cultures only in mouse footpad, armadillo (no *in vitro* growth)
lepromin skin test to determine leprosy prognosis:
+ in tuberculoid
− in lepromatous (deficient DTH response)

TREATMENT

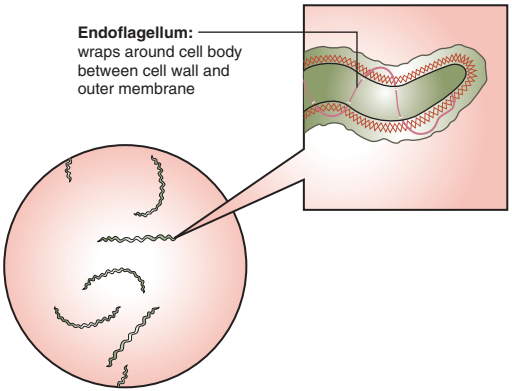
used in combination to prevent resistance: dapsone, rifampin, clofazimine

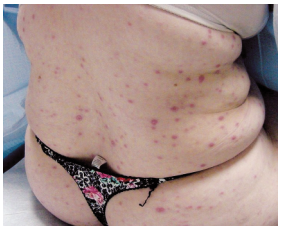
QUICK FACTS

Treatment of leprosy can cause reaction to killed bacteria:
Type 1: DTH response → intensified tuberculoid-like symptoms, treat with prednisone
Type 2: immune complex deposition → Erythema Nodosum Leprosum, treat with thalidomide (only approved use in the U.S.)
Anti-leprosy drugs should not be discontinued despite reactions.

Study Tip

Mycobacteria and *Nocardia* are the two clinically important bacteria that have acid-fast positive staining.





Secondary syphilis

Spirochetes

microaerophilic,
sensitive to high temperatures

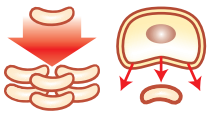
T. pallidum

CLINICAL CASE

A sexually active man seeks medical attention for a wart-like lesion developing on his genitals. He recalls a painless ulcer on his genitals over a month ago, but now is concerned because papules are appearing in his armpits and palms as well. Recently, he has also suffered fever and chills, and the doctor notices a nontender, generalized lymphadenopathy. The doctor questions the man about the health of his sexual partners. A dark-field analysis confirms the doctor's suspicion of the etiology and the patient is prescribed penicillin G.

Treponema pallidum — Syphilis

CLINICAL PRESENTATION



1° syphilis: painless chancre
2° syphilis: condyloma lata; maculopapular rash on palms and soles; meningitis, hepatitis, arthritis, and others
3° syphilis: gummas (granulomas of soft tissue, bone)
- CV: *aortitis, ascending aortic aneurysm*
- CNS: *tabes dorsalis, general paralysis, meningitis, Argyll Robertson pupil* (accommodates to near objects but does not react to light)

congenital syphilis: CN VIII deafness, mulberry molars, saber shins, saddle nose, Hutchinson's incisors

PATHOBIOLOGY

human is only host → transmitted from skin lesions containing spirochete (sexual or casual contact) → spirochete penetrates mucous membranes → systemic spread within hours of inoculation →

- 1° syphilis (visible 6 weeks after exposure): organism multiplies at inoculation site → painless chancre (ulcerated lesion shedding spirochetes) → lesion heals spontaneously over 6 weeks
- 2° syphilis (visible 6 weeks after chancre heals): disseminated spirochetes proliferate → form lesions throughout body including condyloma lata (wart-like painless lesions in moist areas, e.g., genitals) → lesions may heal spontaneously or may become latent syphilis (no symptoms but serologically +) → cycle of 2° syphilis can repeat multiple times
- 3° syphilis (many years later): chronic inflammation against remaining spirochetes → damage to soft tissue and bone (gummas), CV system (aortitis), CNS

transplacental transmission → congenital syphilis: stillbirth, fetal abnormalities

DIAGNOSIS

dark-field microscopy (spirochetes not visible on Gram stain) serological tests:
- VDRL (nonspecific): detects reagin antibodies against cardiolipin
- FTA-ABS (specific): detects anti-treponemal antibodies

TREATMENT

penicillin G

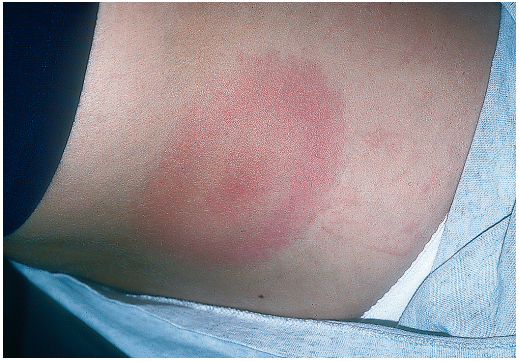
QUICK FACTS

Treatment may lead to Jarisch-Herxheimer reaction: lysis of treponeme → release of endotoxin-like factors → fever, chills, myalgias.
SLE and infectious mononucleosis patients can have false-positive VDRL tests due to anti-cardiolipin antibodies. Clarify with more specific FTA-ABS test.
Syphilis meningitis presents with ↑ lymphs, normal PMNs in CSF.
Treponema pallidum subspecies cause nonvenereal skin ulcers and skin/bone gummas: *T. pallidum endemicum* → endemic syphilis (common in Africa, Middle East); *T. pallidum pertenue* → Yaws (gummas disfigure face); *T. pallidum carateum* → Pinta (red → blue → white lesions, limited to Latin America).

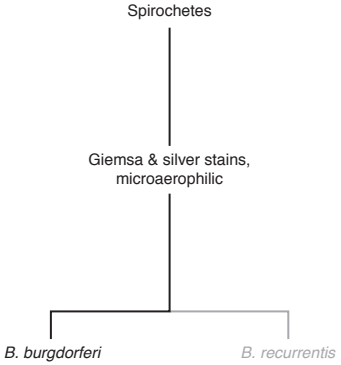
Study Tip

Palm & sole rash:
- Syphilis
- Rocky Mountain spotted fever
- coxsackievirus

Organisms that cross placenta and therefore allow infection to pass from pregnant mother to fetus (TORCHES):
- TOxoplasma gondii
- Rubella
- Cytomegalovirus
- HErpes, HIV
- Syphilis



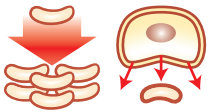
Erythema migrans in Lyme disease



CLINICAL CASE

A woman seeks medical attention for a skin rash expanding on her arm over several days. Her doctor notes an annular, red rash with a clear area in the center. The woman also complains of a fever, headache, arthralgias, and stiffness of the neck following the onset of the rash by a week. When asked if bitten by any insects, the woman cannot answer definitively, but she does remember seeing a tick on her sleeping bag during a camping trip to Connecticut last month. The doctor prescribes doxycycline and checks the woman's electrocardiogram to ensure no heart problems have developed as a result of her illness.

Borrelia burgdorferi — Lyme Disease



CLINICAL PRESENTATION

stage 1
- *erythema chronicum migrans*

stage 2
- CNS: *Bell's palsy, aseptic meningitis, peripheral neuropathy*
- CV: *carditis, AV nodal block*
- Skin: *secondary annular lesions*
- Joints: *migratory myalgias, transient arthritis*

stage 3
- *chronic arthritis; encephalopathy; acrodermatitis chronicum atrophicans*

PATHOBIOLOGY

carried in small mammals such as mice → *Ixodes* tick transmits from mice to humans → spirochetes disseminate systemically →
- stage 1 (10 days after bite): at inoculation site, bacteria multiply and migrate outward → generate a spreading annular red lesion surrounding clear bite mark (erythema chronicum migrans), flu-like symptoms
- stage 2 (weeks later): disseminated spirochetes proliferate → inflammatory response damages: CNS, heart, skin, joints
- stage 3 (months–years later): persistent infection → inflammatory damage in joints, brain, and local areas of skin atrophy (acrodermatitis chronicum atrophicans)

DIAGNOSIS

skin biopsy: spirochete, motile under dark-field microscopy
serology

TREATMENT

doxycycline or amoxicillin for stage 1
ceftriaxone for later stages

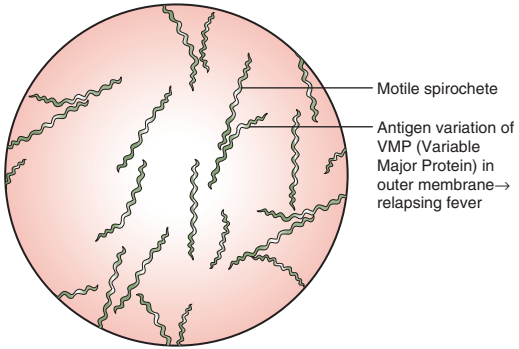
QUICK FACTS

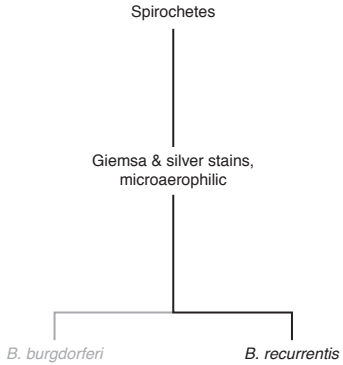
Early detection of tick can prevent disease because tick feeding requires 24 hours to transmit sufficient inoculum.
Lyme disease is the most common vector-borne disease.

Study Tip

Most common diseases in the U.S. spread by vectors:
- Lyme disease
- Rocky Mountain spotted fever
- Tularemia

Borrelia recurrentis





CLINICAL CASE

A man comes to the doctor with a fever of 40°C. He assures the doctor that he would not ordinarily seek medical attention simply for a fever, but that he has had two previous episodes of fever over the past 3 weeks. In these episodes, he suffers from a high fever, rash, myalgias, and nausea. The fever worsens over 2 days and abruptly spikes on the third day, but then just as abruptly drops to normal temperature with a drenching sweat. On history, the patient reports no recent mosquito bites. After noting spirochetes on blood culture, the doctor prescribes penicillin and assures the patient he will be fine.

Borrelia recurrentis

CLINICAL PRESENTATION

relapsing fever

PATHOBIOLOGY

human is only host ⟶ human-to-human transmission by human body louse ⟶ enter bloodstream and multiply ⟶ trigger host inflammatory response and fever ⟶ most bacteria killed

antigenic variation of outer membrane proteins by rearrangement and expression of silent genes ⟶ new antigenic type multiplies ⟶ stimulates new immune response ⟶ relapse of fever

recurring cycles of 5 days febrile / 8 days afebrile continues up to 10 times

DIAGNOSIS

blood sample/culture during fevers: spirochete, motile under dark-field microscopy

Wright and Giemsa stains

serology

TREATMENT

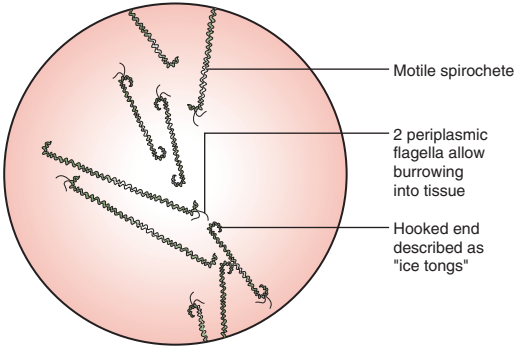
penicillin, tetracycline

QUICK FACTS

Borrelia recurrentis, *Borrelia hermsii*, and other *Borrelia* all cause relapsing fever. *B. recurrentis* is the only one spread by lice; others are spread by ticks.

Treatment may lead to Jarisch-Herxheimer reaction: lysis of treponeme ⟶ release of endotoxin-like factors ⟶ fever, chills, myalgias.

Leptospira interrogans



Spirochetes

aerobic,
"ice tong" appearance

L. interrogans

CLINICAL CASE

A farmer comes to the EW with a 1-week history of flu-like symptoms with photophobia. His severe headache, cough, and myalgias suggest to the physician some kind of respiratory infection. However, more careful physical exam reveals conjunctival suffusion and macular rash. Lab findings include elevated serum bilirubin, alkaline phosphatase, aminotransferases, and creatine phosphokinase. With this clinical picture and lab results, the physician prescribes penicillin G immediately. His suspicions are confirmed later when a spirochete is isolated from the patient's blood.

Leptospira interrogans

CLINICAL PRESENTATION

Leptospirosis
Weil's syndrome (icterohemorrhagic fever)

PATHOBIOLOGY

carried in rodents, dogs, fish, birds → shed in animal urine → transmitted to humans via contaminated water or soil → leptospires enter mucosal abrasions → systemic spread →

1st phase (leptospiremic phase): host immune response → flu-like symptoms, photophobia → resolves within a week as organisms cleared

2nd phase (immune phase): immune response and rise in anti-leptospira IgM associated with mild or severe damage:

- *anicteric leptospirosis* (mild) → aseptic meningitis
- *Weil's disease* (severe) → vasculitis with hemorrhagic complications, kidney damage with renal failure, liver damage with jaundice

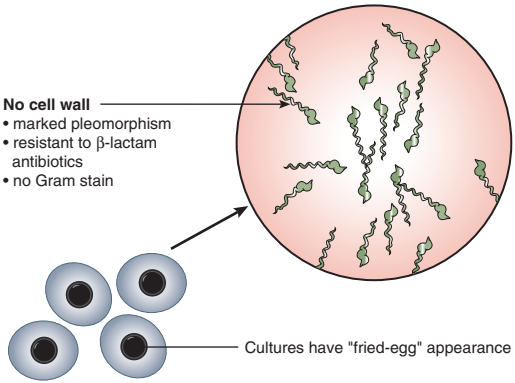
DIAGNOSIS

spirochete detectable in blood, CSF (1st phase) and urine (2nd phase)
serology

TREATMENT

penicillin G
prophylaxis: doxycycline

Mycoplasma pneumoniae



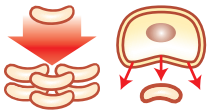
CLINICAL CASE

A young woman at an army base thinks she has a cold and goes to her doctor. She complains of malaise, chills, sore throat, and dry cough. CXR shows interstitial infiltrate more severe than suggested by her symptoms. Laboratory tests indicate that the woman's serum was capable of agglutinating erythrocytes when incubated at 4°C. The doctor prescribes erythromycin.

Mycoplasma pneumoniae

CLINICAL PRESENTATION

tracheobronchitis
"atypical" pneumonia (walking pneumonia)



PATHOBIOLOGY

only human pathogen → transmitted via respiratory droplets → inhaled organism adheres to respiratory epithelium (no invasion) → inhibits ciliary motion, destroys mucosa → inflammation → tracheobronchitis, atypical pneumonia

B-cell response generates antibodies that may autoreact with erythrocytes (IgM cold agglutinins), brain, heart → anemia and systemic manifestations (e.g., arthritis)

DIAGNOSIS

cold hemagglutination
no cell wall, fried-egg appearance (2–3 wk culture on Eaton's agar)
serology

TREATMENT

erythromycin or tetracycline

QUICK FACTS

Mycoplasma pneumoniae most commonly affects young people, especially those in close quarters (prisons, military bases).
CXR often looks worse than symptoms suggest.
Mycoplasma hominis and *Ureaplasma urealyticum*, other mycoplasmas, cause genital infections. *U. urealyticum* is identified by production of urease.
Mycoplasmas are the smallest free-living organisms and are the only bacteria to (1) have no cell wall and (2) have cholesterol in their membranes.

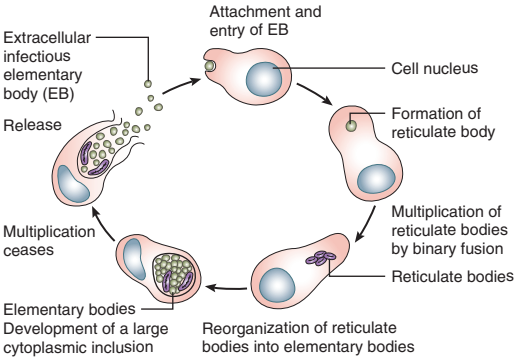
Study Tip

Common causes of atypical pneumonia:

Mycoplasma
Legionella
Chlamydia
Viruses

Most common causes of pneumonia in adults (18–40 yrs):

Mycoplasma
C. pneumoniae
S. pneumoniae



CLINICAL CASE

A bird shop owner visits his doctor complaining of a headache, fever, and dry cough that has worsened over the last few days. The patient also complains of a sore throat and muscle aches. A physical exam reveals bilateral rales and mild splenomegaly. The doctor orders a CXR that reveals a patchy pneumonitis. Diagnosis is confirmed with serological tests. The patient is administered tetracycline, and the fever diminishes within 2 days.

Chlamydia psittaci — *Psittacosis, Ornithosis, Parrot Fever*

CLINICAL PRESENTATION

psittacosis (atypical pneumonia)

PATHOBIOLOGY

carried by birds (e.g., parrots) → microorganism sheds from bird feces and spreads by aerosol → microorganism enters upper respiratory tract epithelium → invades, spreads via blood to alveoli → phagocytosed by macrophages → lymphocyte infiltration → local edema, necrosis, and hemorrhage in alveoli

Chlamydia life cycle has two forms:
- extracellular elementary body (EB)
- intracellular reticular body (RB)

EB is infective form → EB phagocytosed → intracellularly, EB transforms into RB (special cell wall blocks phagosome–lysosome fusion) → RB multiplies within intracellular inclusion body → RB condenses into EB → inclusion body bursts releasing infective EB

DIAGNOSIS

visualize intracytoplasmic inclusions: iodine stain −, Giemsa stain +
serology

TREATMENT

antibiotics that can enter cells: doxycycline

QUICK FACTS

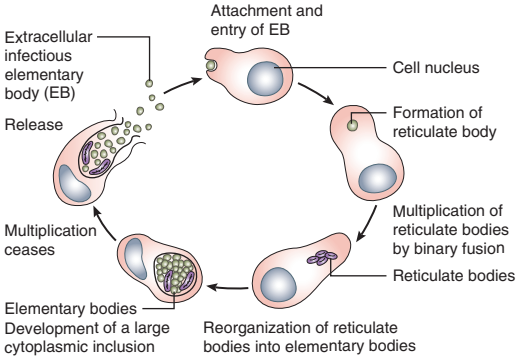
Pet shop owners and veterinarians working with birds are at high risk.

Study Tip

Two obligate intracellular parasites (require host ATP for energy):
- Chlamydiae
- Rickettsiae

Chlamydiae replicate within inclusion bodies, Rickettsiae replicate freely in cytoplasm.

Chlamydia trachomatis

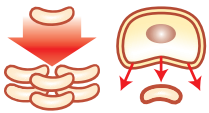


CLINICAL CASE

A woman is brought to the EW complaining of vaginal discharge and RUQ abdominal pain. On history, the patient reports having many sexual partners. Pelvic exam reveals cervical motion tenderness, and labs of vaginal discharge detect numerous PMNs but no organisms on Gram stain. The doctor makes a diagnosis based on these findings and administers doxycycline and ceftriaxone. Later, surgeons, concerned about the patient's abdominal pain, rule out cholecystitis by imaging, but laparoscopy reveals adhesions around the patient's liver capsule.

Chlamydia trachomatis

CLINICAL PRESENTATION



serovars D–K: urethritis, PID; neonatal pneumonia, neonatal conjunctivitis
serovars A–C: trachoma (chronic conjunctivitis)
serovars L1–L3: lymphogranuloma venereum (LGV)
complications: *Fitz-Hugh-Curtis syndrome;* Reiter's syndrome

PATHOBIOLOGY

different serovars have different manifestations:
serovars D–K: infects columnar epithelium → generates inflammation → damages GU tract →
- in females: can spread to fallopian tubes and cause PID → increased risk for ectopic pregnancy → bacteria may spill into peritoneal cavity (peritonitis) → may infect liver capsule (Fitz-Hugh-Curtis syndrome)
- in males: can spread to synovial joints and other organs → arthritis, conjunctivitis → Reiter's syndrome (especially in HLA-B27 patients)

neonatal infection occurs as child passes through birth canal of infected mother → pneumonia, conjunctivitis
serovars A–C (trachoma): transmission by hand–eye contact → infect conjunctiva → inflammation promotes corneal vascularization and scarring → corneal damage → blindness
serovars L1, L2, L3 (lymphogranuloma venereum): sexually transmitted → painless ulceration at site of infection → ulcers heal spontaneously but bacteria spread to regional lymph nodes → lymphadenopathy (buboes) weeks later → buboes fuse, soften, and suppurate → creates multiple draining sinuses → may lead to proctitis, rectal stricture
Chlamydia life cycle has two forms: extracellular elementary body (EB) and intracellular reticular body (RB)—see side 1 for details

DIAGNOSIS

nucleic acid amplification (PCR, transcription-mediated amplification)
visualize intracytoplasmic inclusions: iodine stain + (inclusions contain glycogen), Giemsa stain +
serology
cultured in cell lines (intracellular growth)

TREATMENT

azithromycin
tetracyclines (+ ceftriaxone for concurrent *N. gonorrhea*)
oral erythromycin for neonates of infected mothers
prophylactic erythromycin eye drops for neonates

QUICK FACTS

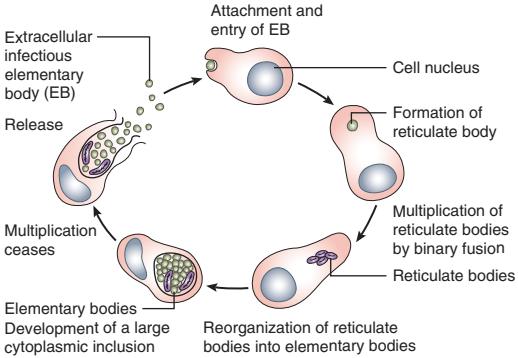
Most frequent cause of bacterial STD in the U.S. and most frequent cause of blindness worldwide
Chlamydiae infections in men are usually silent, so that infected individuals oftentimes unknowingly spread the organism to their partners.

Study Tip

Two obligate intracellular (require host ATP for energy):
- Chlamydiae
- Rickettsiae

Chlamydiae replicate within inclusion bodies, Rickettsiae replicate freely in cytoplasm.
Common causes of non-gonococcal urethritis (NGU):
- *Chlamydia trachomatis*
- *Ureaplasma urealyticum*

Chlamydia pneumoniae (TWAR)



CLINICAL CASE

A 22-year-old student presents with a nonproductive cough, fever, and sore throat. CXR demonstrates diffuse interstitial infiltrate. Sputum Gram stain shows many PMNs but no organisms, and a Giemsa stain reveals intracytoplasmic inclusions in epithelial cells. Doxycycline treatment is begun.

Chlamydia pneumoniae (TWAR)

CLINICAL PRESENTATION

atypical pneumonia

PATHOBIOLOGY

community-acquired → microorganism enters upper respiratory tract epithelium → phagocytosed by macrophages → lymphocyte infiltration at site of infection → local pulmonary edema, necrosis, and hemorrhage

Chlamydia life cycle has two forms:
- extracellular elementary body (EB)
- intracellular reticular body (RB)

EB is infective form → EB phagocytosed → intracellularly, EB transforms into RB (special cell wall blocks phagosome-lysosome fusion) → RB multiplies within intracellular inclusion body → RB condenses into EB → inclusion body bursts releasing infective EB

DIAGNOSIS

Giemsa stain to visualize intracytoplasmic inclusions
serology

TREATMENT

antibiotics that can enter cells: doxycycline

QUICK FACTS

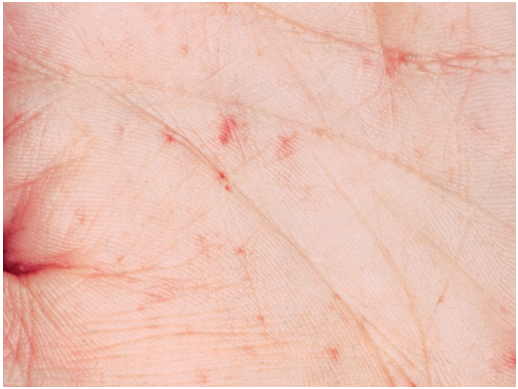
C. pneumoniae most often infects young adults.
TWAR = Taiwan acute respiratory agent, named after the original isolates

Study Tip

Two obligate intracellular parasites (require host ATP for energy):
- Chlamydiae
- Rickettsiae

Chlamydiae replicate within inclusion bodies, Rickettsiae replicate freely in cytoplasm.

Common causes of atypical pneumonia:
- *Mycoplasma*
- *Legionella*
- *Chlamydia*
- Viruses

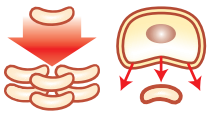


Petechiae on the palms in Rocky Mountain Spotted Fever

CLINICAL CASE

A 10-year-old boy in Virginia presents with a rash, fever, and a severe headache that began several days ago. The rash began on his palms and soles and has now spread centrally to his trunk. His pediatrician also notes conjunctival redness, and lab studies show proteinuria. The boy's history is significant for a hike in the woods a week ago. The child is given tetracycline, and his diagnosis is confirmed by a Weil-Felix test.

Rickettsia rickettsii — Rocky Mountain Spotted Fever



CLINICAL PRESENTATION

rash, fever, headache

PATHOBIOLOGY

carried in dogs, rodents → bite of *Dermacentor* wood or dog tick transmits to humans → organism infects and proliferates in endothelial cells → inflammation of endothelial lining of small blood vessels, capillaries → maculopapular rash on palms & soles spreading proximally to trunk (centripetal spread)

widespread necrotic vasculitis → headache and CNS changes, renal damage → may lead to death if delayed treatment

similar Rickettsial diseases caused by:

Rickettsia akari: mites transmit from mice to humans → papule forms at site of bite → papule vesiculates, fever, headache → vesicles spread over body (Rickettsialpox)

DIAGNOSIS

acute: history, skin biopsy

serology

+ Weil-Felix test (not recommended because it lacks specificity and sensitivity)

TREATMENT

doxycycline

chloramphenicol

QUICK FACTS

The Weil-Felix reaction uses *Proteus vulgaris* antigens to diagnose *Rickettsia*. The *Proteus* antigens cross-react with a patient's serum antibodies against *Rickettsia*.

Despite its name, Rocky Mountain Spotted Fever typically occurs along East Coast due to dog tick bite.

Early detection of the tick can prevent the disease because tick feeding requires 6–10 hours to transmit sufficient inoculum.

Rocky Mountain Spotted Fever (*R. rickettsii*) causes a rash that spreads proximally from the palms and soles vs. epidemic typhus (*R. prowazekii*) causes a rash that spreads outwardly but avoids the palms, soles, and face.

Study Tip

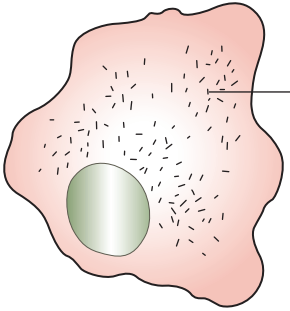
Two obligate intracellular parasites (require host ATP for energy):

- Chlamydiae
- Rickettsiae

Chlamydiae replicate within inclusion bodies, Rickettsiae replicate freely in cytoplasm.

Palm & sole rash:

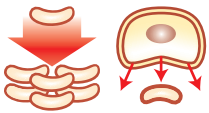
- Rocky Mountain spotted fever
- Syphilis
- Coxsackievirus



CLINICAL CASE

A Kosovo refugee sees a volunteer camp doctor complaining of a rash spreading outward from his trunk but sparing his palms and soles. Two days ago, he experienced abrupt onset of fever, headaches, and confusion. On physical exam, the doctor discovers lice in the man's hair. The doctor treats with a delousing regimen and tetracycline. Were he at a hospital, he might confirm the diagnosis with a Weil-Felix test.

Rickettsia prowazekii — Epidemic Typhus



CLINICAL PRESENTATION

rash, fever, headache
Brill-Zinsser disease

PATHOBIOLOGY

carried in flying squirrels in Southern U.S. → louse transmits to human → organism infects and proliferates in endothelial cells → inflammation of endothelial lining of small blood vessels, capillaries → rash on trunk that spreads outward (centrifugal spread) but spares palms, soles, and face
widespread vascular necrosis → headache and CNS changes, gangrene → may be fatal
if recover without antibiotics → latent microorganisms may remain within cells → may cause recurrent, mild epidemic typhus (Brill-Zinsser disease)
human-to-human spread via louse responsible for epidemics during war

DIAGNOSIS

serology
+ Weil-Felix test

TREATMENT

tetracycline
chloramphenicol

QUICK FACTS

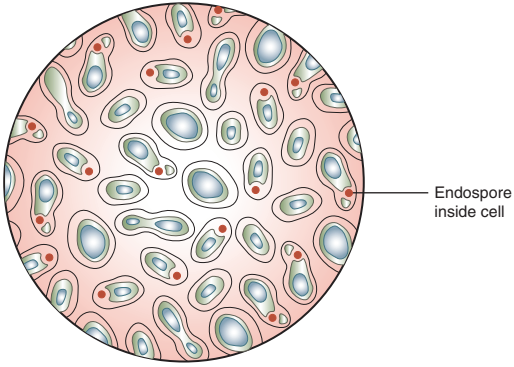
R. prowazekii has caused significant mortality in many major wars.
Other causes of typhus:
R. typhi: fleas transmit from rodents to humans → endemic typhus found in South Texas and California
R. tsutsugamushi: chiggers transmit from rodents to humans → scrub typhus found in Asia and the South Pacific
Epidemic typhus *(R. prowazekii)* causes a rash that spreads outwardly but avoids the palms, soles, and face vs. Rocky Mountain Spotted Fever *(R. rickettsii)* that causes a rash that spreads proximally from the palms and soles.

Study Tip

Two obligate intracellular parasites (require host ATP for energy):

Chlamydiae
Rickettsiae

Chlamydiae replicate within inclusion bodies, Rickettsiae replicate freely in cytoplasm.



CLINICAL CASE

A cattle farmer goes to his doctor complaining of a mild cough and fever. He says that the fever began abruptly several days ago. His occupation as cattle slaughterer leads the doctor toward a diagnosis, and tetracycline is administered. The diagnosis is confirmed by serology and a negative Weil-Felix test.

Coxiella burnetii (a *Rickettsia*) — *Q Fever*

CLINICAL PRESENTATION

atypical pneumonia

PATHOBIOLOGY

carried in cattle, sheep, goats → microorganism shed in animal products → survives extracellularly as spore → inhalation of spores → mild atypical pneumonia → may lead to hepatitis, chronic endocarditis

DIAGNOSIS

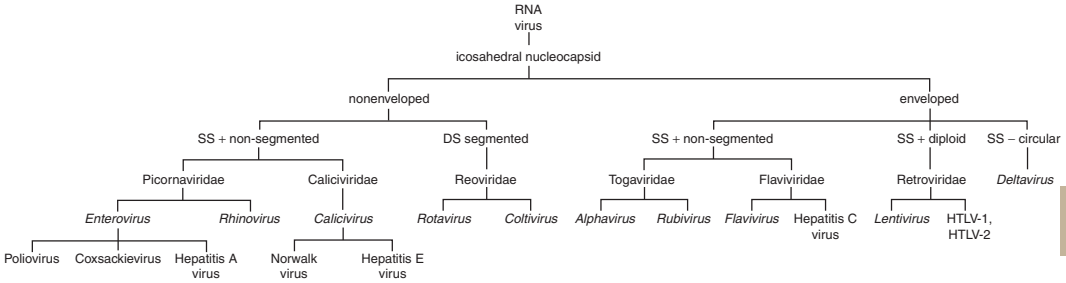
serology
culture in cells (intracellular growth)
Weil-Felix negative

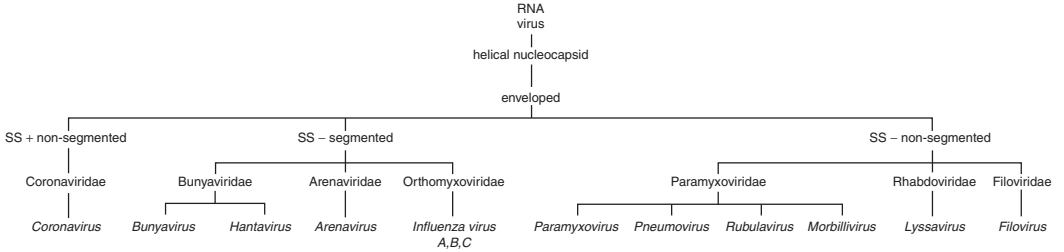
TREATMENT

tetracycline

QUICK FACTS

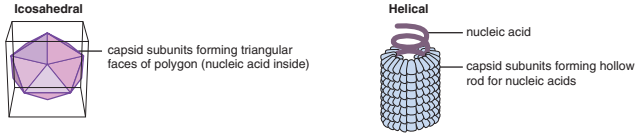
In contrast to other Rickettsial disease:
- *C. burnetii* does not require arthropod transmission because it can survive extracellularly as a spore.
- *C. burnetii* does not cause rash.


RNA virus
icosahedral nucleocapsid
nonenveloped
enveloped
SS + non-segmented
DS segmented
SS + non-segmented
SS + diploid
SS – circular
Picornaviridae
Caliciviridae
Reoviridae
Togaviridae
Flaviviridae
Retroviridae
Deltavirus
Enterovirus
Rhinovirus
Calicivirus
Rotavirus
Coltivirus
Alphavirus
Rubivirus
Flavivirus
Hepatitis C virus
Lentivirus
HTLV-1, HTLV-2
Poliovirus
Coxsackievirus
Hepatitis A virus
Norwalk virus
Hepatitis E virus

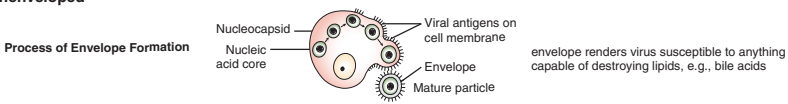

RNA virus
helical nucleocapsid
enveloped
SS + non-segmented
SS – segmented
SS – non-segmented
Coronaviridae
Bunyaviridae
Arenaviridae
Orthomyxoviridae
Paramyxoviridae
Rhabdoviridae
Filoviridae
Coronavirus
Bunyavirus
Hantavirus
Arenavirus
Influenza virus A,B,C
Paramyxovirus
Pneumovirus
Rubulavirus
Morbillivirus
Lyssavirus
Filovirus

RNA Viruses

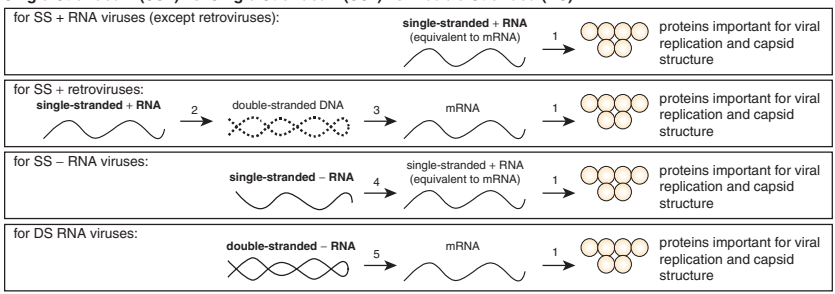
Icosahedral vs. Helical Nucleocapsid



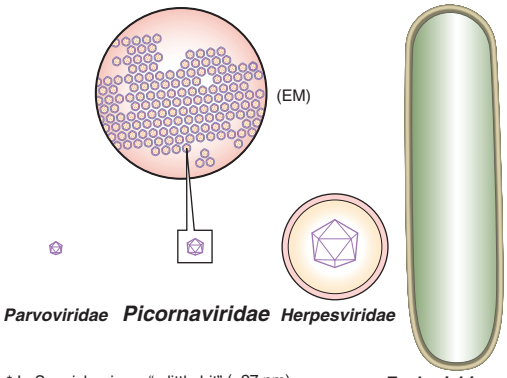
Enveloped vs. Nonenveloped



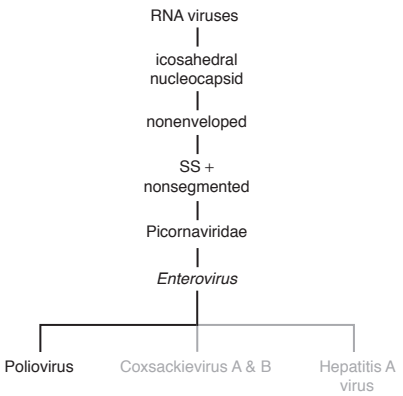
Single-Stranded + (SS+) vs. Single-Stranded – (SS–) vs. Double-Stranded (DS) RNA



1. host cell translation machinery
2. viral reverse transcriptase
3. host cell transcription machinery
4. viral ss RNA polymerase
5. viral ds RNA polymerase



* In Spanish, pico = "a little bit" (~27 nm)



CLINICAL CASE

A woman in India complains of fever, muscle pains, and weakness of her trunk, abdomen, and legs. This morning, she notes difficulty in swallowing and neck pain, which prompts her to come to the hospital. Physical exam reveals fasciculations and flaccid paralysis of the lower limbs and trunk. Breathing seems to be troubled. A CSF analysis reveals lymphocytosis, PMNs, and normal glucose and protein levels. The physician confirms the diagnosis by checking the woman's vaccination history and prepares respiratory support in case her breathing difficulties worsen.

CLINICAL PRESENTATION

paralytic poliomyelitis
nonparalytic poliomyelitis (aseptic meningitis)
abortive poliomyelitis (sore throat, malaise)

PATHOBIOLOGY

transmitted by fecal–oral route → travels in GI tract (stable at low gastric pH) → infects small intestine/oral pharynx epithelium → replicates in submucosal lymphoid tissue (Peyer's patches, tonsils) → transient viremia
spreads to CNS by viremia and/or retrograde transport in peripheral nerves (exact mechanism unknown) → binds receptors of anterior horn motor neurons → replicates, lyses motor neurons innervating:
- distal muscles (lower motor neuron disease)
- proximal muscles → respiratory insufficiency → possible death

infection generates IgG and secretory IgA → protects against future infections

DIAGNOSIS

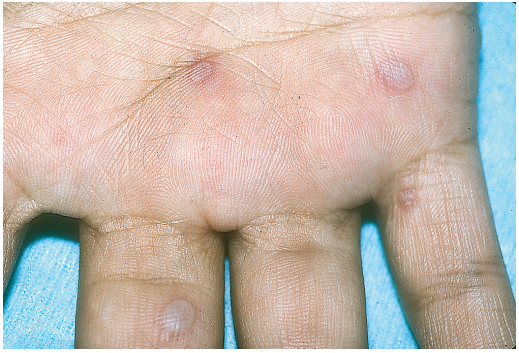
in meningitis: ↑ lymphocytes, normal glucose, normal/↑ protein
throat, stool, or spinal specimen: isolate cytopathic effect
serology

TREATMENT

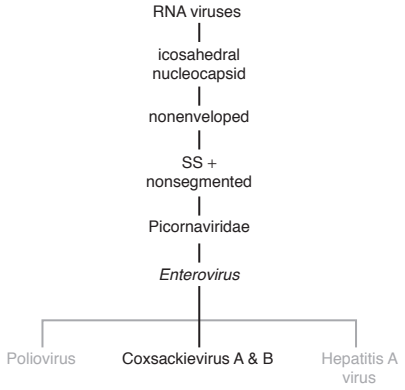
symptomatic support (e.g., "iron lungs")
passive immunization with IgG
vaccines:
Inactivated Polio Vaccine (IPV)—Salk Vaccine, killed virus
Oral Polio Vaccine (OPV)—Sabin Vaccine live, attenuated virus

QUICK FACTS

In the Western Hemisphere, polio has been eradicated; rare cases have occurred when OPV reverts to virulence.
Infection in adults (vs. infants) more often leads to paralysis. Polio became a problem in the U.S. when better sanitation reduced the number of infant infections; uninfected infants later grew up as unexposed adults vulnerable to paralytic infection.
Post-Paralytic Syndrome, occurring years after initial infection, presents as gradual muscle wasting.



Hand-Foot-Mouth disease vesicles on palm



CLINICAL CASE

A young man presents with chest pain, dyspnea, and early signs of heart failure. His history shows he had an upper respiratory infection 3 weeks ago. Examination reveals tachycardia and a gallop rhythm (S_3), while ECG shows evidence of a conduction defect with nonspecific ST-T changes. Echocardiogram is ordered and shows cardiomegaly with contractile dysfunction. The doctor makes a viral diagnosis by serology and admits the patient for monitoring, assuring the patient that he will likely recover completely.

CLINICAL PRESENTATION

A: herpangina
hand-foot-and-mouth disease
B: pleurodynia
myocarditis, pericarditis
A or B: aseptic meningitis
paralysis
upper respiratory tract infection

PATHOBIOLOGY

typical in summer and fall → fecal–oral or aerosol transmission → travels in GI tract (stable at low gastric pH) → infects mucosal epithelial cells → replicates and spreads → viremia → infects and can lyse:

- skin and mucosal epithelium (Group A) → forms vesicles → herpangina (red oropharynx vesicles, fever, sore throat), hand-foot-and-mouth disease
- heart and pleural surfaces (Group B) → pleurodynia, myocarditis, pericarditis
- meninges and anterior horn motor neurons (Group A or B) → aseptic meningitis, paralysis

DIAGNOSIS

isolate virus
serology

TREATMENT

symptomatic: anti-inflammatory agents
no antivirals or vaccine available

QUICK FACTS

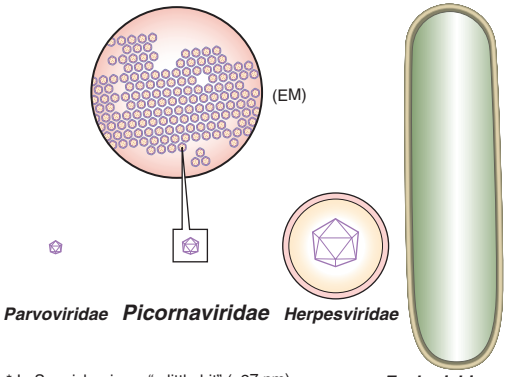
Hand-foot-and-mouth disease (pictured on other side), seen as vesicles on the hands, feet, and mouth, typically occurs in young children.
Coxsackievirus B is associated with 50% of cases of viral myocarditis.
ECHO viruses (*E*nteric *C*ytopathic *H*uman *O*rphan)—"orphan" because once not associated with any disease—are enteroviruses now known to cause diseases similar to those in the coxsackievirus "Group A or B" category above.
Other strains of enteroviruses are the main cause of acute hemorrhagic conjunctivitis.

Study Tip

Most common causes of aseptic meningitis:
Coxsackievirus
Echovirus
Mumps virus

Causes of common cold:
Rhinovirus
Coronavirus
Adenovirus
Influenza C virus
Coxsackievirus

Palm & sole rash:
Syphilis
Rocky Mountain spotted fever
Coxsackievirus



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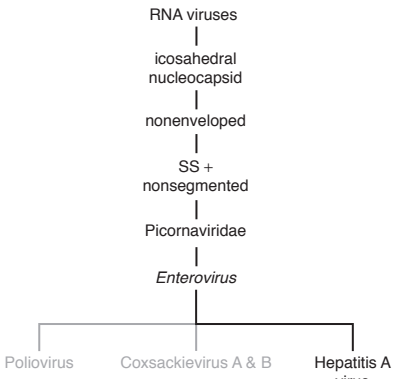
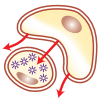


CLINICAL CASE

A Boy Scouts troop master calls the doctor asking about symptoms that have developed in 7 of his 20 Scouts shortly after a camping trip. The ill boys complain of fever, nausea, loss of appetite, and vomiting. The Scout master also notes a yellow hue in some of the boys, especially visible in their eyes. Two of the affected boys are brought to the hospital where their urine is noted to be dark and their feces pale. Liver enzyme assays reveal an elevated ALT and AST level. The physician confirms the diagnosis with an assay of serum IgM and then assures the master and his Scouts that the illness will completely go away in several weeks.



CLINICAL PRESENTATION

acute hepatitis

PATHOBIOLOGY

transmitted by fecal–oral route → travels in GI tract (stable at low gastric pH) → infects mucosal epithelial cells → replicates and spreads (viremia) → reaches liver by portal circulation → infects hepatocytes
CTL response stimulated → kills infected hepatocytes → often asymptomatic but may cause jaundice

DIAGNOSIS

IgM detection in serum (IgG indicates past infections)

TREATMENT

supportive care (self-limiting)
pooled immune globulins
vaccine: formalin-inactivated HAV

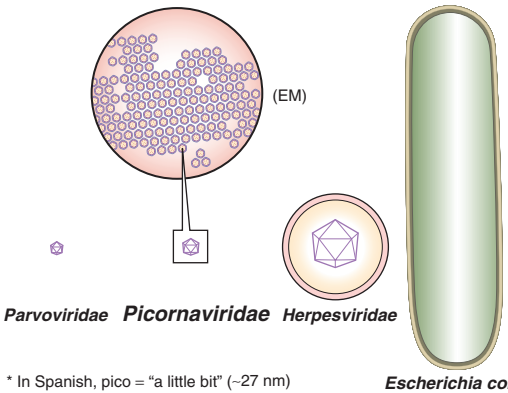
QUICK FACTS

Epidemics among children are the most frequent cases (e.g., in summer camps, schools), spread by fecal–oral transmission. Most adults have been asymptomatically infected, as evidenced by anti-HAV IgG.

Study Tip

HAV and HEV (vs. HBV, HCV, HDV) have:

- Oral transmission
- No chronic carrier state
- No cirrhosis
- No hepatocellular carcinoma



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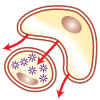
RNA viruses
icosahedral nucleocapsid
nonenveloped
SS + nonsegmented
Picornaviridae
Rhinovirus

CLINICAL CASE

A woman presents with a runny nose, sneezing, an irritable throat, and a slight fever. She suffers similar symptoms every year, often at the same time as other members of her family. Her symptoms go away within a week, except for the nasal discharge that persists for a few more days.



CLINICAL PRESENTATION

common cold

PATHOBIOLOGY

only human reservoir → spreads by contact or aerosol → binds ICAM-1 on upper respiratory tract epithelial cells → extends locally without killing cells → local inflammation causes exudate, ↑ ICAM-1 expression → further viral binding and infection

exudate may block passageways → secondary bacterial sinusitis or otitis media

acquire IgA immunity to particular serotype after infection

DIAGNOSIS

symptoms

TREATMENT

supportive care

no vaccine because of too many viral serotypes

QUICK FACTS

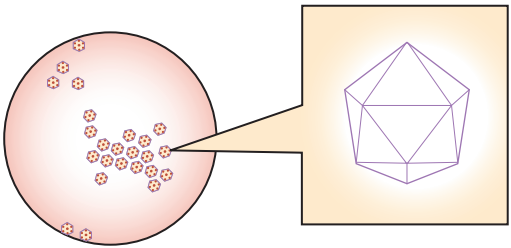
50% of colds are due to rhinoviruses.

Rhinovirus preferentially replicates at the cooler 33°C of the nose and upper airways (the warmer 37°C of the lungs precludes rhinovirus pneumonia).

Study Tip

Causes of common cold:

- Rhinovirus
- Coronavirus
- Adenovirus
- Influenza C virus
- Coxsackievirus



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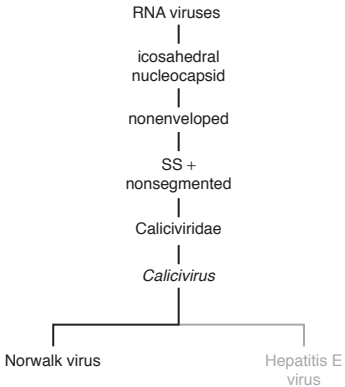
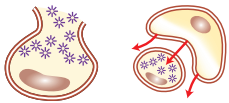


CLINICAL CASE

Thirteen people attending an oyster dinner abruptly develop nausea and abdominal pains 2 days later. Soon after the onset of pain, they begin to vomit and some also have diarrhea.

Caliciviridae Calicivirus — *Norwalk Virus, Norovirus*



CLINICAL PRESENTATION

gastroenteritis

PATHOBIOLOGY

transmitted by contact or contaminated food/water → local infection and inflammation in proximal small intestine → gastroenteritis

DIAGNOSIS

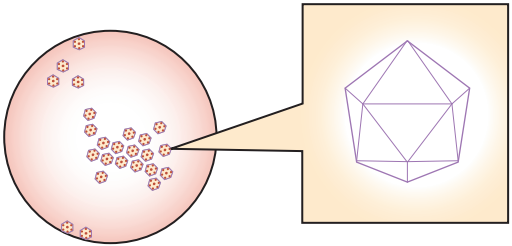
not typically done
stool specimens: visualize virus

TREATMENT

usually not required because it is self-limited
rehydration if severe fluid loss

QUICK FACTS

Norwalk virus is a major cause of group-related or institutional diarrhea.



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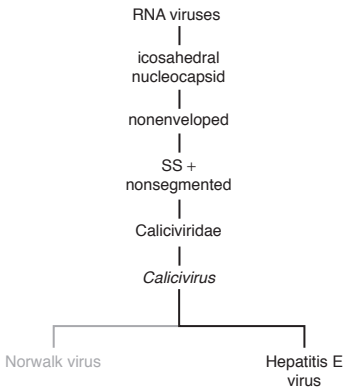
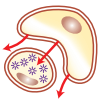


CLINICAL CASE

A man goes to India on a hiking trip in the Himalayas. Upon returning, he develops nausea, vomiting, malaise, and headache. His doctor notices jaundice and hepatomegaly on physical exam, and labs detect increased AST, ALT, and direct serum bilirubin levels. Immunization records show that the man had received HAV and HBV vaccines before leaving. The symptoms are traced back to a shared water supply along the hiking route.



CLINICAL PRESENTATION

acute hepatitis

PATHOBIOLOGY

transmitted by fecal–oral route → travels in GI tract (stable at low gastric pH) → infects mucosal epithelial cells → replicates and spreads (viremia) → reaches liver by portal circulation → infects hepatocyte

CTL response stimulated → kills infected hepatocytes → often asymptomatic but may cause jaundice

DIAGNOSIS

symptoms, rule out HAV

TREATMENT

none developed

QUICK FACTS

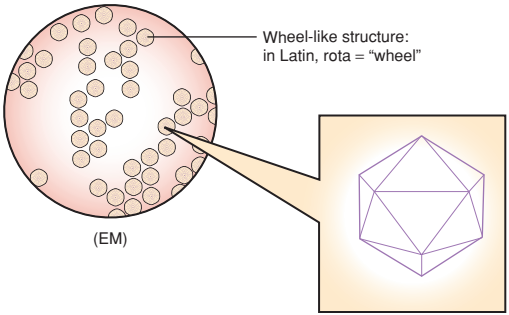
HEV resembles HAV, but is also associated with high mortality in pregnant women.

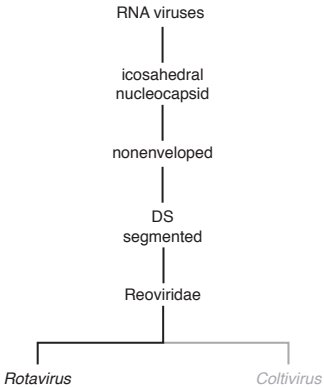
Hepatitis E may be responsible for two-thirds of epidemic "non-A, non-B" hepatitis cases in India, Russia, and other Asian countries.

Study Tip

HEV and HAV (vs. HBV, HCV, HDV) have:

- Oral transmission
- No chronic carrier state
- No cirrhosis
- No hepatocellular carcinoma





- Genome has 11 segments of dsRNA, allowing for frequent gene reassortment

CLINICAL CASE

A mother brings her 3-year-old son to the doctor after severe bouts of vomiting and diarrhea for the past 2 days. The diarrhea is watery, although the mother denies seeing any blood in it. The doctor makes a diagnosis by an ELISA on the child's stool and assures the mother he will be fine with good rehydration.

CLINICAL PRESENTATION

gastroenteritis

PATHOBIOLOGY

transmitted via fecal–oral route → infects villus cells of proximal small intestine → replicates within and lyses cell → impaired absorption of carbohydrates and other nutrients → vomiting followed by watery diarrhea

DIAGNOSIS

stool specimen: immunoassay for virus

TREATMENT

rehydration
rotavirus vaccine (live oral attenuated)

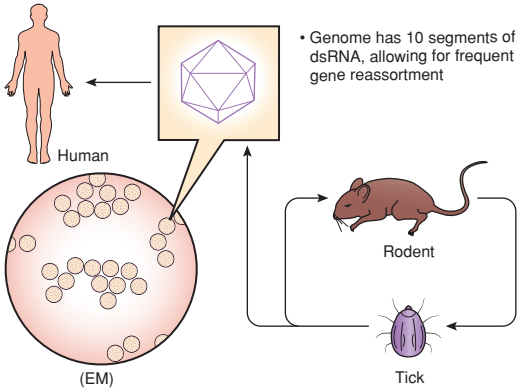
QUICK FACTS

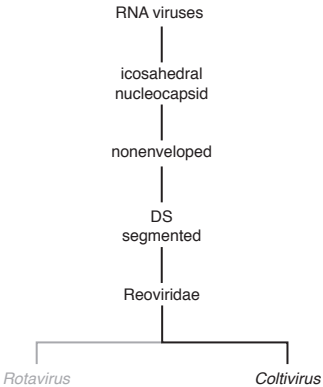
Because rotaviruses cause no inflammation, diarrhea has no blood.
Infection before 6 months is uncommon due to passive IgA immunity from the mother's colostrum. However, by age 3, almost every individual worldwide has been infected and develops lifelong immunity.
REO = *R*espiratory *E*nteric *O*rphan ("orphan" because once not associated with any disease).

Study Tip

Rotaviruses are the most common cause of infectious diarrhea in infants and young children.

Reoviruses are the only RNA viruses that are double-stranded.





CLINICAL CASE

A hiker in the Rocky Mountains stops at a ranger station complaining of fever and muscle aches. The symptoms have worsened since the day before, and he is also beginning to feel head and neck pain upon movement. When asked if he had been bitten by any ticks, the hiker seems alarmed, affirming that he thinks he was bitten several times. The ranger, now more certain of a diagnosis, informs the hiker that several hundred people suffer the same infection every year. He instructs the hiker to report to the base hospital and to avoid any aspirin or sharp bruising hits for fear of hemorrhage.

Reoviridae Coltivirus — Colorado Tick Virus

CLINICAL PRESENTATION

fever, myalgias, ocular pain, headache

PATHOBIOLOGY

carried in rodents ⟶ transferred to humans via wood tick bite ⟶ virus may spread systemically (viremia) ⟶ virus may infect and cause lesions in any body organ

if virus infects bone marrow cells ⟶ infected erythrocytes, leukopenia, thrombocytopenia

DIAGNOSIS

serology
isolation of virus from blood
detection of viral antigens on erythrocytes

TREATMENT

none available

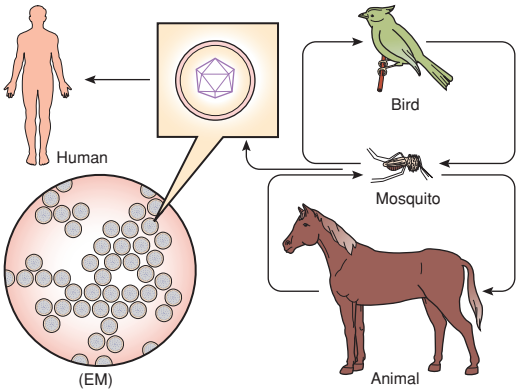
QUICK FACTS

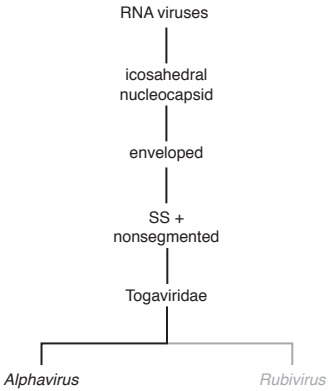
Endemic to Rocky Mountains where hikers or campers are often infected following tick bites.
REO = *R*espiratory *E*nteric *O*rphan ("orphan" because once not associated with any disease).

Study Tip

Differential diagnosis:
- Rocky Mountain spotted fever
- Tularemia

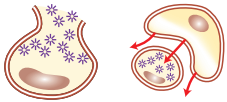
Reoviruses are the only RNA viruses that are double-stranded.





CLINICAL CASE

Late July, a father brings his daughter to the emergency ward for fever, vomiting, and strange behavior that developed the day before. The EW physician notes that the daughter has head and neck pains and is photophobic. A quick neurological exam reveals hemiparesis and some cranial nerve deficits. The physician asks the father about any recent mosquito bites she may have had, and the father affirms that they are swarmed by mosquitoes in their Florida home. The physician fears a grave diagnosis with a high mortality rate or at least a slow recovery lasting weeks. This diagnosis is confirmed by detection of virus, PMN pleocytosis, normal glucose, and slightly ↑ proteins in the CSF.



CLINICAL PRESENTATION

encephalitis

PATHOBIOLOGY

carried in birds or horses ⟶ transferred to humans via mosquito bite ⟶ enters circulation and infects endothelial cells, reticuloendothelial cells ⟶ lyses cells to produce primary viremia

if viremia persists, infects CNS endothelial cells and neurons ⟶ hemorrhage, inflammation, necrosis ⟶ CNS symptoms including headache, meningitis, photophobia ⟶ high mortality rate (EEE > WEE > VEE)

DIAGNOSIS

serology
at autopsy: isolation of virus in brain tissue

TREATMENT

symptomatic
vaccine: formalin-inactivated or attenuated virus

QUICK FACTS

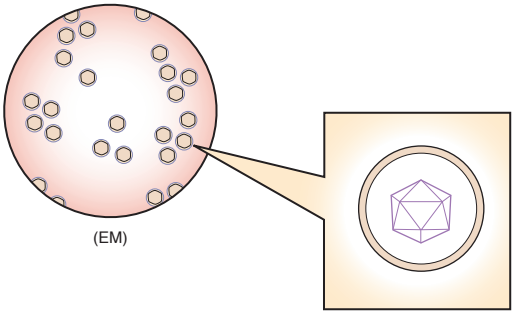
Incidence of arboviral encephalitis is seasonal and regional:

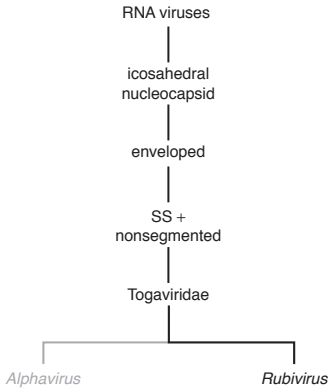
Eastern Equine Encephalitis (EEE) localizes to swampy areas of the U.S. eastern coast.
Western Equine Encephalitis (WEE) localizes to western and central U.S. and Canada.
Venezuelan Equine Encephalitis (VEE) localizes to Venezuela, Colombia, Central America, and Texas.

Study Tip

Arboviruses
(arthropod-borne virus):

- Togaviridae
  - WEE
  - EEE
  - VEE
- Flaviviridae
  - West Nile virus
  - Yellow fever
  - Dengue fever
  - St. Louis encephalitis
  - Japanese encephalitis
- Bunyaviridae
  - California encephalitis
  - Rift Valley fever
  - Sandfly fever





CLINICAL CASE

A woman goes to her doctor complaining of a red rash on her face. She reports having a fever that resolved just before the rash appeared. During a physical exam, the doctor notes that the rash has spread to the arms. Swollen lymph nodes are felt in the cervical region and behind the ears. The doctor inquires about the woman's vaccination record and makes a diagnosis to be confirmed by serological studies. The doctor also makes sure that the woman is not pregnant. The woman is relieved to know the rash will go away in several days, although she may experience arthritis for some time thereafter.

CLINICAL PRESENTATION

rubella: fever followed by descending rash
congenital rubella: congenital malformations (deafness, patent ductus arteriosus, pulmonary artery stenosis, cataracts, microcephaly)

PATHOBIOLOGY

transmitted by aerosol → virus infects nasopharynx and replicates in local lymph nodes → systemic spread via blood (viremia) → antibody-mediated reaction leads to maculopapular rash beginning in face and spreading to extremities → antibody complexes may result in arthritis in women
if it infects pregnant woman in first trimester → may cross placenta to fetus → infects fetal cells and promotes mitotic arrest, necrosis, or chromosomal damage → congenital defects in brain, heart, or eyes
lifelong immunity following infection

DIAGNOSIS

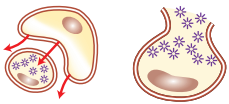
detection of anti-rubella antibodies:
IgM if recent infection
IgG if immune
blocks CPE of ECHO virus in culture
virus in amniocentesis indicates congenital rubella

TREATMENT

self-limiting (no antiviral treatment available)
vaccine: live-attenuated rubella virus in measles–mumps–rubella (MMR) vaccine

QUICK FACTS

Pregnant women are screened for rubella immunity. However, the rubella vaccine is not administered until after delivery for fear of fetal infection.
An infant with congenital rubella may transmit the virus up to the age of 2, complicating control of infection from such patients.
Unlike other *Togaviridae*, rubella is not an arbovirus because it is not transmitted by an arthropod.
MMR is the only live viral vaccine that can be given in HIV-positive individuals.



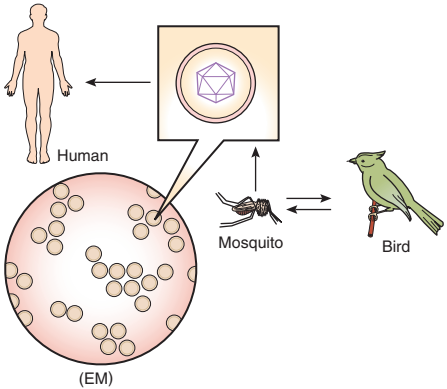
Study Tip

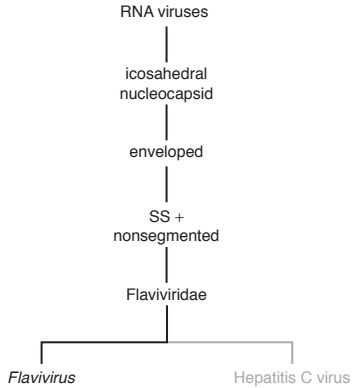
Five most common pediatric diseases with rash:

- Measles (measles virus)
- Rubella (rubella virus)
- Scarlet fever (*S. pyogenes*)
- Roseola (HHV 6)
- Erythema infectiosum (Parvovirus B19)

Organisms that cross placenta and therefore allow infection to pass from pregnant mother to fetus (TORCHES):

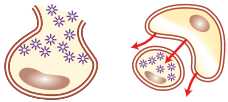
TOxoplasma gondii
Rubella
Cytomegalovirus
HErpes, HIV
Syphilis





CLINICAL CASE

A 75-year-old man from New York is brought to the ED after reporting 1 week of fever, headache, nausea, and muscle ache. On exam, he appears confused and has a course tremor in his hands. CT and MRI are unrevealing. A lumbar puncture is performed, and CSF analysis demonstrates elevated protein, normal glucose, and lymphocytosis. His family reports that he was visiting them for the summer, but they have avoided the outdoors after several dead crows were found in their neighborhood.



CLINICAL PRESENTATION

Most infections are asymptomatic
West Nile fever: fever, fatigue, headache, myalgia, anorexia, eye pain, nausea, vomiting, diarrhea, rash
West Nile encephalitis: neuroinvasive disease causing encephalitis (more typical in elderly) or meningitis (more typical in children) ⟶ symptoms range from mild confusion to tremor, extrapyramidal symptoms, flaccid paralysis, or severe encephalopathy that may progress to coma or death, particularly in elderly or immunocompromised

PATHOBIOLOGY

virus maintained in cycle between birds and mosquitoes ⟶ spreads to incidental human host by mosquito bite ⟶ replicates in skin Langerhans cells, which migrate to regional lymph nodes ⟶ viremia and infection of multiple organs including CNS

DIAGNOSIS

IgM antibody in serum or CSF
PCR of CSF

TREATMENT

supportive
prevention: mosquito control

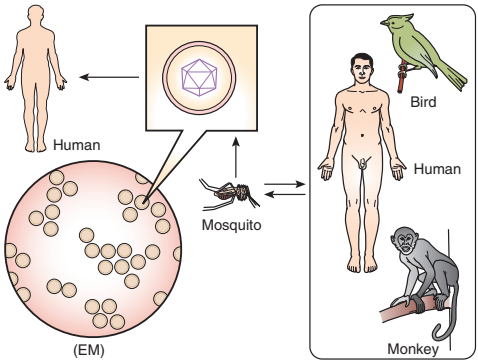
QUICK FACTS

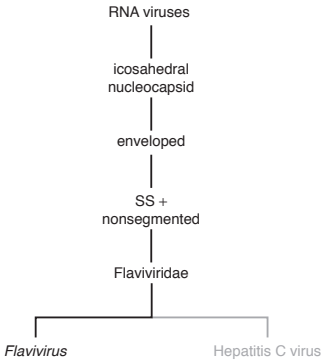
West Nile virus is named after the West Nile province of Uganda where it was first isolated. It first appeared in North America in 1999, causing several deaths in New York.
Crows and other birds are the hosts for West Nile virus. Clusters of dead crows have heralded human cases.
Rare transmission of West Nile virus has been reported via transfused blood products, donated organs, and breast milk.

Study Tip

Arboviruses (arthropod-borne virus):

- Togaviridae
  - WEE, EEE, VEE
- Flaviviridae
  - West Nile virus
  - Yellow fever
  - Dengue fever
  - St. Louis encephalitis
  - Japanese encephalitis
- Bunyaviridae
  - California encephalitis
  - Rift Valley fever
  - Sandfly fever





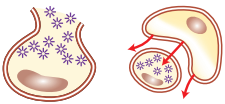
CLINICAL CASE

A diplomat plans to make a trip to Central America. However, just before leaving, his doctor receives a CDC report of jungle log cutters that have fallen ill with jaundice, instances of hemorrhage, and liver dysfunction. He insists that the diplomat be immunized against this infectious agent before traveling to the area.

For a summer trip, a woman visits the tropics for a short time. One week upon returning, she shows signs of fever, headache, and pain behind the eyes and in the back and joints. She also notices a generalized rash forming. The doctor explains that the illness will pass but that a second infection by a similar agent might lead to more devastating symptoms.

Flaviviridae Flavivirus

Yellow and Dengue Fever Viruses, St. Louis and Japanese Encephalitis Viruses



CLINICAL PRESENTATION

Yellow Fever Virus: *Yellow Fever* (hepatitis, jaundice)
Dengue Fever Virus:
Dengue Fever: "*breakbone fever*" (flu-like + severe joint/muscle pain)
Dengue Hemorrhagic Fever (dengue fever + hemorrhage, shock)
St. Louis, Japanese Encephalitis viruses: *encephalitis*

PATHOBIOLOGY

normal reservoir in monkeys, birds, or humans → transmitted by mosquito bite → enters bloodstream with transient viremia → infects:

- hepatocytes (Yellow Fever) → necrosis → hepatitis, jaundice
- macrophages (Dengue Fever) → acute inflammation → pyrogens and pain mediators released → "breakbone fever"
  if second infection by different serotype → antibodies against first serotype increase → cross-react to form immune complexes → type III hypersensitivity reaction → hemorrhage, shock (Dengue Hemorrhagic Fever)
- CNS (St. Louis or Japanese Encephalitis) → direct damage to neurons, inflammation → neurological abnormalities

DIAGNOSIS

isolate virus from infected tissue (from CSF in encephalitis)
serology

TREATMENT

prevention: monitor mosquito count in an area
vaccine:
Yellow Fever Virus live-attenuated vaccine
Japanese Encephalitis formalin-killed vaccine

QUICK FACTS

Epidemics have geographic specificity: Yellow Fever in tropical South America, Africa; dengue fever in tropics worldwide; Dengue Hemorrhagic Fever in southern Asia; St. Louis encephalitis in southeastern U.S.; Japanese encephalitis in Japan.
Two forms of Yellow Fever exist: *jungle* (has reservoir in tropical monkeys) and *urban* (has reservoir in humans). Each is transmitted by a different mosquito.
Yellow Fever plagued many workers in the Panama Canal project, and only after its control was the canal completed.

Study Tip

Most common human disease caused by an arbovirus:

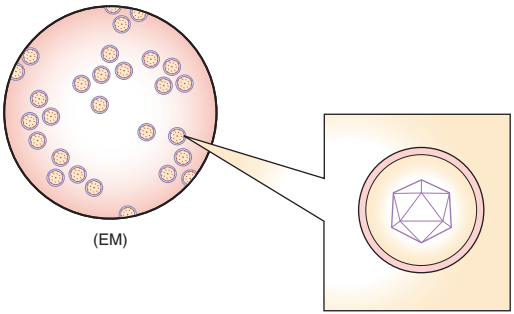
dengue fever.

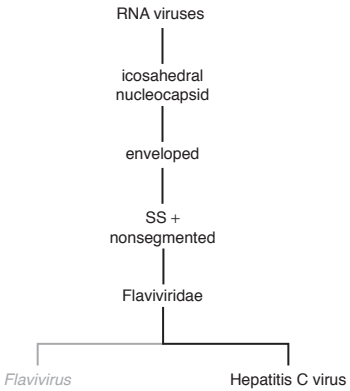
Most common cause of epidemic encephalitis:

Japanese encephalitis virus.

Arboviruses (arthropod-borne virus):

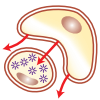
- Togaviridae
  WEE, EEE, VEE
- Flaviviridae
  West Nile virus
  Yellow fever
  Dengue fever
  St. Louis encephalitis
  Japanese encephalitis
- Bunyaviridae
  California encephalitis
  Rift Valley fever
  Sandfly fever





CLINICAL CASE

Feeling fatigued, a man visits his doctor. On physical examination, the patient has reduced liver size. After a thorough history, the doctor learns that the patient had jaundice 5 years ago following a car accident for which he was hospitalized and received a blood transfusion. The doctor is not surprised to see an elevated serum level of ALT in his blood workup and awaits an ELISA to differentiate the causes of this illness.



CLINICAL PRESENTATION

acute hepatitis
- jaundice, fever

chronic hepatitis
- carrier state (asymptomatic)
- cirrhosis
- predisposes to hepatocellular carcinoma

PATHOBIOLOGY

human reservoir → transmission by blood (especially transfusion, IV drug use), semen, *in utero* →
virus infects hepatocytes → immune response by CTLs kills infected hepatocytes → acute hepatitis
in 50–70% of cases, virus not eliminated → asymptomatic carrier state or may become chronic active hepatitis →
cirrhosis, predisposition to hepatocellular carcinoma

DIAGNOSIS

serology for anti-HCV antibody

TREATMENT

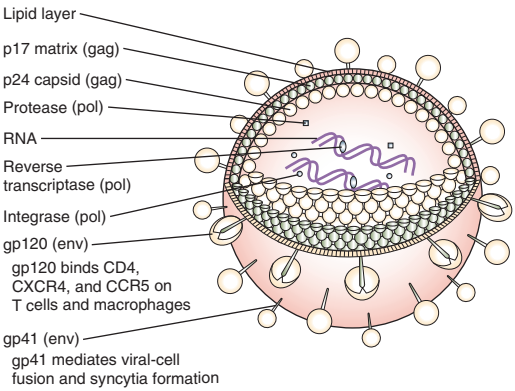
pegylated α-interferon
ribavirin
no vaccine available

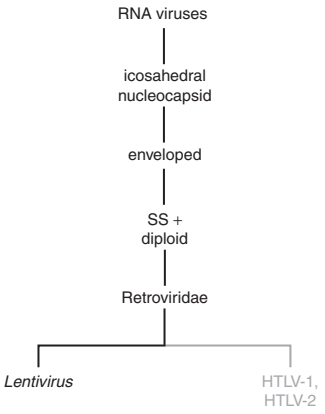
QUICK FACTS

HCV poses a major problem to IV drug users and in blood transfusion banks.
HCV is clinically indistinguishable from HAV and HBV infections and is responsible for most cases of non-A and non-B hepatitis. HCV infections are more often chronic.
2 HCV negatives:
- virus alone is NOT cytotoxic (host response needed)
- virus does NOT cause hepatocellular carcinoma by integration into host genome

Study Tip

HBV, HCV, and HDV have:
- Blood transmission
- Chronic carrier state
- Cirrhosis
- Hepatocellular carcinoma

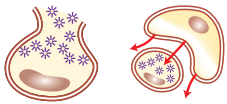




CLINICAL CASE

A 45-year-old homeless man complains to an EW doctor of fever, cough, and a burning pain in his chest. These symptoms have "lingered on and off" for several weeks, and weight loss forces him to resolve the vague illness once and for all. The physician notes no chest sounds, and chest X-ray reveals only a faint interstitial infiltrate. Suspecting some sort of pneumonia, the physician requests a sputum analysis. Lab results reveal the presence of *Pneumocystis jirovecii* confirmed by PCR. Concerned about this fungal infection, the physician administers trimethoprim/sulfamethoxazole and requests a blood count. The results—a white blood cell value of 2,000 cells/μL and CD4+ T-cell count of 500 cells/μL—confirm a grave suspicion. The physician tells the patient the likely diagnosis and asks if he would like a social worker's help.

CLINICAL PRESENTATION



AIDS and opportunistic infections

PATHOBIOLOGY

1° infection stage (first months): transmission by bodily fluids: sexual contact, blood transfer, maternal transfer (transplacental, during birth, via breast milk)⟶ infects CD4+ cells, including T_h lymphocytes in blood and macrophages in epidermis ⟶ replicates in spleen and lymphoid organs ⟶ viremia ⟶ contained by vigorous host immune response ⟶ mononucleosis-like symptoms ⟶ equilibrium established between viral production and host containment

Clinical Latency Stage (7–10 years): mutations in antigens help virus evade host response ⟶ virus replicates, especially in lymphoid organs ⟶ host responds with (1) increased T_h cell production and (2) CTL response against infected cells ⟶ no or low-level symptoms
continued viral evasion by mutations ⟶ viral load gradually increases, CD4+ count gradually drops
CD4+ cells depleted by various mechanisms, including:
- immune attack on infected cells by CTLs
- cell lysis from extensive viral budding
- syncytia formation between infected and uninfected cells (via gp120-CD4 interactions)

Advanced Disease (AIDS): CD4+ T-cell count <200 cells/μL ⟶ common opportunistic infections/neoplasms causing death: *Pneumocystis jirovecii* pneumonia, *Candida albicans* thrush, disseminated HSV, CMV, histoplasmosis, toxoplasmosis, cryptococcal meningitis, *Mycobacterium tuberculosis*, *Mycobacterium avium-intracellulare*, Kaposi's sarcoma
infection of brain microglia, oligodendrocytes, astrocytes ⟶ neuropathy, encephalopathy, dementia

(see HIV life cycle card for information on viral and host protein interactions, e.g., gp120-CD4 interactions)

DIAGNOSIS

detection of virus by ELISA, Western, PCR

TREATMENT

NRTI = nucleoside reverse transcriptase inhibitors (nucleoside analogs) (e.g., AZT, ddI, lamivudine, abacavir, tenofovir, emtricitabine)
NNRTI = nonnucleoside reverse transcriptase inhibitors (bind outside active site) (e.g., efavirenz, nevirapine, delavirdine)
PI = protease inhibitors (e.g., indinavir, nelfinavir)
FI = fusion inhibitors (e.g., enfurvitide)
HAART = Highly Active AntiRetroviral Therapy is a drug cocktail (e.g., NNRTI + 2 NRTI, PI + 2 NRTI) initiated for symptomatic HIV or low CD4 count
Prevention: protected sex, screening of blood, AZT to infected pregnant mothers

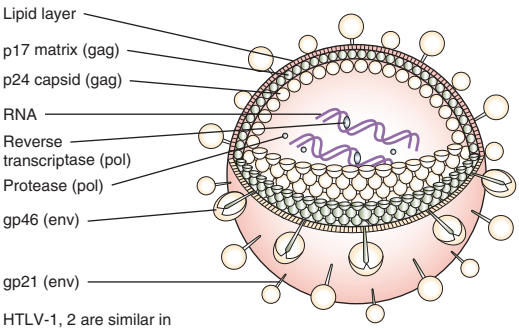
QUICK FACTS

HIV-1 and HIV-2 have similar clinical presentations and share common antigens. HIV-1 is found throughout the world, whereas HIV-2 is found mainly in West Africa.
Monocytes and macrophages advance HIV infection in two ways: (1) they transport HIV to the CNS and (2) they are a reservoir for HIV, especially when T-cell counts are low.
Kaposi's sarcoma has been associated with human herpesvirus 8 (HHV 8) infection.
HHV 8 can be transmitted sexually.

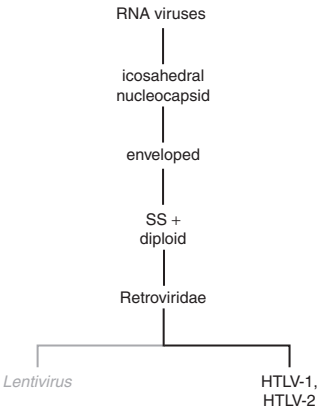
Study Tip

Organisms that cross placenta and therefore allow infection to pass from pregnant mother to fetus (TORCHES):

TOxoplasma gondii
Rubella
Cytomegalovirus
HErpes, HIV
Syphilis

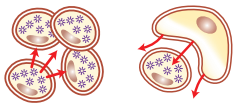


HTLV-1, 2 are similar in structure to HIV-1, 2 but:
- have different surface and matrix proteins
- lack an integrase



CLINICAL CASE

A 57-year-old Caribbean woman seeks the attention of her physician when her legs "do not seem to function appropriately." She tells the physician that she began to feel a stiffness in her left leg and then both legs over the past few weeks, as well as occasional back pain. A neurological exam reveals slight sensory losses, hyperreflexia, and extensor plantar responses in both legs; no cognitive or cranial nerve dysfunction is noted. The physician requests an MRI, which reveals lesions in the white matter of the brain and spinal cord as well as in the paraventricular gray matter of the brain. Although the woman does not have leukemia or lymphoma, the physician suspects a diagnosis that is confirmed by detection of specific antibodies in her CSF. He begins the patient on a regimen of glucocorticoids and explains that her symptoms may progress to paraplegia.



CLINICAL PRESENTATION

T-cell leukemia, lymphoma
tropical spastic paraparesis

PATHOBIOLOGY

transmission by sexual contact or blood transfer → infection of CD4+ T cells, B cells → proviral DNA integrates into genome → viral genes expressed → viral proteins increase production of cytokines and cytokine receptors → IL-2 promotes hyperproliferation of infected cells → rapidly dividing cells accumulate mutations → transformation → T-cell leukemia, lymphoma

if infection of CNS → antibodies produced and CTLs activated → attack neural cells → weakness/stiffness in legs (tropical spastic paraparesis)

DIAGNOSIS

antibody titers in serum, CSF

TREATMENT

supportive

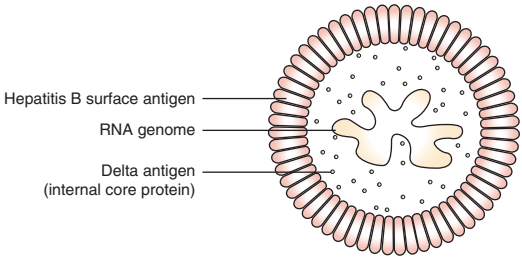
QUICK FACTS

HTLV-1 and HTLV-2 have 60% homology, cannot be distinguishable by serology, but can be distinguished by PCR.

HTLV-1 was first isolated from a patient with cutaneous T-cell lymphoma, and HTLV-2 was first isolated from a patient with hairy cell leukemia.

T-cell leukemia associated with HTLV-1 is endemic to Japan and the Caribbean. HTLV-2 is endemic to Native American populations.

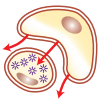
Multiple sclerosis has been associated with HTLV-1 infection and its autoimmune consequences in the CNS.



RNA viruses
↓
icosahedral nucleocapsid
↓
enveloped
↓
SS – circular
↓
Deltavirus

CLINICAL CASE

A chronic drug user previously diagnosed with hepatitis B presents with a recurrence of symptoms, most notably yellow sclerae. Typical signs of chronic hepatitis—serum AST and ALT elevation, jaundice, hepatomegaly, splenomegaly—seem more severe in this patient. The physician suspects that hepatitis B is only part of his clinical picture and recommends treatment with α-interferon to reduce the symptoms. The patient is informed that he is at risk for liver failure.



CLINICAL PRESENTATION

hepatitis

PATHOBIOLOGY

transmitted through blood, sexual contact, or transplacentally → travels in blood to hepatocytes → infects cells → replicates and released only from those cells also infected with HBV, because it requires hepatitis B surface antigen to form infectious particle (HDV is defective and cannot replicate alone)

viral antigens on infected hepatocytes recognized by host immune response → CTL activated → inflammation, hepatocyte necrosis → hepatitis more severe than with HBV alone

DIAGNOSIS

delta antigen detection

anti-delta antigen IgM antibodies

TREATMENT

α-IFN (controls HBV infection, which limits HDV infection)

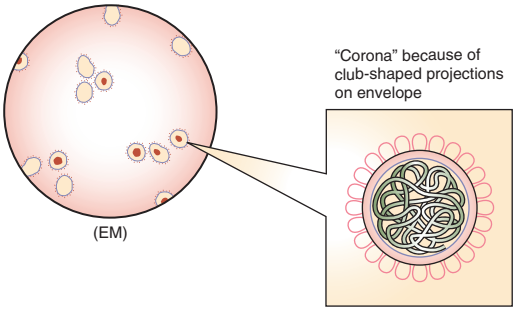
vaccine: recombinant Hepatitis B Surface Antigen to prevent HBV infection

QUICK FACTS

HBV carriers who become superinfected with HDV have a much poorer prognosis, with a greater chance of fulminant hepatitis and liver failure.

HDV may also have a cytopathic effect independent of a host immune response.

The HDV genome is a ribozyme, which is an RNA particle able to cleave and ligate itself. No other human viruses behave this way, but many plant viruses in the viroid group do.



RNA viruses
helical nucleocapsid
enveloped
SS + nonsegmented
Coronaviridae
Coronavirus

CLINICAL CASE

A mother calls her pediatrician, concerned about her son's "cold." Her son has developed a runny nose and a headache. By the time she brings her son to the doctor—a week after the onset of the symptoms—the son has recovered completely.

CLINICAL PRESENTATION

common cold

PATHOBIOLOGY

transmission by respiratory secretions → virus infects upper respiratory tract cells → 3-day incubation → 6- to 7-day common cold

DIAGNOSIS

serology (no laboratory diagnosis usually made)

TREATMENT

no treatment or vaccines developed

QUICK FACTS

Coronavirus infections account for 10–20% of common colds, second only to Rhinovirus infections. These infections are clinically indistinguishable.

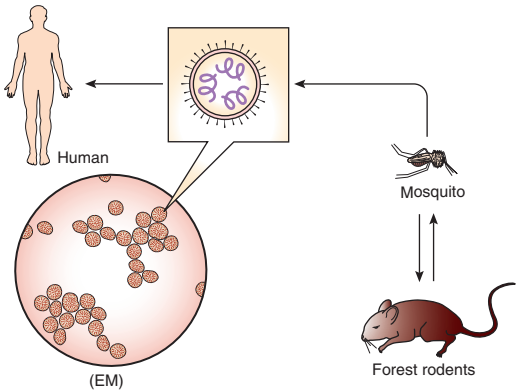
The SARS coronavirus (SARS-CoV) is responsible for Severe Acute Respiratory Syndrome. The virus caused a deadly outbreak of viral pneumonia from 2002 to 2003, spreading from China to over 35 countries in a few weeks.

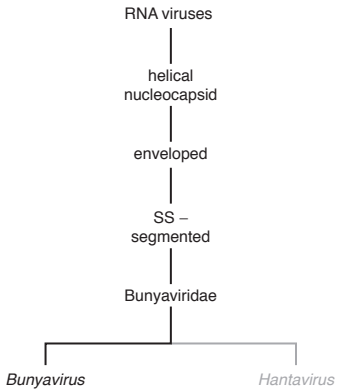
SARS is a rapidly progressive respiratory illness caused by coronavirus. First detected in 2002 in China. SARS commonly presents with fever, dyspnea, and cough that can progress to respiratory failure and death.

Study Tip

Causes of common cold:

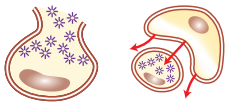
- Rhinovirus
- Coronavirus
- Adenovirus
- Influenza C virus
- Coxsackievirus





CLINICAL CASE

A father brings his daughter to the EW a day after she develops severe headache, fever, and "seizures in her arms." During physical exam, the daughter seems to be confused; she manifests a + Babinski sign and partial paresis on the left side. CSF assay shows normal glucose and protein but the presence of PMNs and mononuclear cells. The doctor orders an ELISA to make a definitive diagnosis. The father is astonished to learn that his daughter may continue to exhibit seizures for several weeks and may suffer permanent cognitive changes. The doctor suggests that the illness was acquired from mosquitoes near their forest home in Michigan.



CLINICAL PRESENTATION

encephalitis

PATHOBIOLOGY

reservoir in forest rodents → spread to humans via mosquito bite → viremic spread to CNS → direct damage to neurons, inflammation → encephalitis, especially in children → low mortality but possible residual cognitive disorders

DIAGNOSIS

antiviral antibodies in serum or CSF

TREATMENT

supportive
ribavirin (experimental)

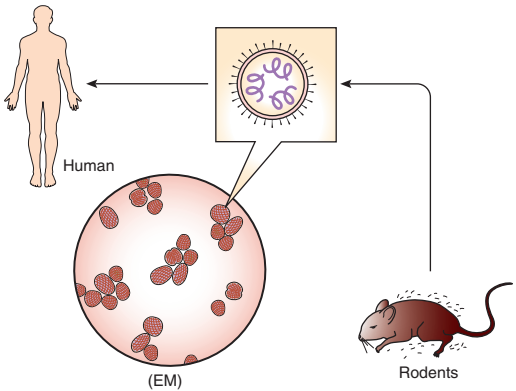
QUICK FACTS

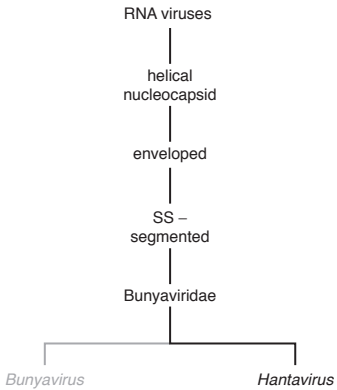
High risk of infection in Midwest forests.
Another *Bunyaviridae*, *Bunyaviridae phlebovirus*, causes fever:
Rift Valley Fever (in sub-Saharan Africa)—spread by mosquito, can be fatal
Sandfly Fever (in Asia, South America)—spread by sandfly, "3-day fever" with quick resolution

Study Tip

Arboviruses
(arthropod-borne virus):

- Togaviridae
  - WEE
  - EEE
  - VEE
- Flaviviridae
  - West Nile virus
  - Yellow fever
  - Dengue fever
  - St. Louis encephalitis
  - Japanese encephalitis
- Bunyaviridae
  - California encephalitis
  - Rift Valley fever
  - Sandfly fever





CLINICAL CASE

A recent college graduate has been camping in Arizona in a wooded area heavily populated with deer mice. He cuts his vacation short, however, when he develops a fever and begins vomiting. By the time he reports to the hospital 3 days later, he is hypotensive, cyanotic, and tachypneic. Fearing shock, emergency physicians begin to administer fluids but stop this treatment when chest X-rays reveal interstitial pulmonary edema. The patient develops respiratory failure within 24 hours and dies by the second day of hospitalization. A diagnosis is confirmed by IgM serum assay and a lung biopsy.

CLINICAL PRESENTATION

Hantavirus Respiratory Syndrome

PATHOBIOLOGY

rodent hosts chronically shed virus in feces/urine → airborne transmission to humans → viremia → prodrome of flu-like symptoms followed by pulmonary capillary leakage → interstitial pulmonary edema → respiratory failure (Hantavirus Respiratory Syndrome) → high mortality within ~10 days

DIAGNOSIS

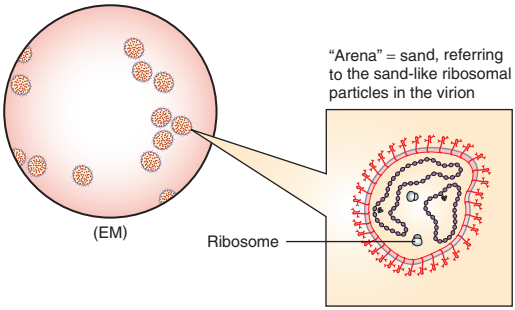
PCR from lung biopsy
IgM antibody in serum

TREATMENT

supportive

QUICK FACTS

Unlike other *Bunyaviridae*, hantavirus is an example of a robovirus (rodent-borne virus), as opposed to an arbovirus (arthropod-borne virus).
Hantavirus respiratory syndrome was first discovered in 1993, following a fatal outbreak in the southwest U.S.
Hantaan virus, a serotype of Hantavirus, causes Korean Hemorrhagic Fever (acute renal failure + fever).
Human metapneumovirus (hMPV), also in the genus *Paramyxoviridae*, is very similar to RSV in structure and function. It is a common respiratory pathogen.



RNA viruses
helical nucleocapsid
enveloped
SS – segmented
Arenaviridae
Arenavirus

CLINICAL CASE

A 34-year-old woman, during a visit to Nigeria, develops a fever over the course of the fifth week of her visit. The fever progresses to headache, nausea, and diarrhea. By the time she arrives at a hospital, her physician notes signs of pericardial effusion. Furthermore, a diarrhea sample contains blood indicating GI hemorrhage. The physician is quite familiar with the symptoms in that region of Nigeria. He explains that she likely contracted her illness from rodents or from someone who had come into close contact with rodents. The woman is required to remain hospitalized because she is considered contagious.

CLINICAL PRESENTATION

hemorrhagic fever

PATHOBIOLOGY

reservoir in rodents → spread to humans by contamination of food or water with animal excretions → can further spread person-to-person → viremia → gradual onset of hemorrhagic fever → internal bleeding at GI tract and other organs → hemorrhagic shock, high mortality

DIAGNOSIS

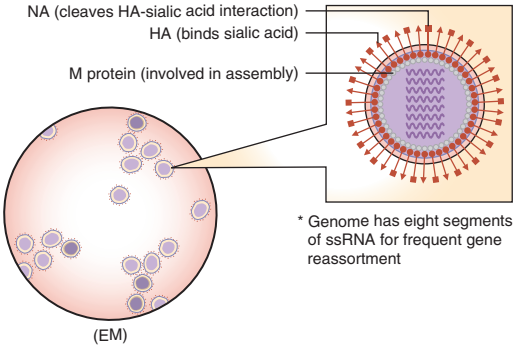
detection of virus
serology

TREATMENT

ribavirin
serum from convalescent individuals (severe cases)
prevention: rodent control

QUICK FACTS

The Lassa virus is a BL4 pathogen and requires maximum precautions when handled.
First identified in 1969 in Lassa, Nigeria, and endemic to central West Africa.
Another arenavirus transmitted from rodents, Lymphocytic Choriomeningitis Virus (LCMV), is a rare cause of aseptic meningitis.



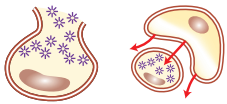
RNA viruses
↓
helical nucleocapsid
↓
enveloped
↓
SS – segmented
↓
Orthomyxoviridae
↓
Influenza virus A, B, C

CLINICAL CASE

A child presents with altered mental status and seizures. During the exam, the doctor notes epistaxis, gum bleeding, and right lower quadrant pain. Further questioning reveals that 3 weeks ago, the child had general weakness, myalgias, fever, and a cough. His mother had similar flu-like symptoms a week before and treated both herself and her child with aspirin. The doctor suspects that the child's serious symptoms would have been prevented had the mother given Tylenol instead of aspirin to her child. Liver function and blood tests are ordered immediately.

Orthomyxoviridae Influenzavirus A, B, C — *Influenza Virus, "The Flu"*

CLINICAL PRESENTATION



Flu (and *croup* in children)
secondary bacterial pneumonia

PATHOBIOLOGY

inhaled through aerosols → infects upper and lower respiratory tract ciliated epithelium via two surface proteins:
- hemagglutinin (HA) envelope protein binds sialic acid on cells → virus endocytosed
- neuroaminidase (NA) envelope protein cleaves HA–sialic acid interaction to permit viral spread

replicates in and lyses cells → necrosis of epithelium → epithelial intracellular contents exposed and stimulate inflammation → macrophages produce fever via IL-1, lymphocytes produce myalgia via IFN-γ → vasodilation and edema in:
- nose → rhinorrhea
- pharynx, larynx → swelling obstructs flow through sinuses and eustachian tubes → croup in children with secondary sinusitis and otitis
- trachea/bronchi → inflammatory mucus cleared by ciliated cells → cough

viral shedding resolves after 2–5 days → IgA secretory immunity against viral HA and NA
if infection persists → ciliary columnar epithelial cells damaged → cannot perform normal task of clearing bacteria → secondary bacterial pneumonia

Study Tip

Causes of common cold:
- Rhinovirus
- Coronavirus
- Adenovirus
- Influenza C virus
- Coxsackievirus

DIAGNOSIS

symptoms
rapid antigen test on nasopharyngeal swab
can culture nasopharyngeal sample and detect HA via RBC agglutination test

TREATMENT

supportive: acetaminophen, hydration, rest
amantadine or rimantadine for treatment and prophylaxis of Influenza A; zanamivir and oseltamivir are neuraminidase inhibitors used for treatment of influenza A and B
Vaccines: inactivated (with HA and NA antigens from Influenza A and B) live, attenuated

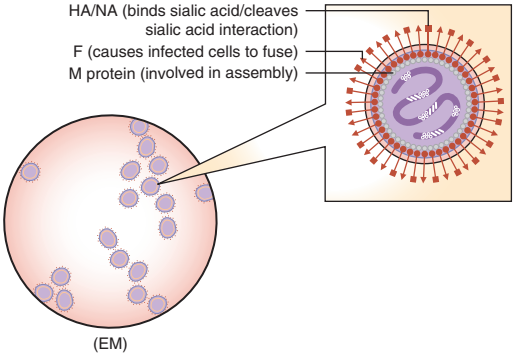
QUICK FACTS

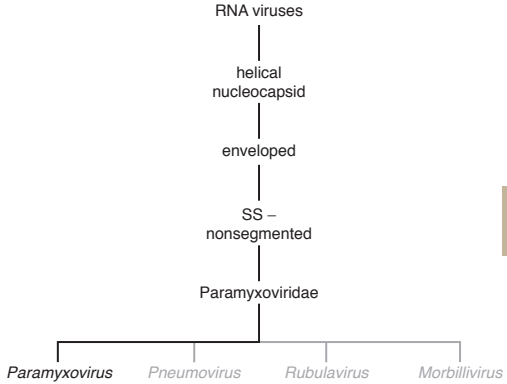
HA and NA undergo antigenic variation, allowing new outbreaks resistant to previous vaccinations:
antigenic shifts (~ every 20 years)—exchange of RNA segments between human and animal viruses → radically new HA or NA acquired → pandemics
antigenic drifts (every year)—spontaneous mutations → slightly altered HA or NA → endemic infections

The 2009 "swine flu" pandemic was caused by the H1N1 subtype of influenza A and contained genes from human, pig, and avian influenza viruses. Most commonly reported symptoms include fever, cough, headache, sore throat, vomiting, and diarrhea. A vaccine is available, and zanamivir or oseltamivir can be given for treatment and prophylaxis.

Influenza B and influenza C differ from influenza A in the following:
- less virulent, with influenza C infections often asymptomatic
- no animal reservoir → no antigenic shifts
- unresponsive to amantadine or rimantadine.

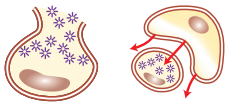
Reye's syndrome (liver damage, encephalomyelitis): associated with aspirin treatment for influenza in children.





CLINICAL CASE

A father brings his baby girl to the EW in the middle of the night. Before leaving the house, the girl had a high fever, nasal discharge, and barking cough. Now, however, the barking cough seems to have disappeared. The doctor on call realizes that the cool night air probably relieved the child's symptoms before she arrived at the hospital. Because no inspiratory stridor is noted on physical exam, the doctor sees no need to give the girl corticosteroids and assures the father that the illness will go away in a few days.



CLINICAL PRESENTATION

children:
- *croup (laryngotracheobronchitis)*
- *pneumonia*

adults:
- *common cold*

PATHOBIOLOGY

inhaled through aerosols → infects larynx mucosa via two surface proteins:
- hemagglutinin (HA) envelope protein binds sialic acid on cells → virus endocytosed
- neuroaminidase (NA) envelope protein cleaves HA–sialic acid interaction to permit viral spread

infection progresses downward to tracheal and bronchial epithelium → inflammation and swelling of mucous membranes → narrowing of lumen → obstruction of inspiration (inspiratory stridor) and expiration (barking cough) → croup

may invade lower respiratory tract → pneumonia

DIAGNOSIS

symptoms
detection of virus: hemagglutination activity in respiratory secretions
serology (anti-HA antibodies inhibit hemagglutination)

TREATMENT

supportive (cool mist; oxygen in severe cases)
corticosteroids

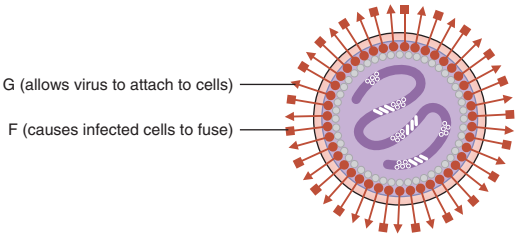
QUICK FACTS

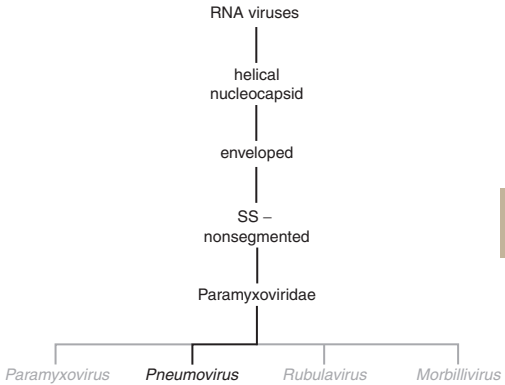
In contrast to croup in children, upper respiratory tract infections in adults present as bad colds.
Viral fusion (F) surface proteins, common to all *Paramyxoviridae*, cause infected cells to form multinucleate giant cells.
Parainfluenza viruses 1 and 3 belong to genus *Paramyxovirus*; parainfluenza viruses 2 and 4 belong to genus *Rubulavirus*.

Study Tip

Most common causes of pneumonia in young children:

RSV
Parainfluenza virus

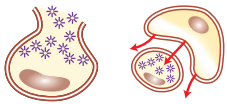




CLINICAL CASE

An infant girl who was hospitalized and released for a previous illness returns to the hospital 2 days later with fever, cough, and wheezing. The parents, both asthmatic, think their child is now developing asthma. A CXR reveals hyperinflated lungs with infiltrates. The doctor is convinced that this is a nosocomial viral infection, as many other children admitted to the hospital develop the same symptoms. He transfers the baby to the neonatal intensive care unit, where she is treated with aerosolized ribavirin.

CLINICAL PRESENTATION



children:
- *bronchiolitis*
- *pneumonia*

adults:
- *common cold*

PATHOBIOLOGY

discharged in nasal secretions → transmitted easily by hand-to-hand contact or aerosol → attaches to bronchiolar and alveoli epithelium via protein G on viral envelope → lower respiratory tract infection → necrosis and inflammation of:
- bronchioles → mucous obstruction of airway → bronchiolitis, wheezing
- alveoli → pneumonia

recurrent infection builds IgA immunity against further infection

DIAGNOSIS

detection of virus in respiratory secretions
serology

TREATMENT

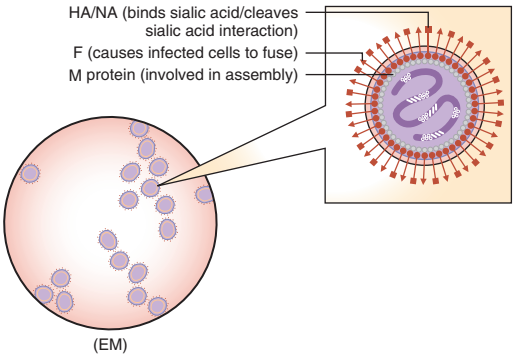
supportive
albuterol, aerosolized ribavirin (severe cases)
Synagis (F antigen vaccine) to prevent infection in high-risk infants (e.g., premature, lung disease, heart disease)

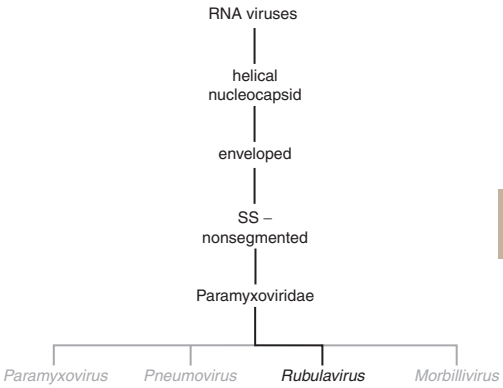
Study Tip

Most common causes of pneumonia in young children:
- RSV
- Parainfluenza virus

QUICK FACTS

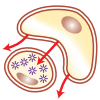
This virus is named respiratory syncytial virus because viral fusion (F) surface proteins cause infected cells to fuse and form syncytia.
RSV is the major respiratory pathogen in young children, infecting virtually everyone by age 3. Infections in adults are milder.
Worldwide outbreaks of RSV occur every winter, unlike outbreaks of other cold viruses, which occur every few years.
Asthma and RSV bronchiolitis both present with wheezing, but the mechanisms of disease probably differ: whereas asthma involves smooth muscle constriction, RSV bronchiolitis can occur before smooth muscle has formed in the bronchioles (at age 2–8 months).
Human metapnuemovirus (hMPV), also in the genus *Paramynoviridae*, is very similar to RSV in structure and function. It is a common respiratory pathogen.





CLINICAL CASE

A 16-year-old male requests the private attention of a doctor for testicular pain. He explains that his left testis became tender and enlarged yesterday. A few days before, he recalls suffering from a mild fever and muscle aches. The doctor also recognizes a remarkable swelling of both parotid glands, and the teenager reveals swallowing difficulties. The doctor confirms a diagnosis after seeing the teenager's vaccination records and receiving lab reports that show elevated serum amylase.



CLINICAL PRESENTATION

parotitis
orchitis
pancreatitis
aseptic meningitis

PATHOBIOLOGY

transmitted by respiratory droplets → attaches and invades upper respiratory tract epithelium via viral hemagglutinin envelope proteins → viremia → 2- to 3-week incubation period → infection of glandular tissues (parotid gland, testes) → inflammatory infiltration and edema → painful enlargement of glands
virus may spread to meninges → aseptic meningitis

lifelong immunity after one infection

DIAGNOSIS

symptoms
detection of virus in saliva, urine, CSF, serum
serology

TREATMENT

supportive: analgesics, compression of parotid
vaccine: live-attenuated rubella virus in measles–mumps–rubella (MMR) vaccine

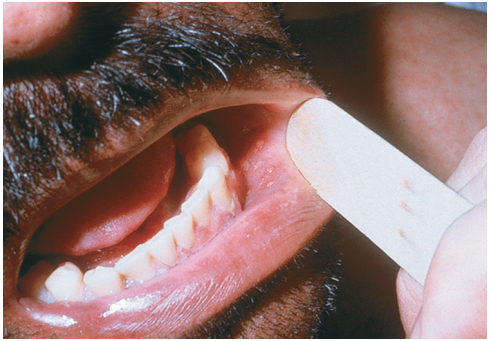
QUICK FACTS

Rarely, orchitis affects both testes, leading to sterility.
A mumps skin-antigen test is used to demonstrate functional cell-mediated immunity.
Viral fusion (F) surface proteins, common to all *Paramyxoviridae*, cause infected cells to form multinucleate giant cells.
MMR is the only live viral vaccine that can be given to HIV-positive individuals.

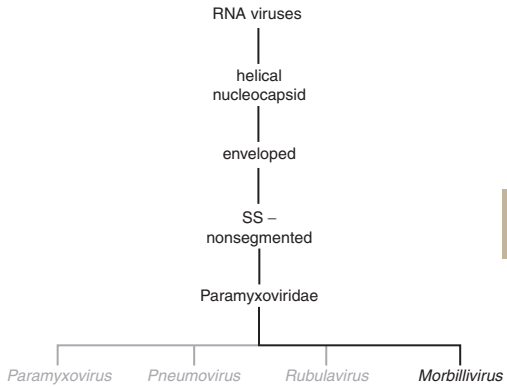
Study Tip

Most common causes of aseptic meningitis:

Coxsackievirus
Echovirus
Mumps virus



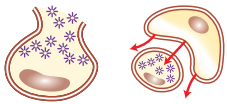
Koplik's spots



CLINICAL CASE

An 11-month-old who attends day care presents with rashes that blanch upon pressing as well as fever, conjunctivitis, and runny nose. The rashes have spread from the hairline to the trunk and then to extremities over time and have become bright red and raised. Now, the rash is already starting to disappear in the same sequence it appeared. While the symptoms resolve over a week, the doctor wonders whether the child will ever have neurological problems from a latent recurring infection, and whether other children in the day care will have the same illness. To contain the illness, the doctor urges the mother to keep the child away from others for at least a few weeks. He also writes a note to the day care center reminding them that all children ages 12–15 months should receive a vaccination for this illness.

CLINICAL PRESENTATION



flu-like symptoms
Koplik's spots, followed by rash
encephalitis
complications: *SSPE (Subacute Sclerosing Panencephalitis)*

PATHOBIOLOGY

spread between humans via respiratory aerosol droplets → infects, replicates within, lyses respiratory epithelial cells → 1° viremia → infects and replicates in reticuloendothelial cells → 2° viremia → spread to:

- mucosa → promotes inflammation around capillaries → in the mouth, Koplik's spots (red lesions with a blue-white center) form
- dermis → promotes inflammation around capillaries → rash forms starting at head and progressing to feet, disappearing in the order it appears
- respiratory tract, lung → giant cells form with inclusion bodies (Warthin-Finkeldey cells) → cell damage leads to cough, rhinorrhea
- brain → meningitis, encephalitis

if infected with a variant of measles virus → over years, chronic low-level infection of CNS → inflammatory lesions of brain → gradually presents as personality and cognitive changes (subacute sclerosing panencephalitis or SSPE) → death

DIAGNOSIS

isolate virus from nasopharyngeal secretions, blood, and urine
Warthin-Finkeldey cells (multinucleated giant cells with inclusion bodies in nucleus and cytoplasm, pathopneumonic for measles) in respiratory secretions
serology

TREATMENT

vaccine: live-attenuated measles virus in measles–mumps–rubella (MMR) vaccine
severe cases in infants: high doses of vitamin A

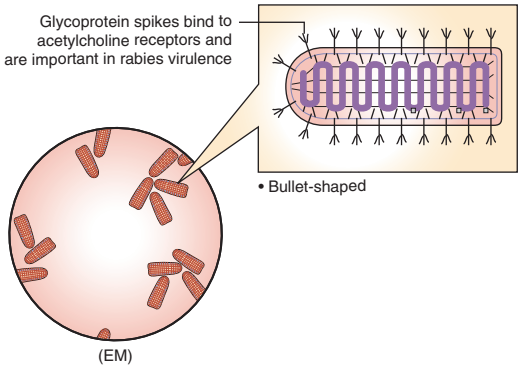
QUICK FACTS

Measles is one of the most transmissible viral infections.
Killed virus vaccine is no longer used because it promotes a hypersensitivity reaction on subsequent exposure to the virus (atypical measles syndrome).
Pneumonia, secondary to respiratory tract cell infection, is the most common reason for measles hospitalization.
MMR is the only live viral vaccine that can be given to HIV-positive individuals.

Study Tip

Five most common pediatric diseases with rash:

- Measles (measles virus)
- Rubella (rubella virus)
- Scarlet fever (*S. pyogenes*)
- Roseola (HHV 6)
- Erythema infectiosum (Parvovirus B19)



RNA viruses
helical nucleocapsid
enveloped
SS – nonsegmented
Rhabdoviridae
Lyssavirus

CLINICAL CASE

A graduate student, while vacationing in India, is bitten by a wild dog. Because he is not near a hospital and because he is eager to continue his trip, he washes his wound thoroughly with water and continues on. When he returns to the U.S. a few months later, the student is admitted to the university hospital complaining of pain on swallowing, increased muscle tone, and hallucinations. He appears agitated, confused, and sensitive to bright light. A neurological exam reveals cranial nerve dysfunction and upper motor neuron problems. Despite intensive supportive measures, the patient falls into a coma and soon dies.

CLINICAL PRESENTATION

dysphagia, encephalitis

PATHOBIOLOGY

infects many mammalian species, including dogs → transfers to humans via animal bite → localizes to bite site for days to months → binds to acetylcholine receptors and enters peripheral nerves → travels proximally to CNS (distance determines incubation time) → infects neurons of brainstem and brain → cytoplasmic inclusions (Negri bodies) form → cell necrosis → cranial nerve palsies and encephalitis → dysphagia, agitation, and seizures → coma → death

DIAGNOSIS

identify Negri bodies in neurons and other infected cells
PCR for viral RNA
serology

TREATMENT

wash wound immediately
HRIG (Human Rabies Immune Globulin) antibodies for passive immunity
Human Diploid Cell Vaccine: live-attenuated virus (often administered following bite)
prevention: immunize domesticated (dogs, cats) and wild (skunks, foxes, bats, wolves, coyotes, raccoons) animals

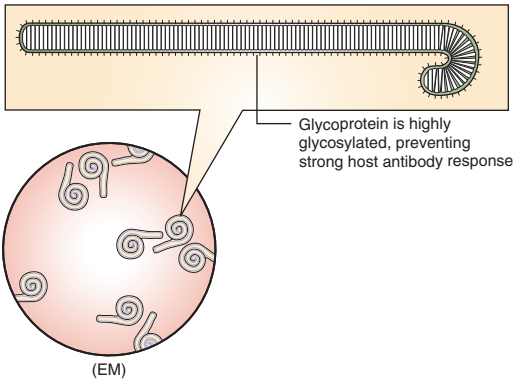
QUICK FACTS

The human rabies vaccine is the only vaccine administered after viral exposure and works by boosting the immune system during the long viral incubation period.

"Foaming of the mouth" is a classic sign of rabies. It reflects an inability to clear saliva because of painful spasms of pharyngeal muscles on swallowing. As a result, patients avoid drinking (hydrophobia).

Rabies virus multiplies in the CNS and travels via axons to many different organs (especially the well-innervated submaxillary gland).

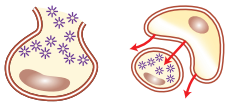
Rabies causes a few deaths at most in the U.S. per year but causes many more in countries with unvaccinated animals (e.g., tens of thousands of deaths by dog bites in India each year).



RNA viruses
helical nucleocapsid
enveloped
SS – nonsegmented
Filoviridae
Filovirus

CLINICAL CASE

An anthropologist is brought to the emergency room one evening for high fever, vomiting, headache, confusion, and bloody diarrhea. He explains that he had cut an expedition in Zaire short and returned to the U.S. when he developed the high fever. Physical exam is remarkable for a 40°C fever, slight hypotension, a nonpruritic rash on the neck and arms, and a nosebleed. Upon reviewing the history, the ER physicians order an immediate hospital quarantine of the anthropologist and his family. They then investigate his exact itinerary in Zaire and all his close contacts in the past 3 weeks. The next day, the patient dies with disseminated intravascular coagulation.



CLINICAL PRESENTATION

hemorrhagic fever

PATHOBIOLOGY

reservoir in monkeys (Marburg) or unknown (Ebola) → transferred to humans by direct contact (e.g., bites, infected bodily fluids) → incubation period of 3–9 days → viremia with fever, flu-like symptoms → viral infection of almost all organs including brain, liver, and heart → focal necrosis and hemorrhagic manifestations (especially of GI, renal systems) → shock, multiorgan failure → high mortality 1–2 weeks after onset of symptoms

transmission to other humans via bodily fluids

DIAGNOSIS

detection of virus
serology

TREATMENT

none developed
future: serum from survivors

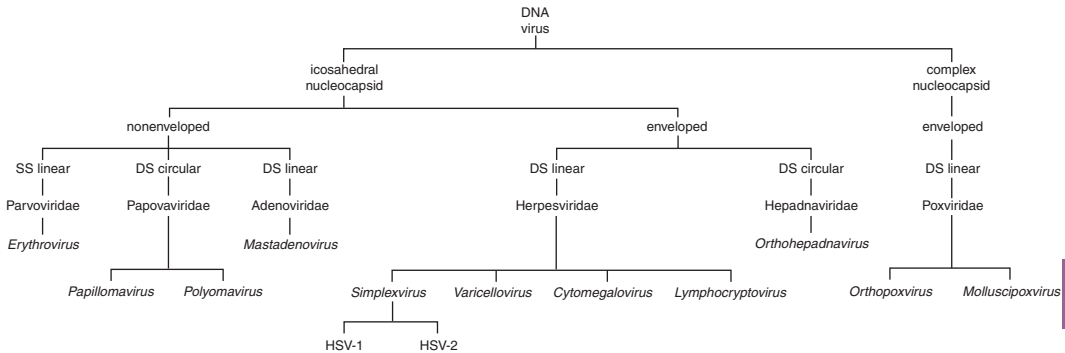
QUICK FACTS

Most outbreaks of Ebola have originated in sub-Saharan Africa.

Marburg virus is named after a 1967 outbreak in Marburg, Germany. The virus was spread to scientists from sub-Saharan monkeys.

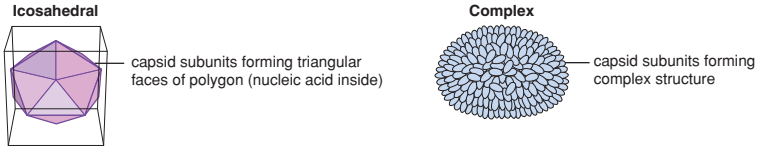
The Ebola virus and Marburg virus are BL4 pathogens and require maximum precautions when handled.

DNA Viruses

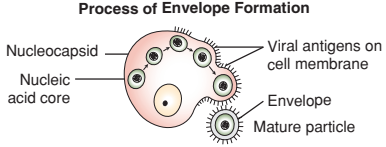

DNA virus
icosahedral nucleocapsid
complex nucleocapsid
nonenveloped
enveloped
enveloped
SS linear
DS circular
DS linear
DS linear
DS circular
DS linear
Parvoviridae
Papovaviridae
Adenoviridae
Herpesviridae
Hepadnaviridae
Poxviridae
Erythrovirus
Mastadenovirus
Orthohepadnavirus
Papillomavirus
Polyomavirus
Simplexvirus
Varicellovirus
Cytomegalovirus
Lymphocryptovirus
Orthopoxvirus
Molluscipoxvirus
HSV-1
HSV-2

DNA Viruses

Icosahedral vs. Complex Nucleocapsid

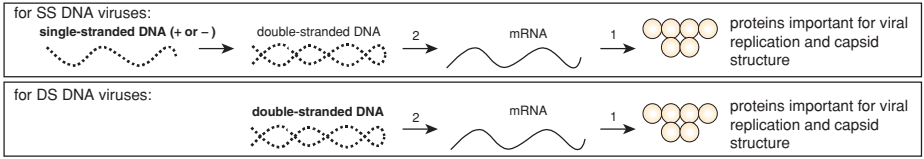


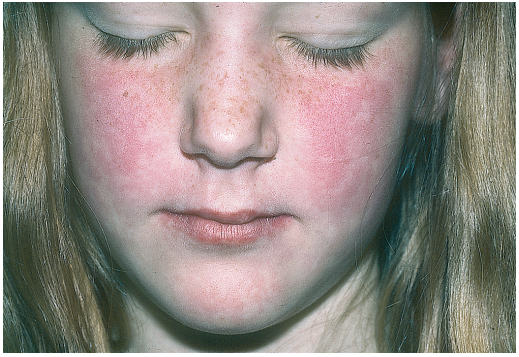
Enveloped vs. Nonenveloped



envelope renders virus susceptible to anything capable of destroying lipids, i.e., bile acids

Single-Stranded (SS) vs. Double-Stranded (DS) DNA



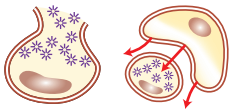


Erythema infectiosum: “slapped-cheek” rash

DNA viruses
↓
icosahedral nucleocapsid
↓
nonenveloped
↓
SS linear
↓
Parvoviridae
↓
Erythrovirus

CLINICAL CASE

An African American girl with sickle cell anemia visits the doctor after developing weakness, fatigue, and pallor. She tells her physician that several days before, she felt a fever, headache, and muscle aching. She also began to feel joint pain and developed a rash that had a “slapped-face” appearance on her face. A blood test reveals severe anemia, as well as a decline in neutrophils and lymphocytes. The myeloid lineage seems normal. Serology confirms the diagnosis, and the doctor orders a transfusion of erythrocytes to prevent life-threatening anemia.



CLINICAL PRESENTATION

erythema infectiosum ("fifth disease")
transient aplastic anemia crisis

PATHOBIOLOGY

inoculates nasal cavity → 6-day incubation → viremia and fever → virus infects and lyses erythroid precursor cells in the bone marrow → mildly reduced reticulocytes, lymphocytes, neutrophils, platelets (normal hosts can tolerate lack of erythropoiesis for 1 week)
immune complexes form and deposit → erythema infectiosum: rash with "slapped-cheek" appearance, arthralgias for several days
in patients requiring increased erythropoiesis (e.g., sickle cell anemia, thalassemias) → transient aplastic crisis: severe reticulocytopenia, normal myeloid lineage

DIAGNOSIS

detect viral DNA
serology

TREATMENT

supportive: RBC transfusion
in immunodeficient patients: Ig transfer

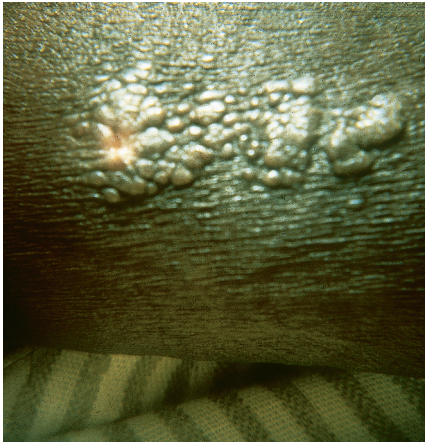
QUICK FACTS

In immunodeficient patients, parvovirus infection can lead to chronic severe anemia.
Fetuses, who require higher RBC production and are immunodeficient, are especially vulnerable to parvovirus infections. Infected fetuses may develop severe anemia and hydrops fetalis.
Erythema infectiosum is called "fifth disease" because it is one of the five most common pediatric diseases with rash.

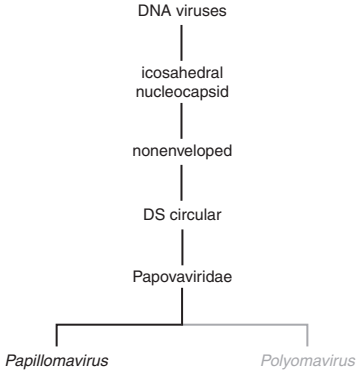
Study Tip

Five most common pediatric diseases with rash:

- Measles (measles virus)
- Rubella (rubella virus)
- Scarlet fever (*S. pyogenes*)
- Roseola (HHV 6)
- Erythema infectiosum (parvovirus B19)



Condyloma acuminatum warts

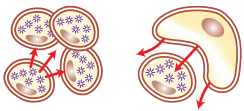


CLINICAL CASE

A 22-year-old sexually active man complains of warts on his penis. He does not report pain, but he is concerned that he might be spreading them to his female sexual partner. The doctor, diagnosing the warts as condyloma acuminata, treats the patient by ablating the warts. He also decides to test the sexual partner, fearing that if she contracted the patient's illness, she would be at increased risk for cervical cancer.

Papovaviridae Papillomavirus — *Human Papilloma Viruses (HPV)*

CLINICAL PRESENTATION



Acute: *warts* (on penis, vulva, cervix, fingers, hands, soles, knees, elbows, oropharynx, larynx)
Chronic: *asymptomatic; carcinomas (cervical carcinoma, squamous cell carcinoma, laryngeal carcinoma)*

PATHOBIOLOGY

transmitted by close contact → virus infects squamous epithelial cells in epidermis or mucous membranes →

- Lysogenic cycle: infects basal cells → attempts to replicate → basal cell environment disfavors viral replication → virus can transform basal cells via E6 (blocks p53) and E7 (blocks Rb) viral proteins → benign cell growth and vacuolization (warts)
- Lytic cycle: infects upper keratinized epithelium or progresses with basal cell as it rises/differentiates → keratinized cell environment favors viral replication → replicates DNA, assembles → vacuolizes cytoplasm → lyses cell, viral particles released for further infection

infection controlled by cell-mediated immunity

DIAGNOSIS

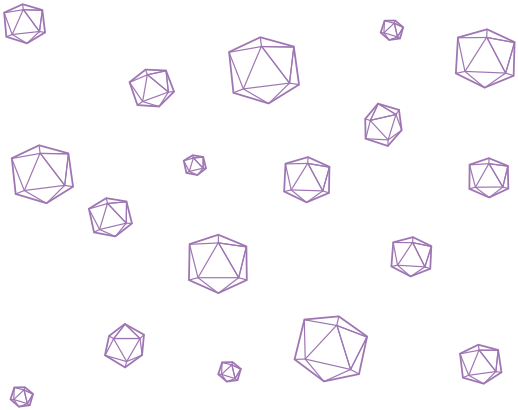
1% acetic acid turns lesions white
colposcopy + biopsy of white lesions
PCR using viral specific primers

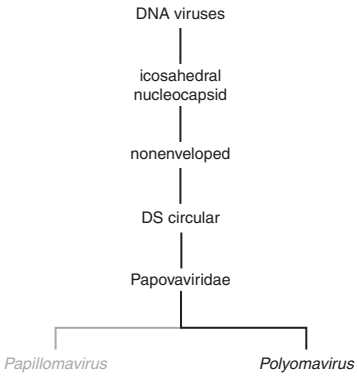
TREATMENT

50% of warts spontaneously regress in 1–2 years
ablation
HPV vaccine available to prevent cervical cancer. Gardasil protects against HPV 6, 11, 16, and 18. Cervarix protects against HPV 16 and 18.

QUICK FACTS

HPV virus 16 and 18 cause genital warts that can progress to cervical carcinoma.
Warts in the larynx (which can be acquired by infants vaginally borne to mothers with genital warts) cause airway swelling, hoarseness, and secondary bacterial pneumonia.
Epidermodysplasia verruciformis presents as many flat warts on the skin, which may progress to squamous cell carcinomas.
HPV is a very parsimonious virus, using host machinery for most of its replicative functions. It also codes for proteins in all three reading frames of a single DNA strand.
Papanicolaou testing ("Pap smears") has been effective in detecting dysplastic HPV-infected cells before they transform into neoplastic cells.
Papovaviridae is derived from *PA*pillomaviruses, *PO*lyomaviruses, and *VA*cuolating viruses.





CLINICAL CASE

A middle-aged man, diagnosed with AIDS, presents to the EW complaining of "seeing double." Physicians perform a complete neurological examination and further discover problems in talking, coordinating movements, and remembering things. Imaging of the brain reveals deep densities localized to the white matter that span the frontal, parietal, and temporal lobes. The doctors make an infectious disease diagnosis and discuss how to best tell the patient about his very grave prognosis.

Papovaviridae Polyomavirus — JC Virus

CLINICAL PRESENTATION

Progressive Multifocal Leukoencephalopathy (PML)

PATHOBIOLOGY

virus infects children → produces a mild illness, which is contained by host immune response → virus becomes latent in CNS

immunocompromise (AIDS, chemotherapy) allows latent virus to activate → infects myelinating oligodendrocytes in white matter throughout CNS → demyelination → impairs coordination, speech, memory (PML)

DIAGNOSIS

symptoms
imaging
detection in CNS biopsy

TREATMENT

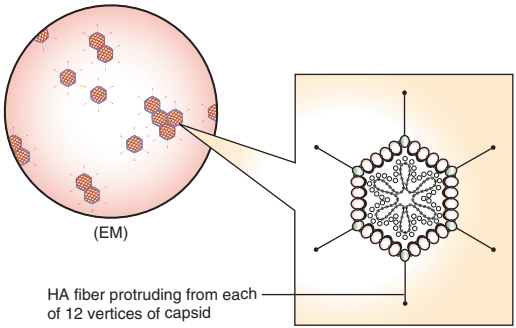
no treatment available

QUICK FACTS

Papovaviridae is derived from *PA*pillomaviruses, *PO*lyomaviruses, and *VA*cuolating viruses.

Another polyomavirus, BK virus, causes mild infections in children and was first isolated from the urine of an immunosuppressed kidney transplant patient.

Worldwide, most people carry anti-JC virus antibodies by age 14 and anti-BK virus antibodies by age 5.



DNA viruses
icosahedral nucleocapsid
nonenveloped
DS linear
Adenoviridae
Mastadenovirus

CLINICAL CASE

A mother brings her 4-year-old child to the doctor because of a swollen, red right eye. She is frustrated, complaining that the symptoms appeared after she had taken her child to a local ophthalmologist. The doctor diagnoses conjunctivitis. Later that evening, the doctor learns that many other children have presented with similar symptoms after appointments with the same ophthalmologist.

CLINICAL PRESENTATION

respiratory tract infection
conjunctivitis
hemorrhagic cystitis
gastroenteritis

PATHOBIOLOGY

spread by aerosol, fecal–oral route, or direct contact → binds via hemagglutinin → enters and lyses mucosal cells of:

- upper respiratory tract → rhinitis, sore throat → may progress to lower respiratory tract → atypical pneumonia
- conjunctiva → conjunctivitis
- bladder → hemorrhagic cystitis → hematuria, dysuria
- gastrointestinal tract in young children→ gastroenteritis with non-bloody diarrhea

DIAGNOSIS

serology
isolation of virus in cell culture

TREATMENT

vaccine: live viruses of specific serotypes (only used in the military)

QUICK FACTS

Adenovirus is so named because latent viruses often remain in the tonsillar adenoids following infection.
There are over 40 serotypes of adenoviruses, each associated with specific sites of infection and diseases.
Live virus vaccines confer immunity without illness by being administered away from their primary site of infection (e.g., oral route for vaccine to respiratory serotypes).
Adenovirus, as well as retrovirus and herpesvirus, are potential vectors for gene therapy.

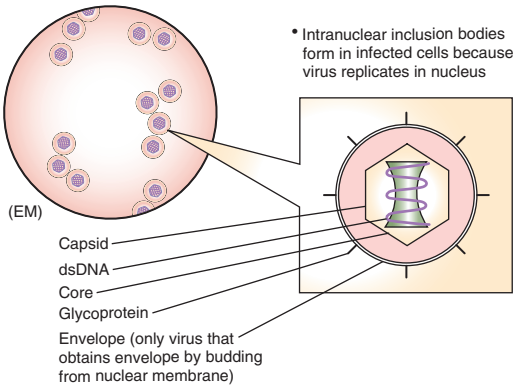
Study Tip

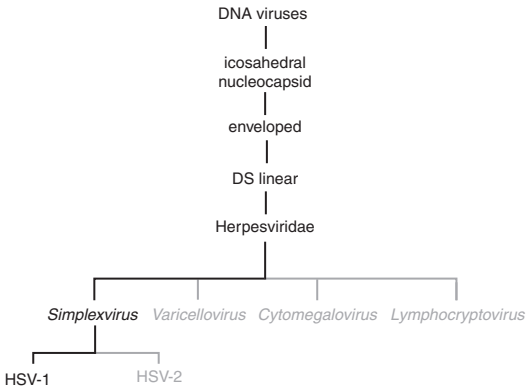
Causes of common cold:

Rhinovirus
Coronavirus
Adenovirus
Influenza C virus
Coxsackievirus

Most common causes of conjunctivitis:

1. *H. influenza*
2. Adenovirus
3. *S. pneumoniae*





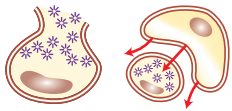
CLINICAL CASE

A 55-year-old man is hospitalized for a recent onset of high fever, headaches, and sporadic sensations of smelling sausages. Physical exam reveals neck stiffness, prompting the physician to perform a lumbar puncture. CSF values indicate elevated lymphocytes, elevated protein, and normal glucose. A CT image confirms encephalitis localized to the temporal lobes. A diagnosis is confirmed by PCR of the CSF. The physician begins treatment with acyclovir and informs the patient that he may suffer permanent neurological abnormalities from the infection.

Herpesviridae Simplexvirus — *Herpes Simplex Virus 1 (HSV-1) or Herpesvirus 1*

CLINICAL PRESENTATION

gingivostomatitis
keratoconjunctivitis
herpes labialis (cold sores)
temporal lobe encephalitis



PATHOBIOLOGY

only human reservoir → transmitted via saliva → virus invades mucous membranes → local primary infection → typically asymptomatic but can cause vesicular lesions that ulcerate in:
- mouth → gingivostomatitis
- eye → keratoconjunctivitis (on cornea, typically presents as branching "dendritic ulcer")

primary infection resolves after 2–3 weeks → virus enters local sensory nerve endings → axonal transport proximally to sensory ganglion cell bodies → latent infection of trigeminal ganglion or other sensory ganglia

stress (fever, menstruation, sunlight) → viral reactivation → axonal transport of virus from ganglia to nerve endings → recurrent local infection → may result in herpetic labialis (cold sores around mouth), gingivostomatitis, or keratoconjunctivitis

rarely, virus may spread via cranial nerves to brain → focal necrotic lesions in temporal lobe → inflammation → encephalitis → permanent neurological abnormalities or death

DIAGNOSIS

detection of virus (PCR, especially for early detection in encephalitis)
multinucleate giant cells on Tzanck smear of skin lesions
eosinophilic Cowdry intranuclear inclusion bodies on skin biopsy

TREATMENT

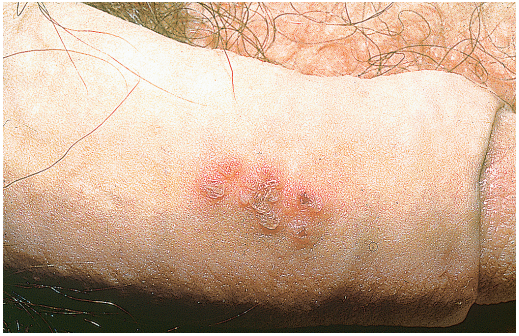
acyclovir
trifluridine (topical, for eye infections)

QUICK FACTS

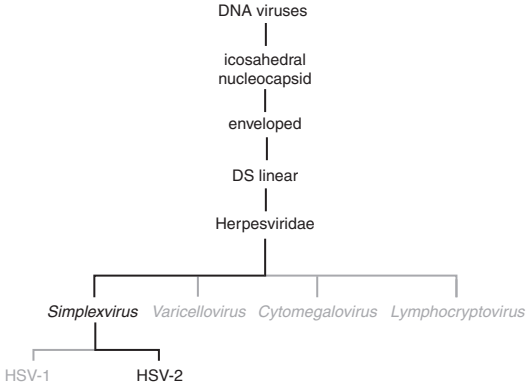
Herpesviruses are the most common cause of sporadic encephalitis in the U.S.: HSV-1 in adults, HSV-2 in neonates.
Most adults have been infected by HSV-1 or -2, but very few infections are symptomatic and only 25% of latent infections exhibit recurrent infections.
Herpetic whitlow is a painful hand vesicle that can occur in health care workers who come in contact with herpetic lesions.
Recurrent keratoconjunctivitis is a common cause of blindness in the U.S.

Study Tip

Typically,
HSV-1 infects ABOVE the waist: eye and mouth lesions
HSV-2 infects BELOW the waist: genital lesions
(oral-genital sex can lead to HSV-1 below and HSV-2 above)



Herpes simplex genitalis



CLINICAL CASE

At a preterm evaluation, a 31-year-old pregnant mother reports pain on urination and a burning, itching sensation in the genital area. A careful exam of her vagina reveals a vesicular rash. The physician confirms a diagnosis with a Tzanck smear of the lesions showing multinucleate giant cells with intranuclear inclusion bodies. The mother is administered acyclovir with assurances that the infection will likely resolve, but she is informed that should the infection persist, her child will have to be delivered by cesarean section.

Herpesviridae Simplexvirus — *Herpes Simplex Virus 2 (HSV-2) or Herpesvirus 2*

CLINICAL PRESENTATION

genital herpes
neonatal herpes

PATHOBIOLOGY

only human reservoir → transmission by sexual contact → virus invades mucous membranes → local primary infection → typically asymptomatic but can cause vesicular lesions in genital/perianal area
primary infection resolves after 2–3 weeks → virus enters local sensory nerve endings → axonal transport proximally to sensory ganglion cell bodies → latent infection of lumbosacral ganglia
stress (fever, menstruation, sunlight) → viral reactivation → axonal transport of virus from ganglia to nerve endings → milder, recurrent vesicular infection at primary site
if pregnant mother is infected: virus may transfer to fetus through placenta or during delivery → child infected → congenital defects, abortion, or neonatal encephalitis

DIAGNOSIS

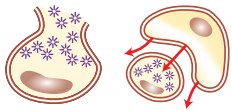
detection of virus
multinucleate giant cells on Tzanck smear of skin lesions
eosinophilic Cowdry intranuclear inclusion bodies on skin biopsy

TREATMENT

acyclovir
prevention: cesarean section in infected mothers

QUICK FACTS

Herpesviruses are the most common cause of sporadic encephalitis in the U.S.: HSV-1 in adults, HSV-2 in neonates.
Most adults have been infected by HSV-1 or -2 and reactivation is common, but not all infections are symptomatic.
Herpetic whitlow is a painful hand vesicle that can occur in health care workers who come in contact with herpetic lesions.

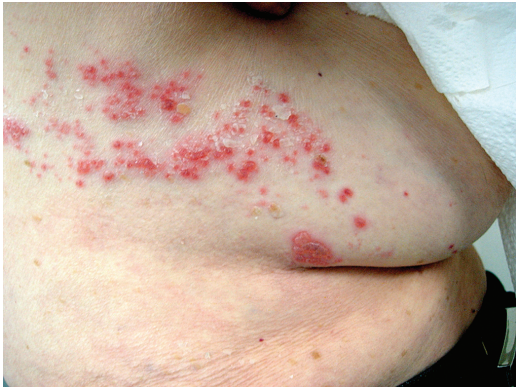


Study Tip

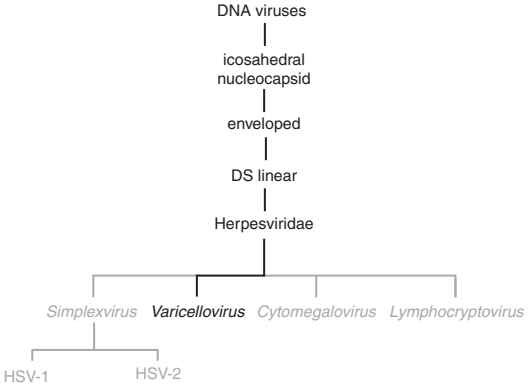
Typically,
HSV-1 infects ABOVE the waist: eye and mouth lesions
HSV-2 infects BELOW the waist: genital lesions
(oral-genital sex can lead to HSV-1 below and HSV-2 above)

Organisms that cross placenta and therefore allow infection to pass from pregnant mother to fetus (TORCHES):

TOxoplasmosis
Rubella
Cytomegalovirus
HErpes, HIV
Syphilis



Herpes zoster



CLINICAL CASE

A 72-year-old woman complains to her doctor of a burning, painful rash on her chest. A physical exam reveals fever and a vesicular, erythematous rash limited to the right side of her chest and overlapping the dermatomal area of T7–T8. The physician confirms a diagnosis by a Tzanck smear of the lesions showing multinucleate giant cells with intranuclear inclusion bodies. The physician administers acyclovir and explains that though the rash will likely ameliorate, the regional pain might persist longer.

Herpesviridae Varicellovirus — *Varicella-Zoster Virus (VZV) or Herpesvirus 3*

CLINICAL PRESENTATION

varicella (chickenpox)
zoster (shingles)

PATHOBIOLOGY

highly contagious from respiratory secretions or ruptured varicella vesicles → virus infects respiratory tract → 2-week incubation period → viremia → flu-like symptoms and widespread vesicles with red base appearing as "dew on a rose petal" (varicella) → rash spreads centrifugally → mild in children, severe and may progress to pneumonia or encephalitis in adults

varicella resolves within 2 weeks → virus enters local sensory nerve endings → axonal transport proximally to sensory ganglion cell bodies → latent infection of dorsal root ganglion

stress or immune-compromise → viral reactivation → axonal transport of virus from ganglia to nerve endings → recurrent painful vesicular rash over sensory dermatome (zoster)

DIAGNOSIS

detection of virus
multinucleate giant cells on Tzanck smear of skin lesions
eosinophilic Cowdry intranuclear inclusion bodies on skin biopsy

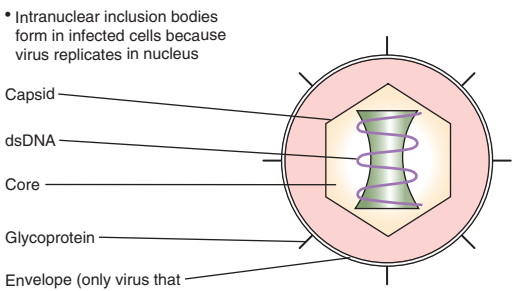
TREATMENT

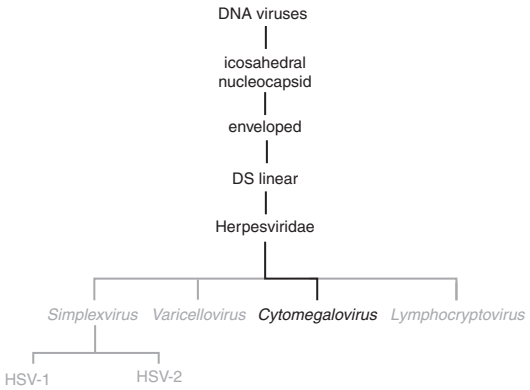
supportive
acyclovir, famciclovir (severe)
anti-VZV immunoglobulin (for immunocompromised)
vaccine: attenuated VZV

QUICK FACTS

The VZV vaccine is controversial for two reasons: (1) immunity may wane, allowing more serious adult varicella infections; (2) a latent state from prior infection is not eliminated, so zoster can still occur.

Reye's syndrome (liver damage, encephalomyelitis): associated with aspirin treatment for chickenpox in children.





CLINICAL CASE

A 34-year-old kidney transplant patient currently on immunosuppressants complains of shortness of breath and coughing. Physical exam reveals fever and abnormal lung sounds while chest X-ray indicates interstitial infiltrates in the lungs. No cysts are detected on silver stain of bronchoalveolar lavage fluid, ruling out *Pneumocystis jirovecii* infection. The doctor makes a diagnosis after viewing a sample of the patient's lung tissue, which shows abnormal giant cells with "owl's eye" intranuclear inclusions.

Herpesviridae Cytomegalovirus — *Cytomegalovirus (CMV) or Herpesvirus 5*

CLINICAL PRESENTATION

cytomegalic inclusion disease (newborns)
heterophil-negative mononucleosis
immunocompromised: *retinitis, pneumonia, esophagitis*

PATHOBIOLOGY

transmitted by close contact (blood, breast milk, saliva, semen), organ transplantation, or transplacentally → can infect a diverse array of cells → replicates within cells and eventually kills them, causing:
- cytomegalic inclusion disease: deafness, hepatosplenomegaly, microencephaly in newborns
- mononucleosis: flu-like symptoms, abnormal lymphocytes

infection contained by host immune response → virus remains latent in leukocytes → reactivates when host becomes immunocompromised, causing:
- retinitis (especially in AIDS patients)
- pneumonia (especially in transplant patients)
- esophagitis

DIAGNOSIS

giant cells with "owl's eye" intranuclear inclusion bodies found in tissues/urine
serology (negative monospot test as compared to EBV mononucleosis)
detection in buffy coat culture (CMV infects WBCs)

TREATMENT

ganciclovir (NOT acyclovir, because no viral thymidine kinase is made)
foscarnet

QUICK FACTS

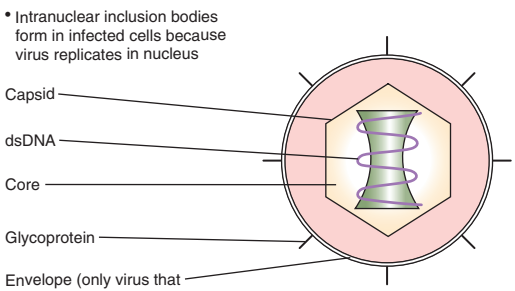
The giant cells, or "cytomegalo" cells, that form during infection give CMV its name.
Most adults have been infected but show few symptoms because their normal immune response limits the infection.
Other viruses that infect lymphocytes are human herpesvirus 6 and 7 (HHV 6, HHV 7). They infect B and T cells causing *roseola* (fever and rash on trunk) in infants.

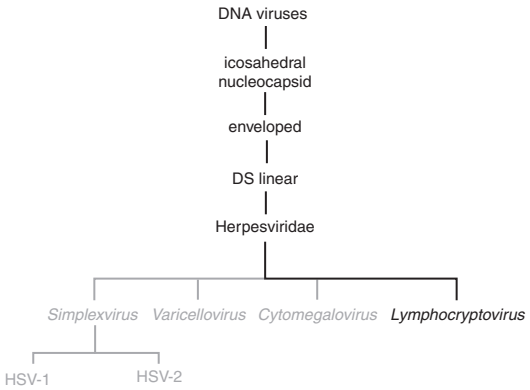
Study Tip

CMV is the most common viral cause of mental retardation in the U.S.

Organisms that cross placenta and therefore allow infection to pass from pregnant mother to fetus (TORCHES):

TOxoplasmosis
Rubella
Cytomegalovirus
HErpes, HIV
Syphilis

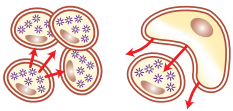




CLINICAL CASE

A 20-year-old female college student reports to the medical center complaining of "the flu." She reports fever, night sweats, a very painful sore throat, and headaches. She thought she could endure the illness, but she became frustrated after feeling "so sleepy all the time." Physical exam reveals enlarged lymph nodes and a slight splenomegaly. Results from a blood smear later that day reveal lymphocytosis with about 20% lymphocytes having an abnormally large nucleus and vacuolated cytoplasm. The student is assured that the illness will spontaneously resolve within 2–3 weeks, but that she should avoid contact sports during that time. She is also told not to share drinks to prevent spread of the illness.

Herpesviridae Lymphocryptovirus — *Epstein-Barr Virus (EBV) or Herpesvirus 4*



CLINICAL PRESENTATION

infectious mononucleosis ("kissing disease")
lymphoid organ-related cancers: Burkitt's lymphoma, nasopharyngeal cancer (in East Asians)

PATHOBIOLOGY

transmitted by saliva, respiratory secretions (e.g., kissing) → infects oropharynx epithelium → viremia → virus binds to and infects B cells via C3d complement receptor → virus remains latent in B cells as episomal DNA → infected B cells are transformed and multiply → immune response to infected cells → lymph nodes, spleen enlarge with flu-like symptoms, and painful pharyngitis (mononucleosis)
immune response controls infected B-cell proliferation → mononucleosis resolves
if immune system is compromised → uncontrolled B-cell proliferation → unrepaired mutations accumulate → may increase chances for neoplasms (e.g., Burkitt's lymphoma)

DIAGNOSIS

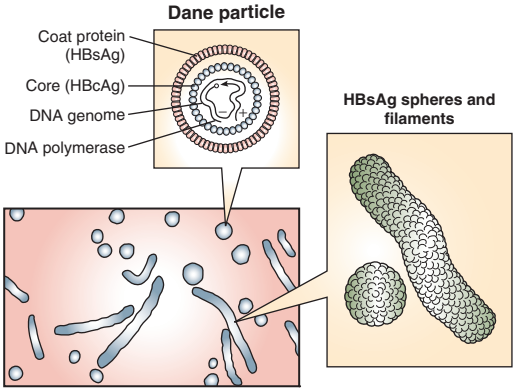
monospot test: detects heterophil antibody (nonspecific antibody that agglutinates sheep RBCs)
blood smear: atypical lymphocytes (cytotoxic T lymphocytes that react against infected B cells)
serology: anti-EBV IgM (acute infection), IgG (past infection)

TREATMENT

acyclovir (severe cases)

QUICK FACTS

Patients with infectious mononucleosis are at risk for splenic rupture secondary to splenomegaly and should avoid contact sports.
A rash occurs in few cases of mononucleosis; however, if ampicillin is given to treat tonsillitis (before viral etiology is known), rash occurs in most cases.
Similar to chickenpox and polio illnesses, EBV infections are more severe in higher socioeconomic classes that have better sanitation and thus are infected later in life.

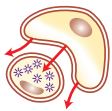


DNA viruses
↓
icosahedral nucleocapsid
↓
enveloped
↓
DS circular
↓
Hepadnaviridae
↓
Orthohepadnavirus

CLINICAL CASE

A middle-aged immigrant from China presents with right upper quadrant pain and a "full stomach" despite a recent history of weight loss. He remembers having bouts of "turning yellow" since childhood and recalls many in his family—including his mother—having similar experiences. Immunization records are unavailable, and lab values show elevated ALT levels and alpha-fetoprotein levels. Further imaging reveals the presence of hepatocellular carcinoma.

CLINICAL PRESENTATION



acute hepatitis: jaundice, fever
chronic hepatitis: carrier state (asymptomatic); cirrhosis; predisposes to hepatocellular carcinoma

PATHOBIOLOGY

transmitted through blood, sexual contact, or transplacentally → travels in blood to hepatocytes → infects cells and replicates by:
completing the partially dsDNA viral genome via viral DNA polymerase → now complete dsDNA generates mRNA transcripts → mRNA produces viral proteins → mRNA is also used to make partially dsDNA by RNA-dependent DNA polymerase → partially dsDNA is packaged and particle buds through cell membrane
viral antigens on infected hepatocytes recognized by host immune response → CTL activated → inflammation, hepatocyte necrosis → acute hepatitis
if virus infects host with weak immune response (e.g., infants) → infected hepatocytes are not cleared → virus persists in carrier state → chronic inflammation of hepatocytes → cirrhosis, increased risk of hepatocellular carcinoma

DIAGNOSIS

detection of HBsAg (see graph, card 9)
abnormal liver function tests

TREATMENT

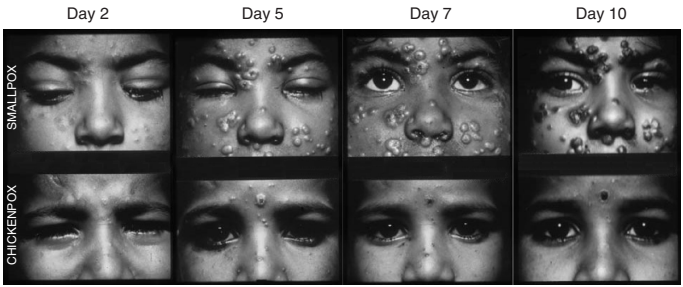
α-Interferon or pegylated α-interferon (but carrier state will persist)
lamivudine
vaccine: recombinant HBsAg
Hepatitis B Immune Globulin (HBIG): contains anti-HBsAg antibodies

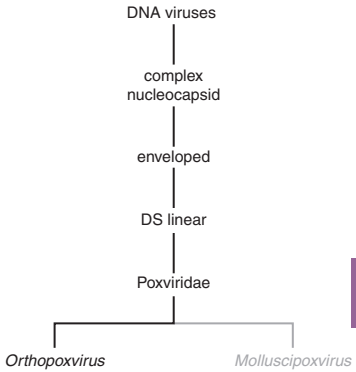
QUICK FACTS

HBV is a common cause of fulminant hepatitis; a severe acute hepatitis that damages the liver.
If a medical student is stuck with a needle exposed to hepatitis-positive blood, the student should receive both "active" (vaccine) and "passive" (immune globulin) treatment.
Infants of HBsAg1 mothers are given HBIG immediately after birth, followed by Hepatitis B vaccination.
Unlike non-enveloped viruses (e.g., HAV) that can survive outside a host, HBV and other enveloped viruses are vulnerable and spread only by close contacts between hosts.
Strength of immune response determines clinical course of infection: A strong response produces a severe course that resolves quickly, whereas a weak response produces a mild but chronic course.

Study Tip

HBV, HCV, and HDV have:
Blood transmission
Chronic carrier state
Cirrhosis
Hepatocellular carcinoma

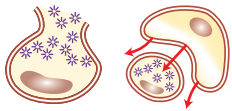




CLINICAL CASE

A physician interested in medical history comes across a narrative recorded in Africa about a group of patients plagued by "vesicles all over their bodies." The vesicles are described as "oozing" and "viscous," causing body surfaces to stick together. Even more dramatic, the story describes how the disease started with a few but soon engulfed an entire village. Little more than supportive care could be offered to these patients, most of who soon died.

Poxviridae Orthopoxvirus — *Smallpox (Variola) Virus*



CLINICAL PRESENTATION

rash (beginning as macules, evolving to vesicles)

PATHOBIOLOGY

inhaled via aerosols → infects upper respiratory epithelium → penetrates mucosa and enters bloodstream → 1° viremia → infects and multiplies within internal organs → large number of virions released into bloodstream → 2° viremia → virus spreads throughout the body, giving focal infections in skin, lungs, intestines, kidneys, brain

when skin is infected: viral particles collect and replicate in epidermis → collections form macules, first in the head and later in the extremities → virus replicates and generates host immune response → macules become pus-filled vesicles → crusts form in 2–3 weeks → infectious particles are released

DIAGNOSIS

(past) detection in vesicular fluid

TREATMENT

vaccines:

- cowpox virus (antigenically similar but benign virus), discovered by Edward Jenner and used in the U.S. and Europe beginning in the 1800s
- vaccinia virus (live-attenuated virus), used in developing countries during the World Health Organization's 1967 successful campaign to eradicate smallpox

(because the virus has been eradicated, vaccinations are now only given to those in the military)

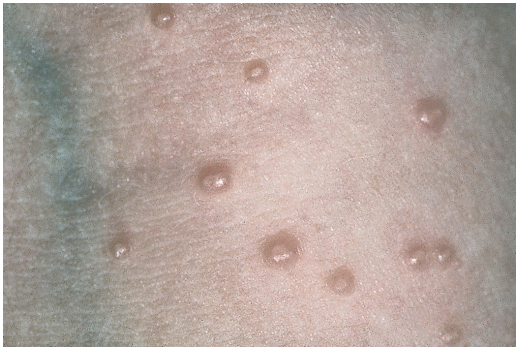
QUICK FACTS

Vaccinia virus may someday serve as a vaccine for many different pathogens, with strains now engineered to carry antigens of various other viruses and bacteria.

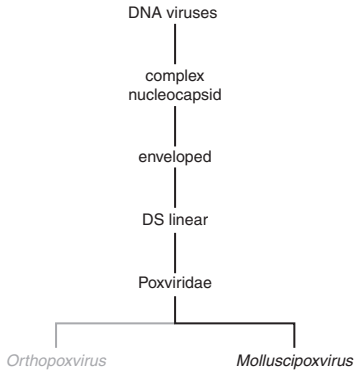
The last case of smallpox was reported in Somalia in 1977; now, only a few vials of the virus exist, including some secured by the U.S. government.

The World Health Organization's eradication effort worked because:
(1) only one smallpox serotype existed; (2) no smallpox carrier state existed; (3) no animal reservoirs of the virus existed.

Another *Poxviridae* causes molluscum contagiosum, small pink skin tumors with a central dimple often on trunk and anogenital regions. It is most often seen in AIDS patients.



Molluscum contagiosum



CLINICAL CASE

A 5-year-old boy is brought to the pediatrician's office for "bumps on his arm." His mother reports that a classmate had similar skin lesions 2 months earlier. The pediatrician notes flesh-colored, pearly nodes with central craters. She reassures the family that the child does not have chickenpox and recommends they cover the lesions to prevent scratching and spread to others.

CLINICAL PRESENTATION

pearly skin papules/nodules

PATHOBIOLOGY

Virus transmitted by casual contact → infects epidermal cells → large eosinophilic inclusion bodies form containing virus particles (molluscum bodies) → molluscum bodies enlarge infected cells, forming dome-like structure → eventual rupture of cells forming central crater

DIAGNOSIS

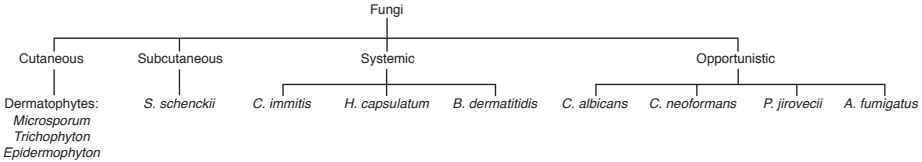
Clinical presentation (non-painful domes with dimpled center)
Skin biopsy (molluscum bodies in epidermal layer, limited inflammation)

TREATMENT

Self-resolves in 6–12 months
Surgically remove lesions (cryotherapy, laser treatment)

QUICK FACTS

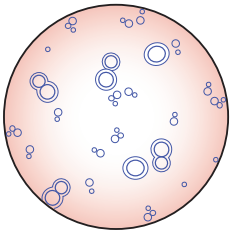
Autoinoculation, in which virus from one lesion spreads to other parts of the body via scratching, is common in children.
Immunosuppressed individuals may have multiple, large lesions that do not resolve spontaneously.
Unlike varicella or HSV infections, MCV infection is limited to the epidermis and does not establish a dormant state.


Fungi
Cutaneous
Subcutaneous
Systemic
Opportunistic
Dermatophytes:
Microsporum
Trichophyton
Epidermophyton
S. schenckii
C. immitis
H. capsulatum
B. dermatitidis
C. albicans
C. neoformans
P. jirovecii
A. fumigatus

Fungi

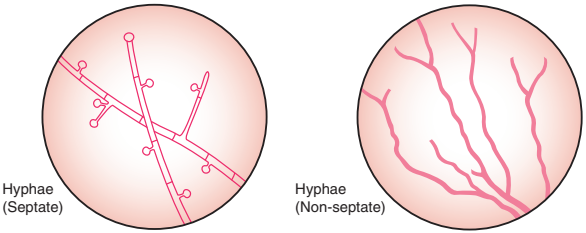
Fungi exist as two life forms, Yeast and/or Molds:

YEAST



- Unicellular
- Reproduce by budding
- Can form pseudohyphae (long chains of cells formed by incomplete budding)

MOLDS



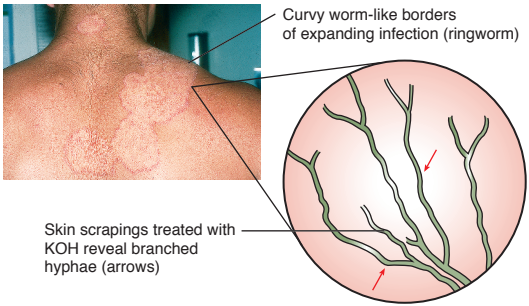
- Multicellular
- Grow as hyphae (elongated tubes of cells attached end-to-end
- Septate hyphae have membranes separating individual cells
- Nonseptate hyphae lack separating membranes and exist as multinucleate cells

Many fungi can assume either life form depending on the growing temperature. Important dimorphic fungi include *C. immitis, H. capsulatum, B. dermatitidis,* and *S. schenkii.* Fungi have cell membranes containing ergosterol (vs. cholesterol found in human cells).

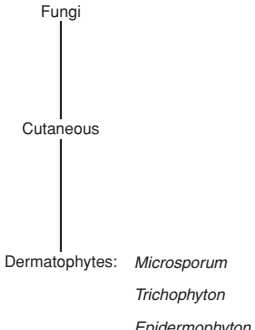
As a result, anti-fungals target ergosterol synthesis and function:

- Ketoconazole inhibits ergosterol synthesis
- Amphotericin B and Nystatin bind to ergosterol and bore holes through the cell membrane

Fungi cell walls contain chitin (vs. peptidoglycans in bacteria). Hence, antibiotics designed to inhibit peptidoglycan synthesis do not affect fungi.



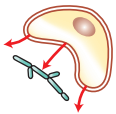
Tinea corporis



CLINICAL CASE

The star high school football player of a small town presents to the local clinic with itchiness between his toes, as well as itchiness and pustules on his index and middle fingers. Skin scrapings from the patient's feet reveal branched hyphae. However, analysis of the pustular fluid shows no such organisms. The nurse prescribes topical ointment to be applied to the toes, and within a few weeks, both the toe and finger itchiness resolve.

Microsporum, Trichophyton, Epidermophyton — *Ringworm (Tinea) Infections*



CLINICAL PRESENTATION

Dermatophytoses:
- jock itch (tinea cruris)
- athlete's foot (tinea pedis)
- scalp infection/alopecia (tinea capitis)
- nail infection (tinea unguium)
- body infection (tinea corporis)

PATHOBIOLOGY

spread by contact with infected individuals or animals → colonizes only keratinized epithelium (dead, horny layer) in warm and moist areas → infection expands centrifugally with curvy wormlike borders ("ringworm") → fungal antigens diffuse locally and trigger delayed-type hypersensitivity → dermatophytoses: inflammation, itching, scaly skin, pustules

fungal antigens (not fungus itself) can diffuse systemically → cause dermatophytid reactions: hypersensitivity responses (e.g., vesicles) at distant sites such as fingers

DIAGNOSIS

analyze skin scrapings: remove keratin with KOH, observe hyphae

Wood's lamp (UV) detects *Microsporum*

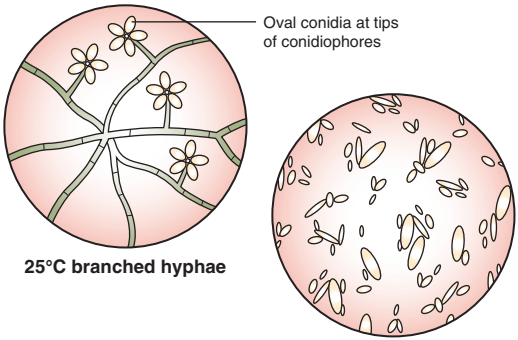
TREATMENT

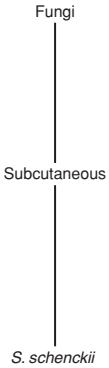
topical antifungal creams (for hair follicle and nail infections, need oral administration)

QUICK FACTS

Of the dermatophytoses, tinea capitis is most common in children, while tinea cruris and tinea pedis are most common in adults.

Other superficial skin fungal infections lead to local pigment changes. They are caused by *Malassezia furfur* (pityriasis versicolor) and *Cladosporium werneckii* (tinea nigra).

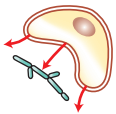




CLINICAL CASE

A man presents with small raised ulcerations extending proximally from his left index finger. The physician learns that the patient enjoys gardening as a hobby. Upon further questioning, the patient reports that he only started using gloves 3 months ago, following a painful thorn prick received while weeding his rose garden. The doctor cultures a nodule specimen and notices organisms shaped differently at different temperatures. Oral potassium iodide is considered as a treatment.

Sporothrix schenckii — *Sporotrichosis, Rose Gardener's Disease*



CLINICAL PRESENTATION

subcutaneous nodules

PATHOBIOLOGY

found on soil, plants → introduced subcutaneously by trauma (e.g., rose thorn prick) → slow local infection forms primary nodule → growing nodule becomes necrotic and ulcerates
secondary nodules form along lymphatic tracts draining primary infection → nodules grow, ulcerate → infection rarely extends beyond local lymphatic region

DIAGNOSIS

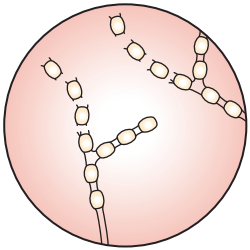
culture at different temperatures:
branched hyphae at 25°C
single cells at 37°C

TREATMENT

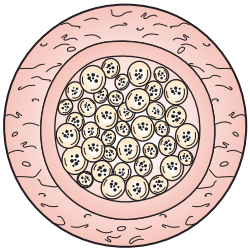
oral potassium iodide (mechanism unclear)
antifungals (for extracutaneous involvement): amphotericin B, itraconazole

QUICK FACTS

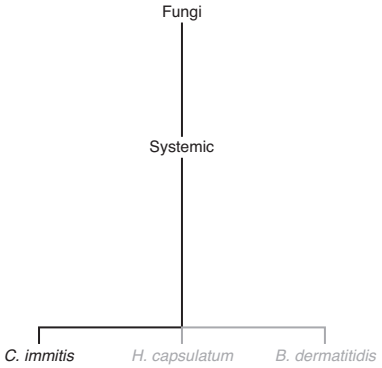
Chromoblastomycosis, another subcutaneous fungal infection, causes wartlike lesions. The responsible fungus grows in tropical climates as copper-colored cells.



25°C branched hyphae



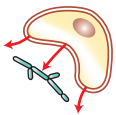
37°C spherule containing endospores



CLINICAL CASE

An old man and his great grandson visit Death Valley National Park in the deserts of Southern California. Upon returning from their visit, the man develops breathing difficulties along with arthralgias, periarticular swellings, and erythema nodosum. X-rays reveal a pneumonic infiltrate as well as granulomas. A diagnosis is confirmed by observing spherules containing individual endospores in tissue specimens. As expected, the child remains unaffected but several weeks later tests positive for a fungal antigen DTH reaction.

Coccidioides immitis — *Coccidioidomycosis, Desert Rheumatism, Valley Fever*



CLINICAL PRESENTATION

immunocompetent: *asymptomatic*
immunocompromised: *pneumonia, systemic infection*

PATHOBIOLOGY

arthrospores form in soil and are inhaled → at body temperature, arthrospores become spherules containing → infective endospores → local infection in lung
if immunocompromised:
- may invade surrounding tissue → pneumonia
- may spread systemically via bloodstream → granulomas form throughout the body (e.g., bones, nervous system)

DIAGNOSIS

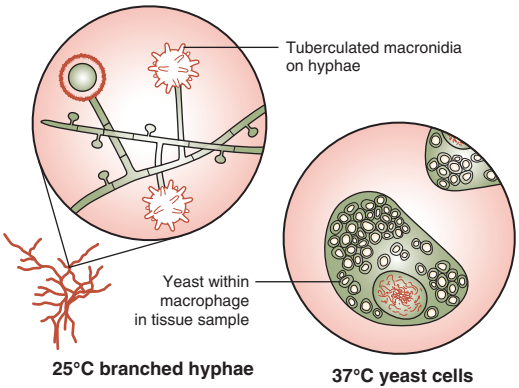
serology
culture at different temperatures:
branched hyphae at 25°C
single cells at 37°C
to detect previous exposure: intradermal injection of coccidioidin antigen causes DTH response

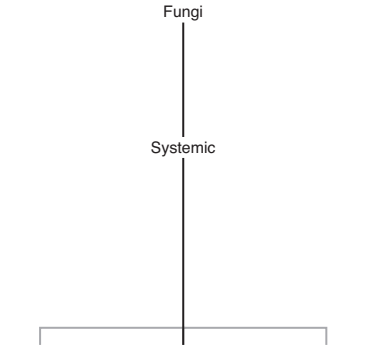
TREATMENT

supportive
antifungals (for systemic involvement): amphotericin B (if CNS not involved), fluconazole (if CNS involved)

Study Tip

Systemic mycoses are endemic to particular areas:
Coccidioidomycosis: Southwest U.S.
Histoplasmosis: Mississippi/Ohio River Valleys, Southeast U.S. river basins
Blastomycosis: east of Mississippi River, Central America

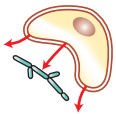




CLINICAL CASE

An elderly cave explorer in Ohio complains to his physician of weakness in the last few months. A physical exam reveals sores in his mouth, and X-ray shows small calcifications throughout the body. A lung biopsy reveals small budding cells within macrophages. Based on his age, location, and biopsy results, the physician begins the patient on oral amphotericin B.

Histoplasma capsulatum — Histoplasmosis



CLINICAL PRESENTATION

immunocompetent: *asymptomatic*
immunocompromised: *systemic infection*

PATHOBIOLOGY

spores from bird droppings are inhaled → macrophages phagocytose spores and carry systemically → inside macrophages, spores form budding yeast → yeast cause local infections throughout body → infection contained within epithelioid granulomas → granulomas appear as small calcium deposits on X-ray
in immunocompromised: local infections poorly contained → severe granulomatous disease throughout the body (especially adrenals, liver, spleen)

DIAGNOSIS

culture at different temperatures:
- branched hyphae at 25°C
- single cells at 37°C

tissue biopsy: yeast cells within macrophages
serology
to detect previous exposure: intradermal injection of histoplasmin antigen causes DTH response

TREATMENT

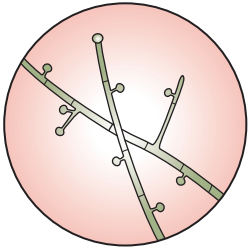
supportive
antifungals (for systemic involvement): amphotericin B, ketoconazole, itraconazole

QUICK FACTS

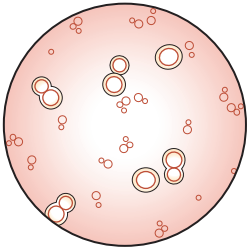
This fungus gets its name because it is found in histiocytes (macrophages); however, despite its name, it is not encapsulated.
Normal individuals can develop a mild pneumonia after prolonged exposure to bird droppings (e.g., chicken farmers).
Disseminated histoplasmosis is often a sign of AIDS in HIV-positive people; it is clinically similar to miliary tuberculosis.

Study Tip

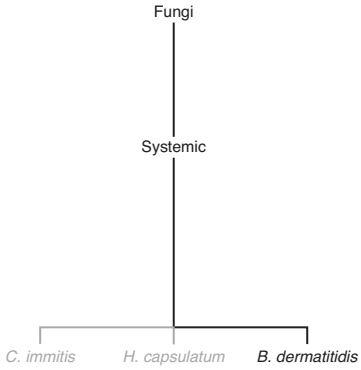
Systemic mycoses are endemic to particular areas:
- Coccidioidomycosis: Southwest U.S.
- Histoplasmosis: Mississippi/Ohio River Valleys, Southeast U.S. river basins
- Blastomycosis: east of Mississippi River, Central America



25°C hyphae with small conidia



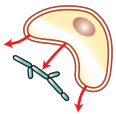
37°C thick-walled budding yeast



CLINICAL CASE

A man from Missouri develops weakness and night sweats. His physician notes sores on the patient's skin. Biopsy of the skin lesions reveals large budding yeast. The doctor informs the patient of his rare yet serious diagnosis and begins a course of antifungals, including amphotericin B.

Blastomyces dermatitidis — Blastomycosis



CLINICAL PRESENTATION

systemic infection
pneumonia

PATHOBIOLOGY

spores form in soil and are inhaled → at body temperature, spores become yeast → local lung infection → acute pneumonia (less common) or yeast spreads systemically over time → granulomas form throughout body → lesions in lungs, bones, skin (start as pimples, then become verrucous or ulcerative)

DIAGNOSIS

culture at different temperatures:
- branched hyphae at 25°C
- single cells at 37°C

tissue biopsy: large budding yeast

TREATMENT

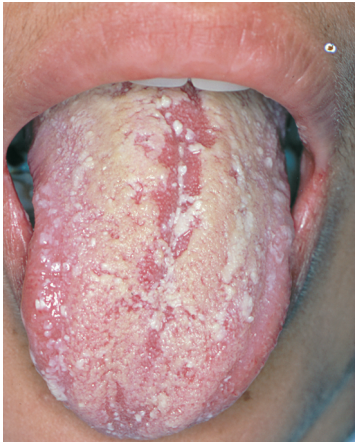
antifungals: itraconazole (for meningeal infection), amphotericin B (for nonmeningeal infection)

QUICK FACTS

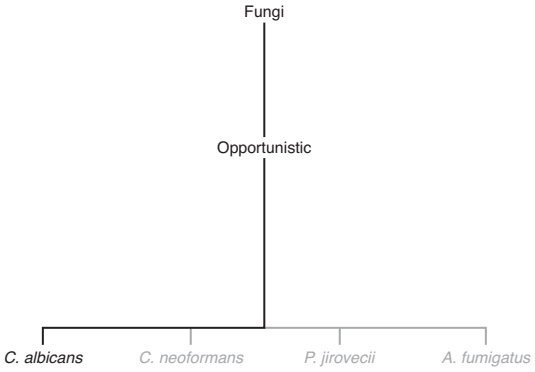
Systemic infection often occurs in the absence of lung disease.
Blastomycosis is the rarest yet most severe of the systemic fungal infections.
Paracoccidioidomycosis is a similar fungal infection endemic to Latin America. However, it is distinguished by yeast with multiple buds, and it affects males much more than females.

Study Tip

Systemic mycoses are endemic to particular areas:
- Coccidioidomycosis: Southwest U.S.
- Histoplasmosis: Mississippi/Ohio River Valleys, Southeast U.S. river basins
- Blastomycosis: east of Mississippi River, Central America



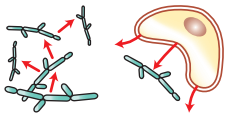
Oral candidiasis



CLINICAL CASE

Several months ago, a patient presented to a free clinic with a thick, white membrane covering the roof of his mouth. After a thorough social history, the doctor suspected a possible HIV infection. However, at the time, the patient refused testing and never returned for follow-ups. Now, the patient revisits the clinic complaining of painful swallowing and severe chest pains. The doctor immediately places the patient on fluconazole and makes arrangements for future treatments and tests.

Candida albicans — Candidiasis



CLINICAL PRESENTATION

normal host:
- *thrush*
- *vaginitis* (yeast infection)

immunocompromised host:
- *esophagitis*
- *systemic infection*

PATHOBIOLOGY

normal flora in mucous membranes of respiratory, GI, and female genital tracts → overgrowth may occur in warm, moist areas:
- mouth: oral thrush (white exudate on mucous membrane)
- female genitals: vaginitis (itching, copious secretion, "cottage cheese"-appearing clumps)
- cutaneous: skin under breasts, nails

if immunocompromised, infection persists chronically → infection may spread:
- from mouth to esophagus: esophagitis
- from local to systemic sites: disseminated candidiasis

DIAGNOSIS

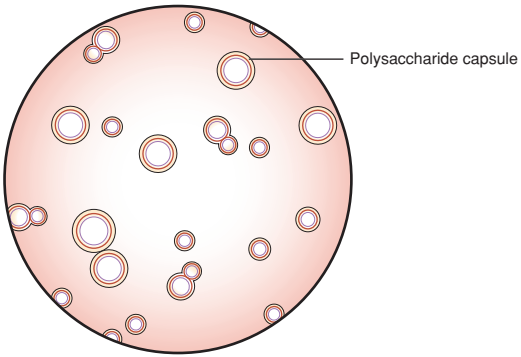
pseudohyphae and budding yeast observed in tissue scrapings
disseminated infection: + blood cultures (not normally found in blood)

TREATMENT

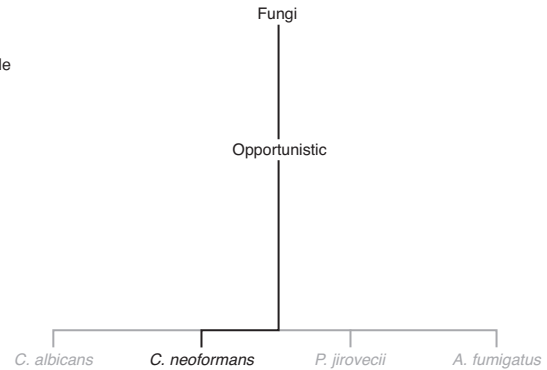
thrush/esophagitis: nystatin mouthwash, fluconazole
vaginitis: fluconazole, topical antifungal
systemic: antifungals (e.g., amphotericin B)

QUICK FACTS

Candidiasis is one of several causes of diaper rash in young children.
Esophagitis and disseminated candidiasis are major opportunistic infections in AIDS patients.



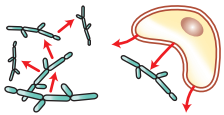
India ink preparation



CLINICAL CASE

An amateur bird keeper presents with headache and a stiff neck. Fearing some form of meningitis, the EW physician orders a CT scan. The image reveals well-circumscribed ringlike lesions in the brain. Subsequent CSF analysis from a lumbar puncture shows ↑ CSF pressure, ↑ protein, ↓ glucose, and encapsulated budding yeast with India ink stain. The patient is administered amphotericin B and flucytosine.

Cryptococcus neoformans — *Cryptococcosis*



CLINICAL PRESENTATION

meningitis
pneumonia

PATHOBIOLOGY

yeast found in pigeon droppings → yeast inhaled → local infection in lung → asymptomatic or pneumonia

yeast may spread via blood, especially to CNS → meningitis → abscess forms → damage results from pressure and displacement of brain tissue, not inflammation

DIAGNOSIS

CSF: elevated opening pressure, India ink stains budding yeast with polysaccharide capsule
CSF or serum cryptococcal antigen

TREATMENT

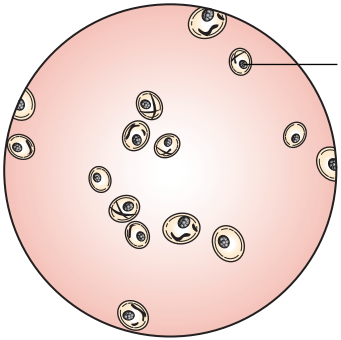
amphotericin B + flucytosine for meningitis
fluconazole for lifetime suppression in AIDS patients

QUICK FACTS

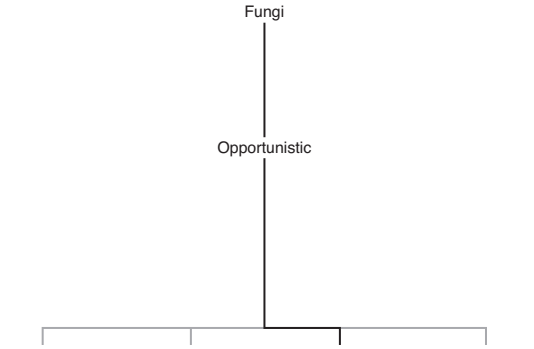
Cryptococcal meningitis is prevalent among AIDS patients; without lifelong treatment, they will relapse.

Study Tip

Most common cause of fungal meningitis.



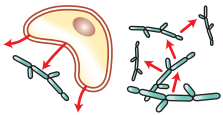
Cysts seen on silver stain



CLINICAL CASE

A homeless man arrives at the EW complaining of difficulty in breathing. His medical history is not obtainable, but the man does report increasing fatigue and weight loss over the past few months. Physical exam reveals lymphadenopathy, tachypnea, and bilateral rales in the lung bases. Chest X-ray shows diffuse infiltrates bilaterally. The doctor decides to perform a bronchial lavage and, with silver stain, reveals numerous cysts containing several dark oval bodies. The doctor begins the patient on TMP-SMX and orders an HIV and blood test.

Pneumocystis jirovecii PCP



CLINICAL PRESENTATION

Pneumocystis pneumonia (PCP)

PATHOBIOLOGY

cyst inhaled by most in childhood → asymptomatic or mild pneumonia → asymptomatic latent infection in lungs
in immunocompromised → uncontrolled growth → inflammatory response → pneumonia

DIAGNOSIS

silver stain of induced sputum, bronchoalveolar lavage, or lung biopsy: cysts containing dark oval bodies

TREATMENT

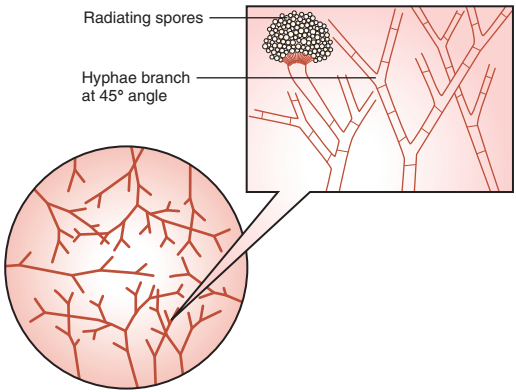
trimethoprim-sulfamethoxazole or pentamidine
prophylaxis (in immunocompromised): trimethoprim-sulfamethoxazole, aerosolized pentamidine, or dapsone

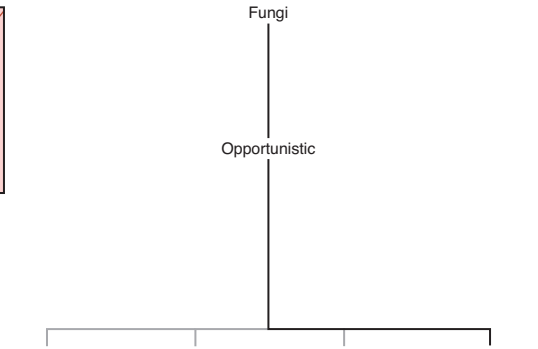
QUICK FACTS

Pneumocystis jirovecii was previously called *Pneumocystis carinii* and was changed to distinguish it from the species that infects rats.

PCP used to be the number one opportunistic infection in AIDS patients, but trimethoprim prophylaxis has limited this. Prophylaxis in AIDS patients is begun when the CD4+ T-cell count is <200.

Although once classified as a protozoan, *P. jirovecii* is most closely related to fungi by rRNA studies.

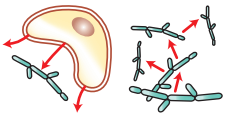




CLINICAL CASE

A woman undergoing chemotherapy for acute myeloid leukemia alarms her physician when she develops a fever, experiences chest pains, and coughs up blood. Chest X-ray shows pulmonary infiltrates, and subsequent biopsy reveals branched hyphae. The physician is quite concerned with the diagnosis and begins treating the patient with antifungals including amphotericin B.

Aspergillus fumigatus



CLINICAL PRESENTATION

allergic bronchopulmonary aspergillosis
aspergilloma
invasive aspergillosis

PATHOBIOLOGY

mold grows on decaying vegetation → spores inhaled → can:

- stimulate IgE response → bronchospasm, allergic bronchopulmonary aspergillosis
- deposit in lung cavity formed from previous tuberculosis or tumor → hyphae grow within cavity but do not invade → aspergillous ball (aspergilloma)
- invade lung tissue and bloodstream in immunocompromised host → occludes blood vessels → pulmonary infarction

DIAGNOSIS

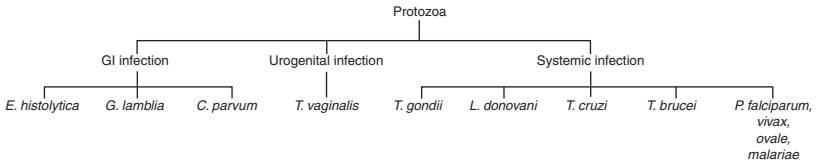
tissue biopsy: branching hyphae with septae
sputum culture: radiating chains of spores
serology
X-ray to detect aspergilloma

TREATMENT

allergic bronchopulmonary aspergillosis: corticosteroids to lessen IgE response
aspergilloma: surgery to remove
invasive aspergillosis: antifungals (e.g., amphotericin B)

QUICK FACTS

Hemoptysis may be indicative of an aspergilloma.
Aspergillus flavus secretes aflatoxin on peanuts, cereal, and rice; aflatoxin is a suspected liver carcinogen.
Mucor and *Rhizopus* are also branched hyphae; however, they branch at 90° without septae, invade nasal mucosa, and mainly affect diabetics.


Protozoa
GI infection
Urogenital infection
Systemic infection
E. histolytica
G. lamblia
C. parvum
T. vaginalis
T. gondii
L. donovani
T. cruzi
T. brucei
P. falciparum, vivax, ovale, malariae

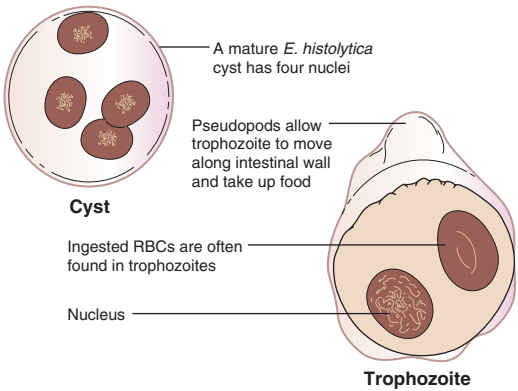
Protozoa

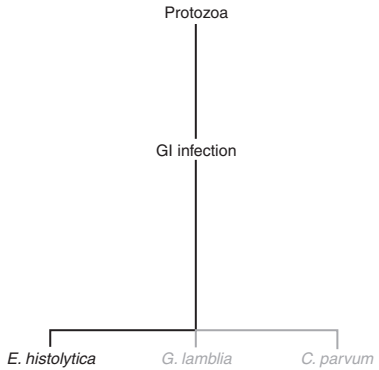
All protozoa are unicellular eukaryotes. Many can exist in two forms:

(1) as trophozoites (the feeding/reproducing form found in favorable environments)
(2) as cysts (the protective/dormant form found in difficult environments)

Protozoa can also be classified based on how they locomote in their trophozoite form.

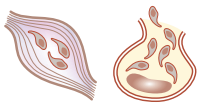
Amoebas (move with pseudopodia)	**Sporozoans (not motile)**	**Flagellates (move with flagella)**	**Ciliates (move with cilia)**
E. histolytica	*C. parvum* *T. gondii* *P. falciparum* *P. vivax* *P. ovale* *P. malariae*	*G. lamblia* *T. vaginalis* *L. donovani* *T. cruzi* *T. brucei*	*Balantidium coli*





CLINICAL CASE

After a camping trip to Mexico, a patient visits her doctor complaining of loose stools and abdominal cramps. The patient describes the stools as having flecks of blood and lots of mucus. The doctor orders a stool specimen in which she finds motile amoeba with ingested RBCs. She starts the patient on metronidazole and considers a CT scan to detect any liver abscesses.



CLINICAL PRESENTATION

amebic dysentery (bloody diarrhea)
liver abscess

PATHOBIOLOGY

fecal–oral transmission from contaminated food or water → cyst ingested → in ileum, cyst differentiates to trophozoite (motile amoeba) → trophozoite can lead to:

- asymptomatic carrier (most common): trophozoite becomes 4-nuclei cyst → cyst released in stools
- intestinal amebiasis: trophozoite invades colonic epithelium → local necrosis → dysentery
- invasive amebiasis: trophozoite invades through colonic epithelium producing raindrop-shaped ulcers → enters portal circulation → travels to liver and forms abscess → abscess enlarges → RUQ pain, weight loss (from liver abscess, trophozoite may invade diaphragm and create pulmonary abscess)

DIAGNOSIS

diarrheal specimen (active state): trophozoite with ingested RBC
hard stool specimen (carrier state): 4-nuclei cyst
serology

TREATMENT

metronidazole (for active state)
iodoquinol, diloxamide furoate (for carrier state)
in severe cases, drain hepatic abscesses
prevention: killed by boiling, not by chlorination

QUICK FACTS

Because cysts survive outside the host, carriers shedding cysts are more contagious than sick patients shedding trophozoites.

Anal–oral transmission of *Entamoeba histolytica* also occurs. This type of spread is seen in homosexual male populations.

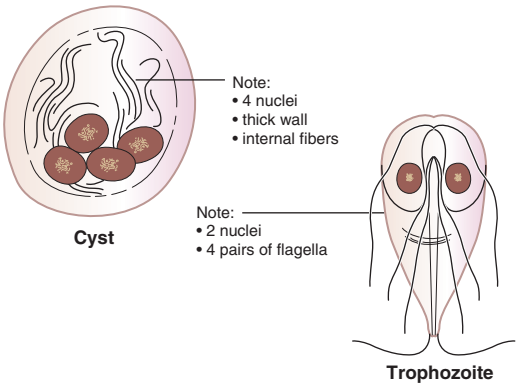
Acanthamoeba species and *Naegleria fowleri*, two other amoebas, can cause meningoencephalitic conditions in immunosuppressed and immunocompetent patients, respectively.

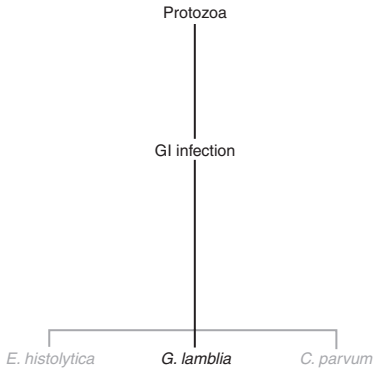
Acanthamoeba species can cause keratitis in people wearing contact lenses. This may lead to blindness.

Study Tip

Diarrhea caused by protozoa:

bloody → *Entamoeba histolytica*
fatty → *Giardia lamblia*
watery → *Cryptosporidium parvum*



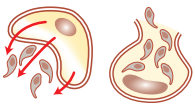


CLINICAL CASE

A student cuts short an extended backpacking trip in Yosemite Park after developing diarrhea. He explains to his doctor that the diarrhea is nonbloody but smells very bad. On further questioning, the student tells his doctor that he has been drinking water from a fresh water spring. The patient appears malnourished on physical exam. A diarrhea sample reveals 2-nuclei motile amoeba with a tear-drop shape and 4 pairs of flagella. The student is given metronidazole.

Giardia lamblia

Giardiasis



CLINICAL PRESENTATION

non-bloody diarrhea
asymptomatic carrier

PATHOBIOLOGY

fecal–oral transmission from contaminated food or water ⟶ cyst ingested ⟶ in duodenum, cyst differentiates into trophozoite ⟶ trophozoite attaches to duodenal wall via "suction" disk (no invasion) ⟶ damage to microvilli, inflammation ⟶ malabsorption, nonbloody & foul-smelling (fatty) diarrhea, weight loss

DIAGNOSIS

stool ova and parasites examination
diarrheal specimen (active state): tear-shaped trophozoite with 2 nuclei, 4 pairs of "moustache" flagella
hard stool specimen (carrier state): 4-nuclei cyst
ELISA for giardia antigen
"string test" for duodenal pathogens: trophozoites can be detected after attaching to swallowed string

TREATMENT

metronidazole
prevention: killed by boiling or iodine treatment

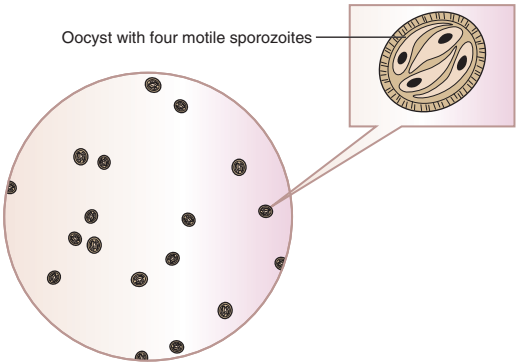
QUICK FACTS

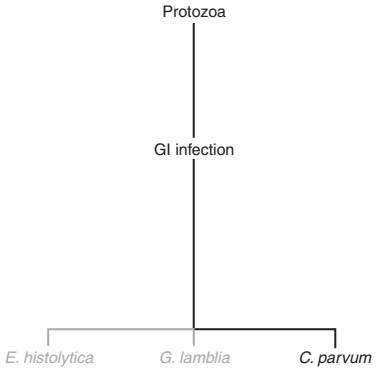
Many infected hosts remain asymptomatic carriers and shed cysts for years.
Giardia is also common in urban centers with poor sanitation and in day care centers with poor hygiene.

Study Tip

Diarrhea caused by protozoa:

- bloody ⟶ *Entamoeba histolytica*
- fatty ⟶ *Giardia lamblia*
- watery ⟶ *Cryptosporidium parvum*





CLINICAL CASE

An HIV patient becomes alarmed after developing a persistent diarrhea. He tells his physician that the diarrhea is watery and without blood. Upon learning that the patient visited a vacation farm before the diarrhea started, the doctor orders an acid-fast stain of the patient's stool sample.

CLINICAL PRESENTATION

watery diarrhea

PATHOBIOLOGY

fecal–oral transmission from animals or humans → oocysts ingested → oocysts release sporozoites in small intestine → sporozoites differentiate into trophozoites and attach to intestinal microvilli → watery, non-bloody diarrhea

in immunocompromised patients, prolonged and more severe diarrhea → malnutrition

DIAGNOSIS

stool sample: oocysts seen using acid-fast stain

serology

TREATMENT

supportive

prevention: water purification

QUICK FACTS

In AIDS patients, *Cryptosporidium* is an important cause of severe watery diarrhea.

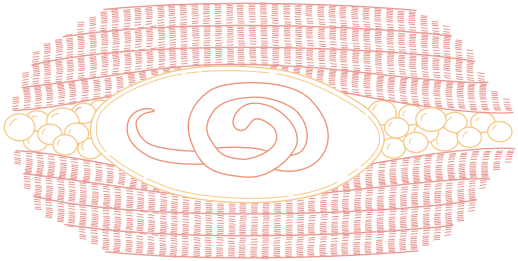
Cryptosporidium can cause diarrhea outbreaks due to contaminated city water reservoirs.

Study Tip

Diarrhea caused by protozoa:

- bloody → *Entamoeba histolytica*
- fatty → *Giardia lamblia*
- watery → *Cryptosporidium parvum*

T. vaginalis is transmitted between humans by sexual contact. Lacking a cyst, it does not survive well in the external environment.



Cysts with larvae in skeletal muscle

Trophozoite resides in vagina or orifice of urethra and is spread in vaginal or prostatic secretions as well as in urine.

Protozoa

Urogenital infection

T. vaginalis

CLINICAL CASE

A teenage girl complains of vaginal itching and burning. Sexual history reveals numerous sexual partners. Her gynecologist performs a pelvic exam and finds a greenish, foul-smelling thin discharge from the vagina. A wet mount of the discharge reveals motile amoeba, each with 1 nucleus and 5 flagella. The patient is started on metronidazole.

Trichomonas vaginalis — Trichomoniasis

CLINICAL PRESENTATION

vaginitis
urethritis (mainly in males)

PATHOBIOLOGY

sexual transmission ⟶ trophozoite colonizes:
- vagina in females ⟶ greenish, watery, & foul-smelling vaginal discharge; itching
- urethra in males ⟶ mostly asymptomatic

DIAGNOSIS

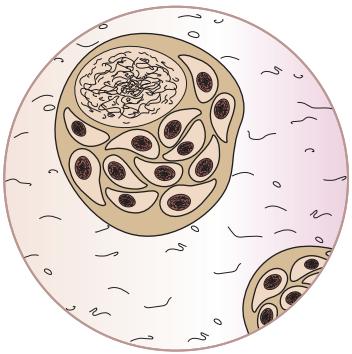
wet mount of vaginal or urethral discharge: tear-drop shaped trophozoites; 5 flagella, 1 nucleus

TREATMENT

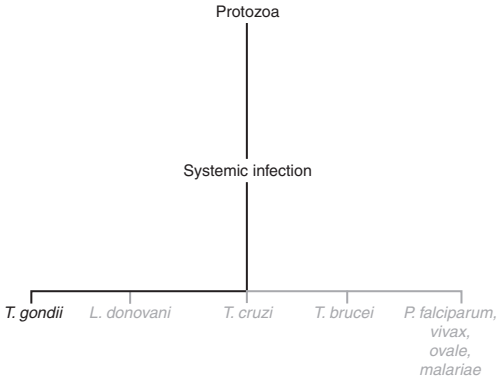
metronidazole to the patient and patient's sexual partner(s)

QUICK FACTS

Trichomonas can be distinguished from other flagellate protozoa in that it lacks a cyst form (by sexual transmission, the organism never leaves a host).

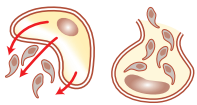


Crescent-shaped trophozoites within macrophage



CLINICAL CASE

An AIDS patient is brought to the EW after suffering a grand mal seizure. The man informs the EW physician that he has suffered a persistent headache in the past few weeks but denies any sensory problems or weakness. Fearing a brain tumor, the EW physician orders a CT scan of the patient. However, the scan, instead, reveals several ring-enhancing masses in the patient's brain. The physician confirms his suspicions when he learns the patient has many cats at home. He expects that a brain biopsy would show crescent-shaped trophozoites.



CLINICAL PRESENTATION

in immunocompetent patients: *asymptomatic, mononucleosis-like illness*
in immunocompromised patients: *encephalitis, chorioretinitis*
congenital infection: *mental retardation, chorioretinitis*

PATHOBIOLOGY

cysts ingested from undercooked meat or cat feces → in small intestine, cysts release invasive form → penetrate intestinal wall → phagocytosed and disseminated by macrophages → infects, damages cells at distant sites → host response contains infections (with mononucleosis-like symptoms) → in tissue, invasive forms become dormant → contained within cyst
if host becomes immunocompromised → cyst ruptures and releases invasive form → encephalitis, chorioretinitis, other infections
if active infection in pregnant mother → invasive form crosses placenta to fetus → congenital toxoplasmosis → mental retardation, chorioretinitis, other birth defects → invasive form becomes dormant and may reactivate later in life

DIAGNOSIS

serology (IgM in infants)
tissue biopsy: trophozoites (active), cysts (dormant)
CT, MRI of head

TREATMENT

sulfonamide + pyrimethamine

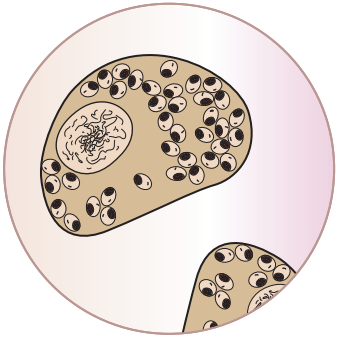
QUICK FACTS

Toxoplasma is the most common cause of encephalitis in HIV patients.
Only pregnant mothers with an active primary infection can result in congenital toxoplasmosis; mothers with previous infections mount an immune response that protects the fetus.
Pregnant mothers, especially those without previous exposure, are encouraged to avoid cats to prevent congenital toxoplasmosis.

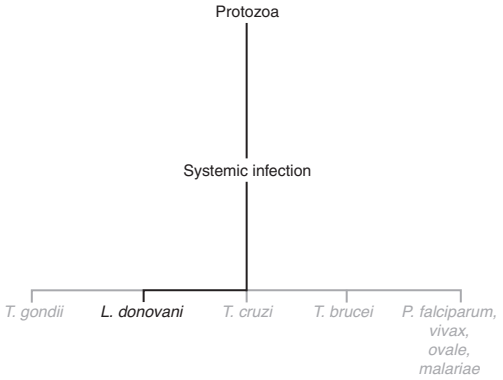
Study Tip

Organisms that cross placenta and therefore allow infection to pass from pregnant mother to fetus (TORCHES):

Toxoplasma gondii
Rubella
Cytomegalovirus
Herpes, HIV
Syphilis



Nonflagellated protozoa within macrophages (flagellated protozoa occur outside macrophages)



CLINICAL CASE

A recent immigrant from a tropical country presents with weight loss and fever. A physical exam reveals massive hepatosplenomegaly with associated edema, as well as hyperpigmented skin patches. The doctor orders a CBC and spleen biopsy. CBC reveals thrombocytopenia, anemia, and leukopenia, while spleen biopsy shows macrophages containing protozoa. The doctor begins the patient on an antimony compound.

Leishmania donovani — Leishmaniasis, "Kala-Azar"

CLINICAL PRESENTATION

visceral leishmaniasis (kala-azar)

PATHOBIOLOGY

reservoir in dogs and rodents, transmitted by sand fly vector → sand fly bite releases protozoan → protozoan engulfed by macrophages → divides within and destroys infected cells → over months, spreads through reticulo-endothelial system → damage to spleen, liver, bone marrow → splenomegaly, thrombocytopenia, anemia, leukopenia

weakened immune state → secondary infections → death

DIAGNOSIS

biopsy: nonflagellated protozoan within macrophages

leishmanin skin test: intradermal injection of killed *Leishmania* causes DTH response

TREATMENT

stibogluconate (an antimony compound)

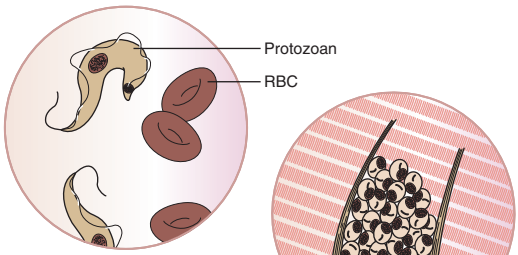
QUICK FACTS

Kala-azar means "black illness," named for the hyperpigmented skin lesions found in infected individuals.

Infections by other *Leishmania* species can result in a spectrum of less severe illnesses, depending on the organism's invasiveness and the strength of host response:

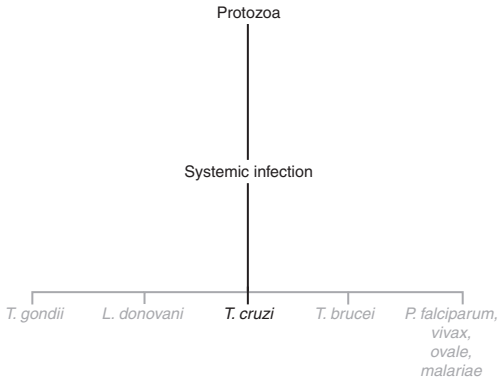
- local cutaneous leishmaniasis (single skin ulcer)
- diffuse cutaneous leishmaniasis (many skin nodules)
- mucocutaneous leishmaniasis (nasal/oral mucosal ulcers)

Cutaneous leishmaniasis was a significant illness among U.S. soldiers returning from the Persian Gulf War.



Flagellated protozoan in blood

Nonflagellated protozoa in cardiac muscle



CLINICAL CASE

A Mexican man complains to his doctor of worsening constipation and stomach pains. On physical exam, the doctor is surprised to find an enlarged heart on auscultation and moderate arrhythmia. Following an abdominal X-ray revealing megacolon, the doctor makes his diagnosis. Unfortunately, the treatments she offers are only symptomatic.

Trypanosoma cruzi — *Chagas' Disease, American Trypanosomiasis*

CLINICAL PRESENTATION

acute: *chagoma, Romaña's sign, congestive heart failure, myocarditis (rare)*
chronic: *arrhythmias, dilated cardiomyopathy, megacolon, megaesophagus*

PATHOBIOLOGY

reservoir in South and Central American animals, transmitted by reduviid bug vector → reduviid bug leaves protozoan-containing feces at bite site → host scratches protozoan into skin
- acute phase: diagnostic chagoma (inflammatory nodule at bite site) → protozoan enters bloodstream and lymphatics → infects tissue, especially cardiac muscle → usually self-limiting inflammation, may cause congestive heart failure, myocarditis
- chronic phase: may lead to inflammation around cardiac tissue or colonic nerves → cardiac arrhythmias, dilated cardiomyopathy, megacolon, dysphagia from megaesophagus

DIAGNOSIS

acute:
- flagellated protozoa in blood
- xenodiagnosis (allow uninfected reduviid bugs to bite patient, then examine bugs for protozoa)

chronic:
- serology
- nonflagellated protozoa in cells

TREATMENT

acute: nifurtimox, benznidazole
chronic: no treatment

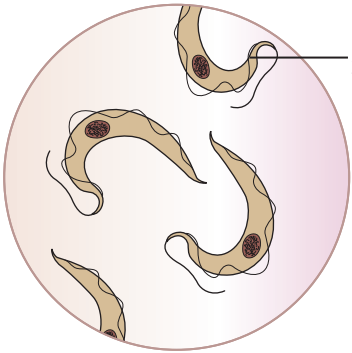
QUICK FACTS

Romaña's sign (soft tissue and lymphoid swelling around the eyes) occurs when the protozoan enters through the conjunctiva.

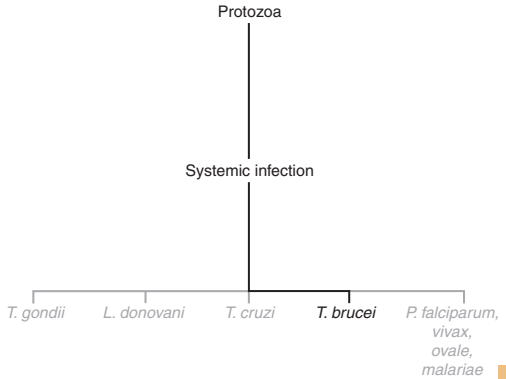
In chronic Chagas' disease, it is unclear if tissue damage results from direct infection by the protozoan or by a slow, chronic inflammatory response.

Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense

Sleeping Sickness, African Trypanosomiasis



Protozoa in blood



CLINICAL CASE

An East African man is asked to leave his job after repeatedly falling asleep. He visits the doctor hoping to cure his somnolence, as well as accompanying headache and dizziness. During the interview, the patient explains that he had suffered recurring bouts of fever and enlarged lymph nodes before the sleepiness started. The doctor decides to perform a lumbar puncture, and after finding a flagellated protozoan in the CSF, he plans to start the patient on melarsoprol.

Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense

Sleeping Sickness, African Trypanosomiasis

CLINICAL PRESENTATION

enlarged lymph nodes, fever (recurring)
somnolence, coma

PATHOBIOLOGY

reservoir in animals or humans, transmitted by tsetse fly vector → tsetse fly bite releases protozoan into bloodstream →divides in blood → host immune response → hard red ulcer at bite site + enlarged lymph nodes, fever

some protozoa change surface coat to escape host antibodies → divide in blood → host immune response → enlargedlymph nodes, fever (cycle recurs every 2 weeks)

after many cycles, protozoa may escape immune response and infect CNS → encephalitis, meningitis → somnolence (sleeping sickness), coma

DIAGNOSIS

blood, lymph node, CSF: flagellated protozoan

TREATMENT

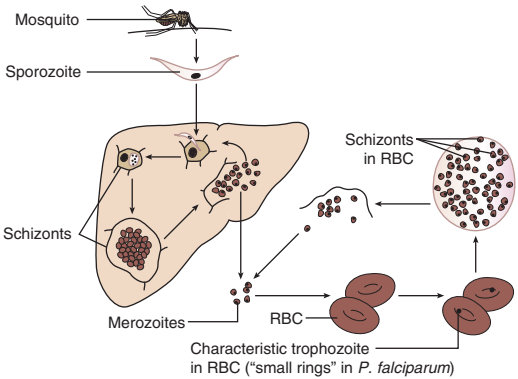
T. b. gambiense:
suramin (before CNS infection because does not cross BBB)
eflornithine (with CNS infection)

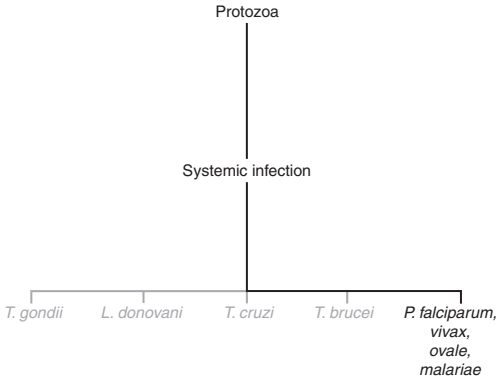
T. b. rhodesiense:
suramin (before CNS infection because does not cross BBB)
melarsoprol (with CNS infection)

QUICK FACTS

West African Sleeping Sickness is caused by *T. b. gambiense* and occurs slowly; East African Sleeping Sickness is caused by *T. b. rhodesiense* and occurs quickly.

Trypanosoma varies its coat by moving different surface genes into transcriptionally active sites (gene shuffling).





CLINICAL CASE

A student reports to his college clinic complaining of "the flu." He explains that he has been suffering from intermittent headaches, fever, and muscle aches. Assuming the flu, the physician sends the student home with acetaminophen. Now, days later, the student returns to the clinic EW with chills, extreme fever, and debilitating fatigue. Physical exam also reveals yellow sclera and severe splenomegaly. CBC reveals low hematocrit, and urinalysis shows hemoglobinuria. Alarmed, the EW doctor questions the student about recent travels and learns that he has just returned from a visit to India. A blood smear showing ring shapes confirms the diagnosis, and the patient is begun on mefloquine.

Plasmodium falciparum, vivax, ovale, malariae

CLINICAL PRESENTATION

anemia, fever, chills in cycles:
- *P. falciparum:* irregular
- *P. vivax/ovale:* every 2 days
- *P. malariae:* every 3 days

P. falciparum complications: cerebral malaria, kidney failure, lung edema

PATHOBIOLOGY

transmitted by *Anopheles* mosquito → mosquito bite releases sporozoite into bloodstream → carried to liver and infects hepatocytes → in hepatocytes, sporozoite divides into merozoites → liver cells burst, releasing merozoites → merozoites invade RBCs → in RBCs, merozoites develop into trophozoites with characteristic shapes → trophozoite divides into many merozoites → merozoites burst infected RBCs and spread to other RBCs → with each burst cycle, fever, chills, and anemia are manifested

infected RBCs become less flexible → accumulated and destroyed in spleen → splenomegaly

P. vivax/ovale (relapsing infection): some sporozoites do not immediately divide in hepatocytes → form dormant hypnozoites in liver → relapses possibly months to years later

P. falciparum (most severe infection): knobs formed in infected RBCs → knobs cause RBCs to stick to capillary/venule walls → vessel occlusion and hemorrhage → damage to the brain (cerebral malaria), kidneys, and lungs

to complete cycle, some merozoites become male and female gametocytes → ingested by mosquito → gametocytes fuse to form diploid zygote → zygote generates haploid sporozoites that are stored in mosquito salivary glands

DIAGNOSIS

blood smear:

	P. falciparum	*P. vivax/ovale*	*P. malariae*
trophozoite shapes	small rings	large, irregular rings	band or rectangular
gametocyte shapes	banana-like	round	round

TREATMENT

prophylaxis and treatment:
- chloroquine (North America, Central America, Haiti, Middle East)
- mefloquine for chloroquine-resistant *P. falciparum* (in Africa, South America, South and Southeast Asia)
- primaquine for *P. vivax/ovale* dormant liver infections

QUICK FACTS

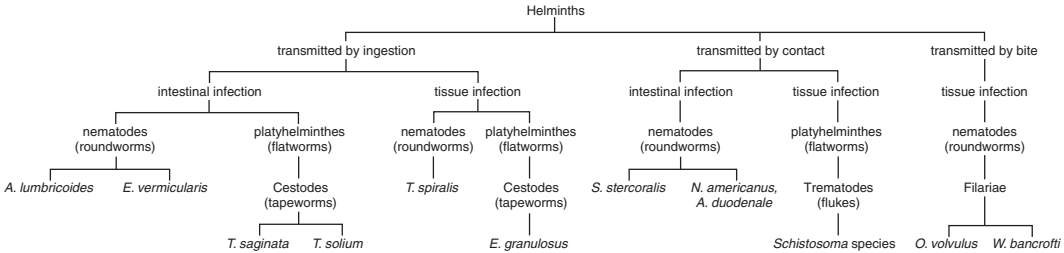
Malaria infects between 200 and 300 million people in tropical climates every year. One million infected children, mostly in Africa, die annually.

Several blood disorders overlap with malaria geographically because they may confer resistance: (1) sickle cell trait—protects against *P. falciparum* because the RBCs are too weak to support parasite; (2) RBCs are lacking the antigens Duffy a and b—protects against *P. vivax* because the protozoan binds to these antigens; (3) thalassemia; and (4) glucose-6-phosphate dehydrogenase deficiency.

Some *P. falciparum* infections are known as "blackwater fever" because of the hemoglobinuria that results from RBC lysis and kidney damage.

P. vivax/ovale infects young RBCs, *P. malariae* infects old RBCs, and *P. falciparum* infects all RBCs. Hence, *P. falciparum* infections are most severe.

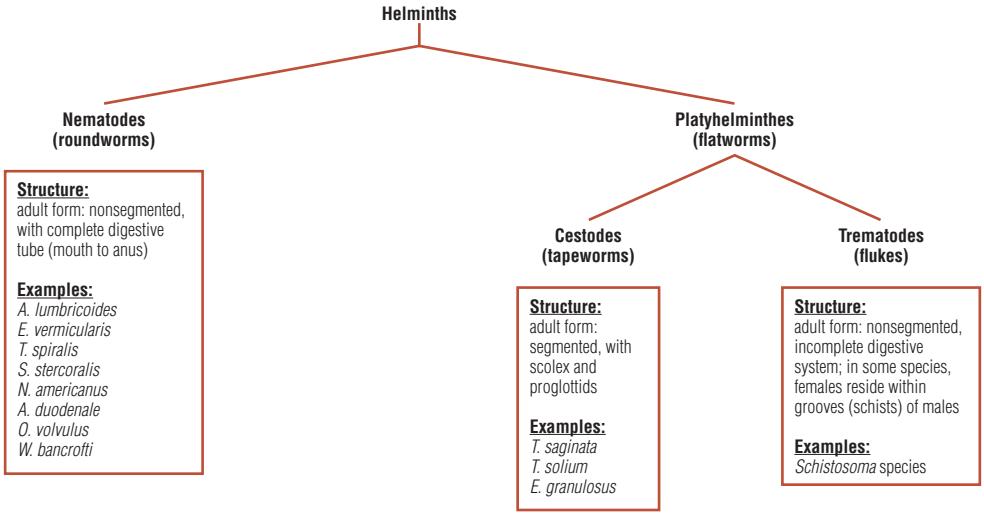
Helminths

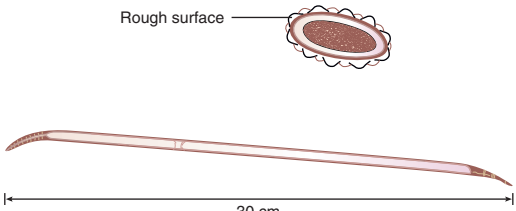

Helminths
transmitted by ingestion
transmitted by contact
transmitted by bite
intestinal infection
tissue infection
intestinal infection
tissue infection
tissue infection
nematodes (roundworms)
platyhelminthes (flatworms)
nematodes (roundworms)
platyhelminthes (flatworms)
nematodes (roundworms)
platyhelminthes (flatworms)
nematodes (roundworms)
A. lumbricoides
E. vermicularis
Cestodes (tapeworms)
T. spiralis
Cestodes (tapeworms)
S. stercoralis
N. americanus, A. duodenale
Trematodes (flukes)
Filariae
T. saginata
T. solium
E. granulosus
Schistosoma species
O. volvulus
W. bancrofti

Helminths

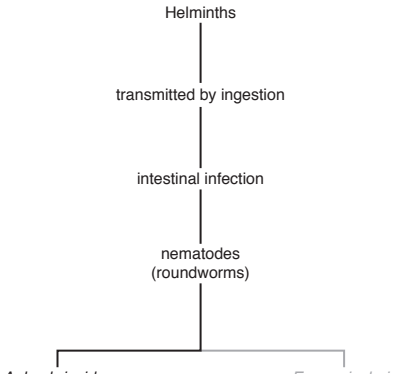
Helminths are multicellular parasites (vs. protozoa, which are unicellular parasites).

Structurally, they are organized as follows:





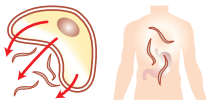
Female and egg



CLINICAL CASE

A man in Louisiana develops coughing, fever, and abdominal pain. His doctor orders a series of X-rays that show pulmonary infiltrates characteristic of pneumonia, as well as intestinal images consistent with obstruction. On CBC, the patient has increased eosinophils. The doctor examines a stool sample from the patient and discovers microscopic oval eggs with rough surfaces. The doctor makes a diagnosis, administers pyrantel pamoate, and forewarns the patient to expect worms in his stool.

Ascaris lumbricoides — Ascariasis



CLINICAL PRESENTATION

asymptomatic
ascaris pneumonia
malnutrition

PATHOBIOLOGY

fecal–oral transmission → eggs ingested in contaminated soil → hatch in small intestine → larvae invade intestinal wall → enter bloodstream and transported to lungs → enter alveoli and ascend toward trachea → respiratory tract inflammation → may cause pneumonia

larvae pass from trachea to pharynx → swallowed → larvae mature into adults in small intestine → adults swim freely in lumen and consume food ingested by host → host malnutrition

adults lay eggs that pass in feces

DIAGNOSIS

stool: detect eggs with rough surface
eosinophilia

TREATMENT

pyrantel pamoate
mebendazole, albendazole

QUICK FACTS

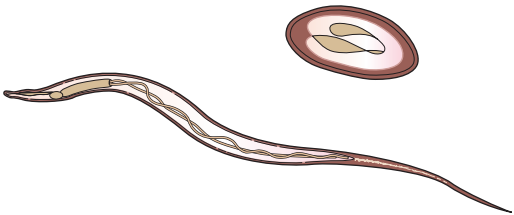
Ascaris is common to tropical climates, causing several hundred million infections annually; in the U.S., infections are found in the South.

Some complications include intestinal occlusion by a mass of worms (worm ball) or biliary obstruction by a single worm migrating up the biliary tree.

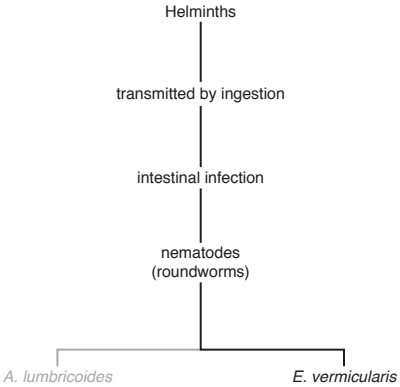
Dog ascaris (*Toxocara canis*) can also infect humans, but their larvae migrate to many organs instead of entering the respiratory tract (visceral larva migrans); the effects are diffuse and include hepatosplenomegaly and blindness.

Study Tip

Ascariasis is the most common helminthic infection.



Female and egg



CLINICAL CASE

A mother brings her child to a developmental specialist. She is concerned because of what she considers "negative" behavior. When asked to elaborate, she explains that her child scratches his anal region continuously, even in public places. Indeed, even his kindergarten teacher mentioned it in the last parent–teacher meeting. Before pursuing psychological studies, the specialist recommends a "Scotch tape" test based on past cases with similar complaints.

Enterobius vermicularis — Pinworm

CLINICAL PRESENTATION

perianal itchiness

PATHOBIOLOGY

fecal–oral transmission → eggs ingested from contaminated surfaces → hatch in duodenum and jejunum → mature into adults in ileum and large intestine → mate in colon → at night, females migrate out of rectum to perianal skin → lay eggs → perianal itchiness

scratching contaminates hand → eggs spread

DIAGNOSIS

"Scotch tape" technique: Adhere tape to perianal region, remove tape, and examine for eggs

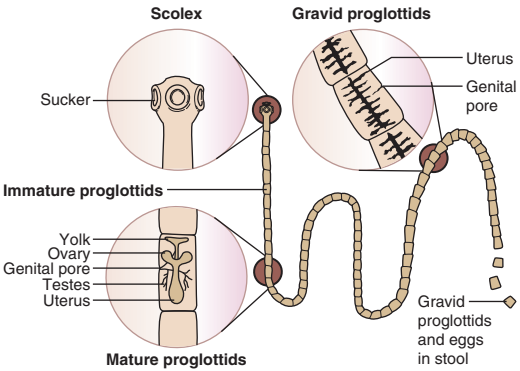
TREATMENT

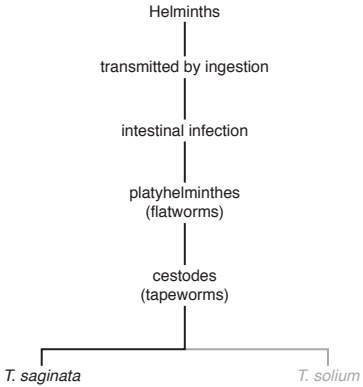
mebendazole, albendazole
pyrantel pamoate

QUICK FACTS

Pinworm infections are the most common worm infections in the U.S. that primarily infects children.

Whipworm (*Trichuris trichiura*) is also a nematode with a similar life cycle; however, it may cause diarrhea (even intestinal ulceration and hemorrhage in severe cases) but not perianal itching.





CLINICAL CASE

A cow rancher arrives at the EW terrified after discovering a wormlike structure protruding from his anus. After reassuring the man and taking a proper history and physical, the doctor examines a stool sample. As expected, the doctor finds rectangular proglottid segments with the naked eye and uses a low-power microscope to detect eggs. The doctor prescribes niclosamide and a cathartic, confident that the patient will be cured with a single dose. The doctor also instructs the patient to avoid poorly cooked beef in the future.

Taenia saginata — Beef Tapeworm

CLINICAL PRESENTATION

asymptomatic
malnutrition, abdominal discomfort

PATHOBIOLOGY

larvae found as cysticerci in cow muscle → ingested in poorly cooked beef → in small intestine, larvae mature and grow → adults consist of scolex (head) and numerous proglottids (autonomous segments) → scolex attaches to intestinal wall, proglottids containing eggs passed in feces → cows ingest eggs to complete cycle
worm consumes food ingested by host → malnutrition

DIAGNOSIS

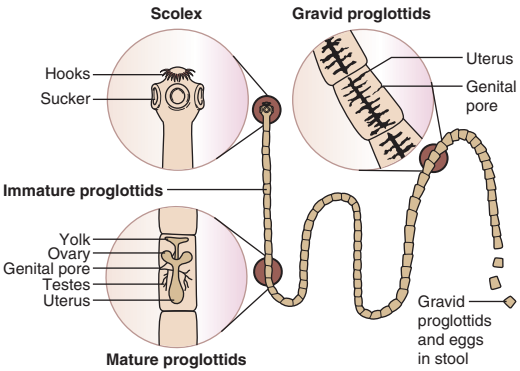
stool: proglottids, eggs

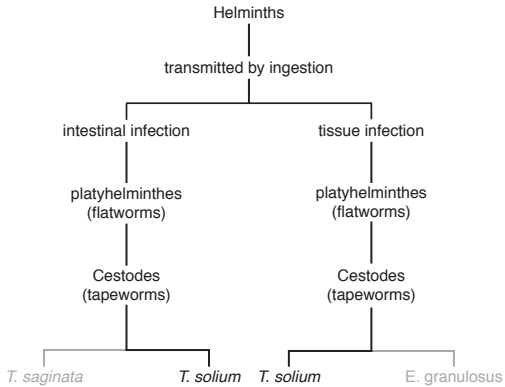
TREATMENT

niclosamide + cathartic
praziquantel

QUICK FACTS

By adding proglottids, the adult worm may extend up to 10 meters long.
Fish tapeworm (*Diphyllobothrium latum*), acquired from poorly cooked fish, most characteristically leads to vitamin B^{12} deficiency (megaloblastic anemia).
In contrast to *T. solium*, *T. saginata* has no hooks on its scolex.

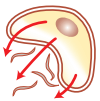
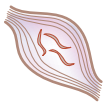




CLINICAL CASE

A Vietnamese immigrant of 10 years presents with severe headaches and seizures. A physical exam reveals several nodules across her body. Concerned about a neurologic disease, the doctor first orders a head CT scan that shows five calcified cysts. This observation, along with high eosinophils on a CBC, prompts the doctor to perform a biopsy of a nodule. A diagnosis is made after the doctor finds cysts in the nodule, and the patient is begun immediately on praziquantel and steroids.

Taenia solium — Pork Tapeworm

CLINICAL PRESENTATION

intestinal infection: *asymptomatic; malnutrition, abdominal discomfort*
tissue infection: *cysticercosis* (neurologic defects, blindness)

PATHOBIOLOGY

intestinal infection:
- larvae found as cystercerci in pig muscle → ingested in poorly cooked pork → in small intestine, larvae mature and grow → adults consist of scolex (head) and numerous proglottids (autonomous segments) → scolex attaches to intestinal wall, proglottids containing eggs passed in feces → worm consumes food ingested by host → malnutrition

tissue infection:
- humans ingest eggs from infected feces (vs. larvae in pork) → eggs hatch into oncospheres in small intestine → oncospheres penetrate intestinal wall and travel to other tissues → form cysticerci containing larvae, especially in brain, skeletal muscle, and eye
- cysts grow slowly → neurologic defects (seizures, focal symptoms) or blindness → when cysts die after several years, increased inflammation → aggravated symptoms

DIAGNOSIS

intestinal infection:
- proglottids, eggs in stool

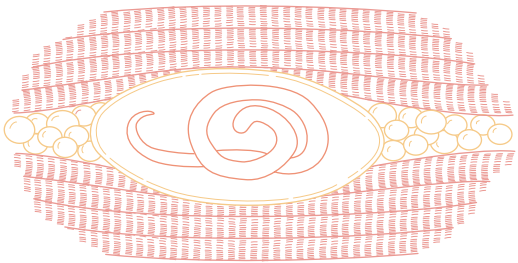
tissue infection:
- calcified cysticerci in muscle, brain on X-ray, CT
- eosinophilia in muscle, brain on X-ray, CT

TREATMENT

intestinal infection: niclosamide + cathartic; praziquantel
tissue infection: praziquantel or albendazole + steroids (reduce inflammation from dying cysts)

QUICK FACTS

In cysticercosis, larvae sometimes can be detected swimming in the vitreous humor of the eyes.



Cysts with larvae in skeletal muscle

Helminths
↓
transmitted by ingestion
↓
tissue infection
↓
nematodes
(roundworms)
↓
T. spiralis

CLINICAL CASE

A pig farmer visits his doctor with muscle aches, fever, and periorbital and facial edema. These symptoms were preceded 2 weeks earlier by an upset stomach and diarrhea. Blood labs show eosinophilia, ↑ IgE, and muscle enzymes. Because the symptoms are not severe, the doctor opts not to perform a muscle biopsy; however, if she had performed the biopsy, she would have expected to find cysts.

Trichinella spiralis — Trichinosis

CLINICAL PRESENTATION

gastroenteritis, myalgia

PATHOBIOLOGY

reservoir in pigs → encysted larvae ingested from uncooked meat → larvae mature into adults in small intestine → adults mate and eggs mature to larvae → larvae penetrate intestinal wall into bloodstream → may cause diarrhea, pain

larvae carried by blood to skeletal muscle (often extraoculars, masseters, tongue, diaphragm) → initial inflammation → myalgia → larvae form fibrous cyst → cysts can last for years, may calcify

if many encysted larvae ingested → severe infection → larvae migrate to heart and brain → myocarditis, encephalitis

DIAGNOSIS

eosinophilia
striated muscle biopsy: cysts with larvae
serology (for chronic infection)

TREATMENT

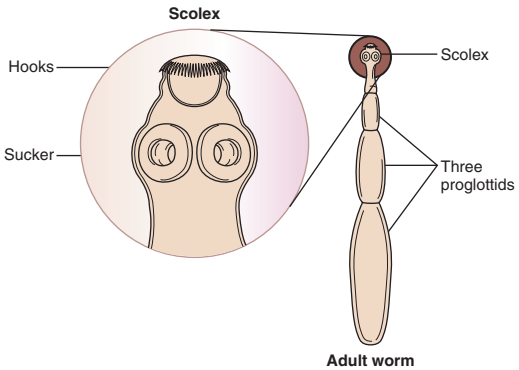
mebendazole/thiabendazole (against adult worms in small intestine)
no treatment to remove cysts from muscle
steroids for severe myositis, myocarditis

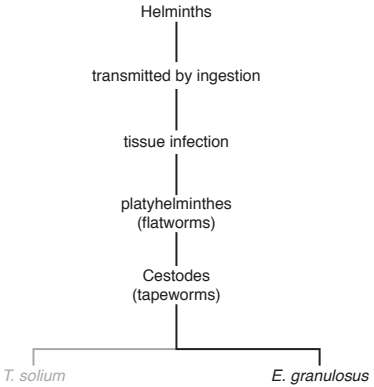
QUICK FACTS

In the U.S., trichinosis infections have decreased following legislation that prohibits feeding pigs uncooked garbage.

Study Tip

Trichinosis is the most common parasitic cause of myocarditis.

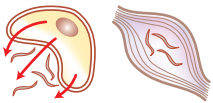




CLINICAL CASE

A woman presents with abdominal discomfort. The discomfort begins as a mild sensation in the RUQ but has become progressively more painful. Physical exam reveals hepatomegaly. The doctor decides to perform an abdominal CT, which shows a large circular mass in the liver with multiple daughter cysts encapsulated by "eggshell" calcifications. Serology, but not stool samples, is used to make a diagnosis. The doctor elects to surgically remove the mass but first neutralizes the cyst contents by injecting ethanol.

Echinococcus granulosus — Dog Tapeworm



CLINICAL PRESENTATION

echinococcosis or hydatid cyst disease

PATHOBIOLOGY

eggs found in dog feces → humans ingest eggs → eggs hatch into larvae in small intestine → larvae penetrate intestinal wall and travel to other tissues → form hydatid cysts in liver, lung, or brain

cysts grow and divide → expansion causes organ displacement → organ dysfunction, especially in liver → enlarged cyst may also rupture:

- release of antigenic cyst contents → severe anaphylaxis
- release of larvae → infection spreads

DIAGNOSIS

X-ray or CT: cysts (presence of daughter cysts within hydatid cyst is pathognomonic)
serology

TREATMENT

surgery to remove cysts (rupture is a major complication)
albendazole

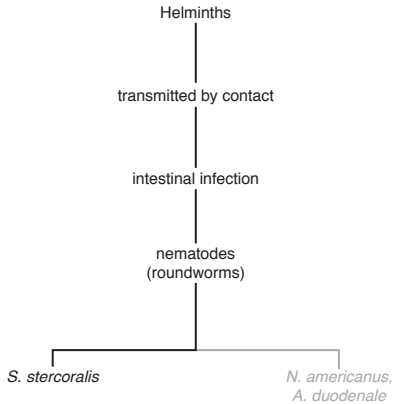
QUICK FACTS

Because rupture may disseminate the infection during surgery, the cyst contents are first killed by injecting larvicidal solutions.

Echinococcosis is common in sheepherders who acquire the tapeworm from sheep dog feces; the sheep dogs become infected after eating raw sheep meat.

Echinococcus, composed of a scolex and only three proglottids, is very small relative to other tapeworms.

Adult and larvae



CLINICAL CASE

A South Carolina woman visits her doctor after developing diarrhea. The doctor performs a blood test and finds elevated eosinophils. Suspecting a parasite infection, the doctor examines a stool specimen. After finding larvae without eggs, the doctor solidifies a diagnosis upon learning that the patient frequently walks around her house barefoot. The patient is started on thiabendazole to cure the symptoms as well as to prevent complications such as peritonitis.

Strongyloides stercoralis — Strongyloidiasis

CLINICAL PRESENTATION

asymptomatic
pneumonia
gastroenteritis
diffuse autoinfection (in immunodeficient)

PATHOBIOLOGY

fecal–cutaneous transmission → infectious (filariform) larvae penetrate skin of feet, causing local itching → enter bloodstream and transported to lungs → enter alveoli and ascend toward trachea → respiratory tract inflammation → may cause pneumonia

larvae pass from trachea to pharynx → swallowed → larvae mature into adults in small intestine → mate → females invade mucosa and lay eggs → eggs hatch into larvae in intestinal wall → inflammation → pain, diarrhea

larvae may:

- exit with feces → contaminate soil
- penetrate intestinal wall → enter bloodstream and transported to lungs → infectious cycle repeated (autoinfection)

DIAGNOSIS

stool: detect larvae, not eggs (vs. hookworm)
eosinophilia
"string test" for duodenal pathogens: swallow a long string to pull out larvae

TREATMENT

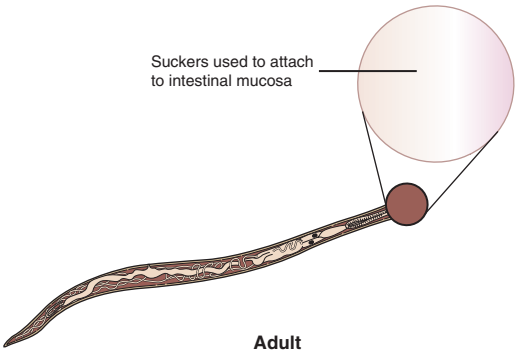
ivermectin, thiabendazole

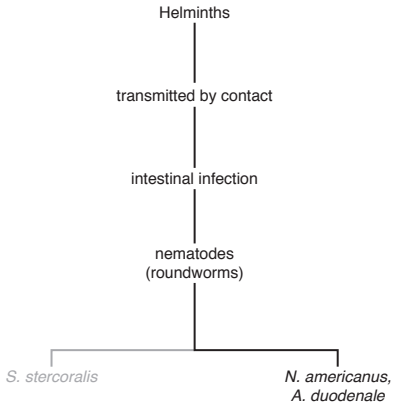
QUICK FACTS

When *Strongyloides* larvae tunnel through the intestinal wall, bacteria may follow into the peritoneum and cause peritonitis.

In immunodeficient patients with autoinfection, invasive larvae may infect other organs in addition to the lungs.

Strongyloidiasis is associated with HTLV-1 infection.





CLINICAL CASE

A child from a small Alabama community presents with severe weakness and pallor. A CBC shows reduced hematocrit with hypochromic microcytic RBCs as well as increased eosinophils. To investigate the possibility of parasites, the physician orders a stool sample in which she finds numerous eggs. The physician prescribes mebendazole and iron tablets and explains that the child may have acquired the illness by walking barefoot.

Necator americanus, Ancylostoma duodenale — Hookworm

CLINICAL PRESENTATION

pneumonia
gastroenteritis
anemia

PATHOBIOLOGY

fecal–cutaneous transmission → infectious (filariform) larvae penetrate skin of feet, causing local itching → enter bloodstream and transported to lungs → enter alveoli and ascend toward trachea → respiratory tract inflammation → may cause pneumonia

larvae pass from trachea to pharynx → swallowed → larvae mature into adults in small intestine → attach to mucosa via cutting plates or teeth → may cause gastroenteritis initially → secrete anticoagulant and suck blood from host → anemia

in lumen, adults mate → eggs passed in feces → eggs hatch to infectious larvae in soil

DIAGNOSIS

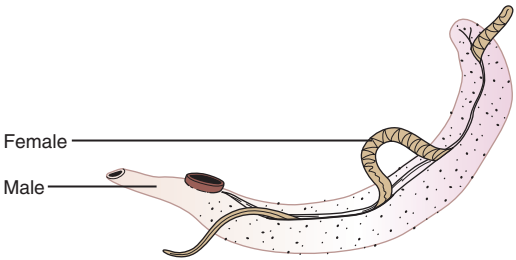
stool: detect eggs, not larvae (vs. *Strongyloides stercoralis*)
eosinophilia

TREATMENT

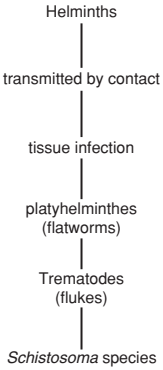
mebendazole
pyrantel pamoate
iron and folic acid for anemia

QUICK FACTS

Cat and dog hookworm larvae can also infect humans but cannot invade the bloodstream; as a result, the larvae travel subcutaneously causing a trail of itchiness until they die (cutaneous larva migrans).



Adult male and female paired



CLINICAL CASE

An African man comes to the EW after vomiting blood. He also reports that his stools have been dark for the last few years. In the history, the patient denies alcohol use and states that freshwater fishing is a hobby. Endoscopy shows esophageal varices, and stool specimens contain eggs. The patient is started on praziquantel.

An African woman visits her doctor after urinating blood. In her history, she states that she worked in freshwater rice fields before coming to the U.S. Cytoscopic examination of the bladder shows inflammatory lesions, and urinalysis demonstrates eggs. Imaging reveals hydronephrosis of the right kidney and a mass extending from the right ureter into the bladder. She is started on praziquantel.

Schistosoma species — *Schistosomiasis, Blood Fluke, Katayama Fever*

CLINICAL PRESENTATION

acute:
- *itchiness at site of infection*
- *fever, chills, lymphadenopathy*

chronic:
- *periportal fibrosis and consequences*
- *intestinal polyps*
- *bladder inflammation, hematuria, carcinoma*

PATHOBIOLOGY

larvae (cercariae) released by snails into fresh water → penetrate human flesh and enter bloodstream → travel to portal vein → larvae mature into adults → adult pairs migrate against portal flow to various venous plexuses:

- in intestinal venous plexus (*S. mansoni, S. japonicum*) → mate → eggs released → acute inflammatory response (Katayama fever, chills, lymphadenopathy) → eggs exit to intestinal lumen → passed in feces

  some eggs carried to portal circulation → chronic inflammatory response → periportal fibrosis and consequences (portal hypertension, splenomegaly, esophageal varices)

  some eggs lodge in intestinal wall → chronic inflammatory response → intestinal inflammation and consequences (polyps)
- in bladder venous plexus (*S. haematobium*) → mate → eggs released → acute inflammatory response (Katayama fever, chills, lymphadenopathy) → eggs exit to bladder lumen → passed in urine

  some eggs lodge in bladder wall → chronic inflammatory response → bladder inflammation and consequences (hematuria, bladder carcinoma)

excreted eggs hatch in fresh water and infect snails

DIAGNOSIS

feces or urine: detect eggs, eosinophilia

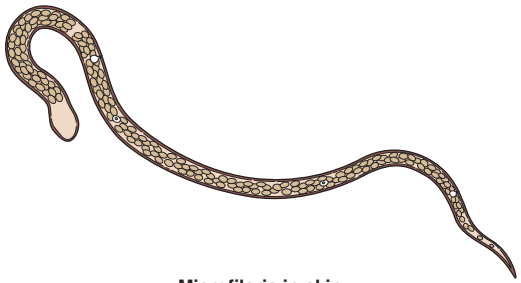
TREATMENT

praziquantel

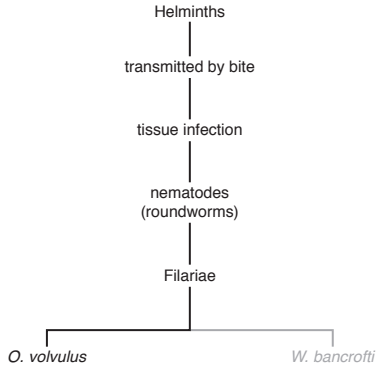
QUICK FACTS

Whereas schistosomal eggs are highly immunoreactive, the adult forms evade the immune system by coating with host antigens; hence, adult forms survive for years in the venous plexuses.

Whereas most bladder cancers are transitional cell carcinomas, *S. haematobium*-associated bladder cancers are more frequently squamous cell carcinomas.



Microfilaria in skin



CLINICAL CASE

A traveling physician visits a remote riverside village in a South American country and discovers that most of the older village inhabitants are blind. On physical exam of some of the members, she notes skin nodules and hyperpigmented rashes. To prevent other village members from becoming blind, she administers donated ivermectin to many people in the village and urges mosquito control.

Onchocerca volvulus — River Blindness, Onchocerciasis

CLINICAL PRESENTATION

skin nodules
thick, hyperpigmented pruritic rash
blindness

PATHOBIOLOGY

transmitted by black fly near rivers → black fly bite releases larvae into skin → larvae move through subcutaneous tissue → mature to adults → fibrosis around adults, creating subcutaneous nodules → adults mate and release microfilariae into subcutaneous tissue
microfilariae move subcutaneously throughout the body → inflammation → thickened, hyperpigmented pruritic rash
microfilariae may reach eye → inflammation → blindness (river blindness)
microfilariae can be ingested by mosquito → form larvae in mosquito, completing cycle

DIAGNOSIS

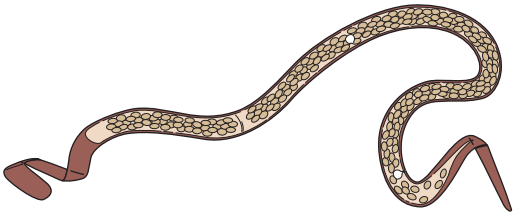
skin biopsy: detect microfilariae (adults in nodules)

TREATMENT

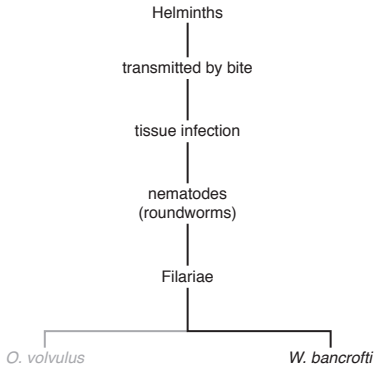
ivermectin (only effective against microfilariae, not adults)
surgical removal of nodules

QUICK FACTS

In endemic areas, this disease causes blindness in large numbers of people.



Microfilaria in blood



CLINICAL CASE

A patient from a tropical village has an enormously swollen scrotum and lower extremity. The skin around the swelling has become scaly and thick. The patient remembers feeling enlarged nodes in the groin months before the swelling began, but because of poor health resources in the area, he never saw a physician. Samples of his blood drawn at night show wormlike organisms under a microscope. A visiting doctor strongly recommends that the patient and other villagers sleep with a mosquito net to prevent more infections.

Wuchereria bancrofti — Filariasis, Elephantiasis

CLINICAL PRESENTATION

fever
edema and scaly skin of legs and genitalia

PATHOBIOLOGY

transmitted by mosquito → mosquito bite releases larvae (microfilariae) into bloodstream → larvae carried to lymph nodes of genitals and lower extremities → larvae mature to adults over the span of a year → adults mate and release larvae into bloodstream
adult worms trigger inflammation → fever, swelling of lymph nodes
with repeated infections → fibrosis around dead adult worms in lymph nodes → obstruction of lymphatic drainage → edema and scaly skin in legs, scrotum (elephantiasis)

DIAGNOSIS

blood: detect microfilariae (most common at night)

TREATMENT

diethylcarbamazine (only effective against microfilariae, not adults)

QUICK FACTS

Brugia malayi is a helminth that causes elephantiasis endemic to Malaysia and Southeast Asia.
Larval forms have a nocturnal schedule: They emerge in the blood at night.

CLINICAL CASE

A 75-year-old man is brought by his family for evaluation of behavioral changes. The man was previously highly functional but has developed confusion, inattentiveness, and insomnia that have progressively worsened over a month. The family also notes his gait is unstable. On exam, he has signs of cerebellar ataxia and myoclonus. Workup including CT, MRI/MRA, and toxicology screen is unremarkable, and Gram stain, viral PCR, and cytology of CSF are unrevealing. Over the next month, the patient has worsening myoclonic jerking and cognitive impairment, and on the fourth week, he dies. Autopsy reveals myriad microscopic holes throughout the cerebral cortex giving a sponge-like appearance.

CLINICAL PRESENTATION

progressive neuropsychiatric changes: depression, anxiety, apathy, dementia, insomnia
motor disturbances: myoclonus, ataxia, gait disturbances, slurred speech

PATHOBIOLOGY

prions (*pr*oteinaceous *in*fectious particles) are misfolded isoforms of a normal cellular protein PrPC → prions bind normal cellular protein PrPC and convert it into misfolded isoform PrPSc → accumulation of misfolded isoform PrPSc in neurons → neuronal cell death, extensive vacuolation causing spongiform appearance, gliosis → neurologic and psychiatric changes

prions have been implicated in several disease that vary in how the prion is acquired:

- sporadic CJD: majority (~90%) of cases
- familial CJD: genetic mutations in PrPC make misfolding more likely
- iatrogenic CJD: from contaminated corneal transplants, dural grafts, liver transplants, or use of contaminated neurosurgical instruments
- variant CJD ("mad cow disease"): ingestion of contaminated beef (cows with bovine spongiform encephalopathy)

DIAGNOSIS

biopsy (PrPSc can be detected in tonsillar biopsy)
autopsy: brain has spongiform appearance; neuronal loss without inflammation

TREATMENT

no treatment available
prevention with rigorous sterilization of medical instruments

QUICK FACTS

Since "mad cow disease" was first recognized in the 1980s as a result of eating beef from cows infected with bovine spongiform encephalopathy, this prion disease has been implicated in the deaths of several hundred people, mostly in Britain. The disease outbreak has led to stricter regulations in recycling animal products for animal feeding.

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