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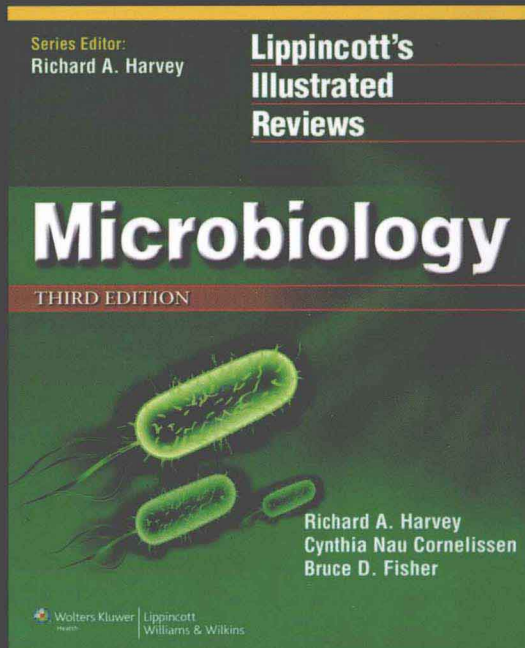
Microbiology

(Third Edition)

微生物学

(第3版)

Richard A. Harvey
Cynthia Nau Cornelissen
Bruce D. Fisher



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Unique Clinical Features

Summaries of bacteria and their diseases

Summary of common diseases

URINARY TRACT INFECTIONS

A Common causes of UTI¹

B Classification of pathogens

Gram (+) cocci

- Staphylococcus saprophyticus

Gram (-) rods

- Escherichia coli
- Klebsiella
- Proteus
- Pseudomonas aeruginosa

C Common complaints

Escherichia coli

- E. coli is the most common cause of urinary tract infections (UTI), including cystitis and pyelonephritis. Women are particularly at risk for infection. Transmission is frequently from the patient's flora.
- Uncomplicated cystitis (the most commonly encountered UTI) is caused by uropathogenic strains of E. coli, characterized by P fimbriae (an adherence factor). Complicated UTI (pyelonephritis) often occurs in settings of obstructed urinary flow, and may be caused by nonuropathogenic strains of E. coli. UTI require treatment with antibiotics.

Staphylococcus saprophyticus

- S. saprophyticus is a frequent cause of cystitis in women, probably related to its occurrence as part of normal vaginal flora. It is also an important agent of hospital-acquired infections associated with the use of catheters.
- S. saprophyticus is a coagulase-negative staphylococcal species. It tends to be sensitive to most antibiotics, even penicillin G. It can be distinguished from most other coagulase-negative staphylococci by its natural resistance to novobiocin.

Other enterobacteria

- Other genera of Enterobacteriaceae, such as Klebsiella, Enterobacter, Proteus, and Serratia, which can be found as normal inhabitants of the large intestine, include organisms that are primarily opportunistic and often nosocomial pathogens. They all frequently colonize hospitalized patients, especially in association with antibiotic treatment, indwelling catheters, or invasive procedures, causing extra-intestinal infections such as those of the urinary tract.
- These organisms produce exotoxins. Wide-spread antibiotic resistance among these organisms necessitates sensitivity testing to determine the appropriate antibiotic treatment.

Pseudomonas aeruginosa

- P. aeruginosa is a significant opportunistic pathogen, and a major cause of hospital-acquired (nosocomial) infections such as UTI, particularly in patients who have been subjected to catheterization, instrumentation, surgery, or renal transplantation or to prior antibiotic therapy.
- P. aeruginosa disease begins with attachment and colonization of host tissue. Pili on the bacteria mediate adherence, and glycoconjugate capsule reduces the effectiveness of normal clearance mechanisms. Host tissue damage facilitates adherence and colonization. Because pseudomonas infections typically occur in patients with impaired defenses, aggressive antimicrobial therapy is generally required.

Figure 33.4 (continued on the next page) Disease summary of urinary tract infections. ¹Uncomplicated cystitis.

Staphylococcus species

Gram (+) coccil

Staphylococcus aureus

- Septicemia
- Necrotizing pneumonia
- Toxic shock syndrome
- Food poisoning (antibiotic therapy not used)

Staphylococcus epidermidis

- Infections of catheters and heart valves

Staphylococcus saprophyticus

- Cystitis in women

Other characteristics:

- Catalase (+)
- Nonmotile
- Do not form spores
- Round coccil tending to occur in bunches like grapes
- Facultative anaerobic organisms
- Cultured on enriched media containing broth and/or blood

Antibiotic susceptibility:

- 1 Oxacillin
- 1 Nafcillin
- 1 Vancomycin
- 1 Trimethoprim/sulfamethoxazole
- 1 Doxycycline
- 1 Daptomycin
- 1 Linezolid
- 1 Vancomycin
- 2 Quinupristin/dalfopristin
- 2 Teicoplanin

Clinical features:

- Colonies are yellow
- Staphylococcus aureus cultured from a wound infection
- Staphylococcus aureus on blood agar surrounded by zone of β hemolysis
- Carbuncle caused by Staphylococcus aureus
- Furuncle caused by Staphylococcus aureus
- Folliculitis caused by Staphylococcus aureus
- Staphylococcal scalded skin syndrome
- Superficial impetigo

Notes:

- 1 Most isolates resistant to penicillin G
- 2 Used in methicillin-resistant isolates

Legend: ■ Staphylococcal disease. ■ Indicates first-line drugs; ■ indicates alternative drugs.

Illustrated Case Studies

Case 1: Man with necrosis of the great toe

This 63-year-old man with a long history of diabetes mellitus was seen in consultation because of an abrupt deterioration in his clinical status. He was admitted to the hospital for treatment of an ulcer, which had been present on his left great toe for several months. Figure 34.1 shows a typical example of perforating ulcer in a diabetic man.

Because of the inability of medical therapy (multiple courses of oral antibiotics) to resolve the ulcer, he underwent amputation of his left leg below the knee. On the first postoperative day he developed a temperature of 101°F, and on the

second postoperative day he became disoriented and his temperature reached 105.2°F. His amputation stump was mottled with many areas of purplish discoloration, and the most distal areas were quite obviously necrotic (dead). Crepitus (the sensation of displacing gas when an area is pressed with the fingers) was palpable up to his patella. An X-ray of the left lower extremity showed gas in the soft tissues, extending beyond the knee to the area of the distal femur. A Gram stain of a swab from the necrotic tissue is shown in Figure 34.2.



Figure 34.1 Perforating ulcer of the great toe.

Herpesviridae
Epstein-Barr virus

- Herpes simplex virus, Type 1
- Herpes simplex virus, Type 2
- Human cytomegalovirus
- Human herpesvirus, Type 8
- Varicella-zoster virus



Figure 34.2 Gram stain of material swabbed from deep within a crepitant area. There are numerous polymorphonuclear leukocytes, and many large gram-negative bacilli, as well as a few gram-negative bacilli and cocci.

Quick Review

Common characteristics

- Linear, double-stranded DNA genome
- Replicate in the nucleus
- Envelope contains antigenic, species-specific glycoproteins
- In the tegument between the envelope and capsid are a number of virus-coded enzymes and transcription factors essential for initiation of the infectious cycle
- All herpesviruses can enter a latent state following primary infection, to be reactivated at a later time

Contents

UNIT I: The Microbial World

- Chapter 1: Introduction to Microbiology 1
 Chapter 2: Normal Flora 7
 Chapter 3: Pathogenicity of Microorganisms 11
 Chapter 4: Diagnostic Microbiology 19
 Chapter 5: Vaccines and Antimicrobial Agents 33

UNIT II: Bacteria

- Chapter 6: Bacterial Structure, Growth, and Metabolism 49
 Chapter 7: Bacterial Genetics 59
 Chapter 8: Staphylococci 69
 Chapter 9: Streptococci 79
 Chapter 10: Gram-positive Rods 91
 Chapter 11: Neisseriae 101
 Chapter 12: Gastrointestinal Gram-negative Rods 111
 Chapter 13: Other Gram-negative Rods 129
 Chapter 14: Clostridia and Other Anaerobic Rods 149
 Chapter 15: Spirochetes 161
 Chapter 16: Mycoplasma 171
 Chapter 17: Chlamydiae 177
 Chapter 18: Mycobacteria and Actinomycetes 185
 Chapter 19: Rickettsia, Ehrlichia, Anaplasma and Coxiella 197

UNIT III: Fungi and Parasites

- Chapter 20: Fungi 203
 Chapter 21: Protozoa 217
 Chapter 22: Helminths 227

UNIT IV: Viruses

- Chapter 23: Introduction to the Viruses 233
 Chapter 24: Nonenveloped DNA Viruses 245
 Chapter 25: Enveloped DNA Viruses 255
 Chapter 26: Hepatitis B and Hepatitis D (Delta) Viruses 273
 Chapter 27: Positive-strand RNA Viruses 283
 Chapter 28: Retroviruses and AIDS 293
 Chapter 29: Negative-strand RNA Viruses 309
 Chapter 30: Double-stranded RNA Viruses: Reoviridae 323
 Chapter 31: Unconventional Infectious Agents 327

UNIT V: Clinical Microbiology Review

- Chapter 32: Quick Review of Clinically Important Microorganisms 331
 Chapter 33: Disease Summaries 367
 Chapter 34: Illustrated Case Studies 393
 Index 419

Introduction to Microbiology

1

I. OVERVIEW

Microorganisms can be found in every ecosystem and in close association with every type of multicellular organism. They populate the healthy human body by the billions as benign passengers (normal flora, see p. 7) and even as participants in bodily functions. For example, bacteria play a role in the degradation of intestinal contents. In this volume, we primarily consider the role of microorganisms (that is, bacteria, fungi, protozoa, helminths, and viruses) in the initiation and spread of human diseases. Those relatively few species of microorganisms that are harmful to humans, either by production of toxic compounds or by direct infection, are characterized as pathogens.

Most infectious disease is initiated by colonization (the establishment of proliferating microorganisms on the skin or mucous membranes) as shown in Figure 1.1. The major exceptions are diseases caused by introduction of organisms directly into the bloodstream or internal organs. Microbial colonization may result in: 1) elimination of the microorganism without affecting the host; 2) infection in which the organisms multiply and cause the host to react by making an immune or other type of response or 3) a transient or prolonged carrier state. Infectious disease occurs when the organism causes tissue damage and impairment of body function.

II. PROKARYOTIC PATHOGENS

All prokaryotic organisms are classified as bacteria, whereas eukaryotic organisms include fungi, protozoa, and helminths as well as humans. Prokaryotic organisms are divided into two major groups: the eubacteria, which include all bacteria of medical importance, and the archaeobacteria, a collection of evolutionarily distinct organisms. Cells of prokaryotic and eukaryotic organisms differ in several significant structural features as illustrated in Figure 1.2.

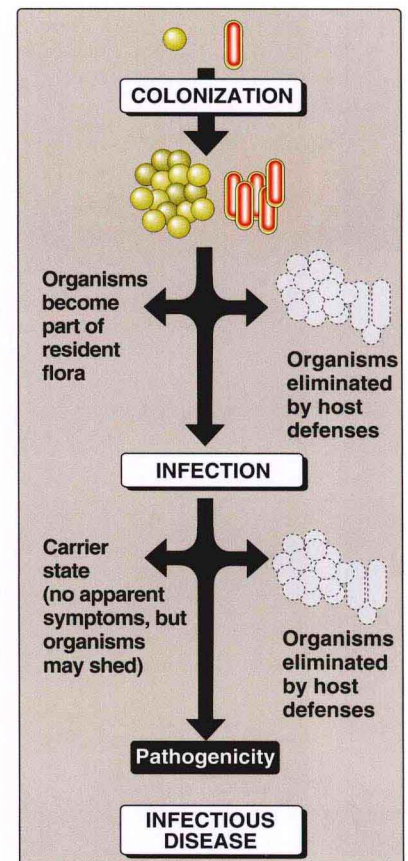


Figure 1.1

Some possible outcomes following exposure to microorganisms.

CHARACTERISTIC	PROKARYOTIC CELLS	EUKARYOTIC CELLS
Chromosome	Usually single, circular ¹	Multiple
Nucleus	No nuclear envelope or nucleoli	Membrane bound, nucleoli present
Membrane-bound organelles	Not present	Present (examples include mitochondria and endoplasmic reticulum)
Cell wall	Usually present, many contain peptidoglycan	Present in plant cells, no peptidoglycan
Plasma membrane	No carbohydrates, most lack sterols	Sterols and carbohydrates present
Ribosome	70S	80S (70S in organelles)
Average size	0.2–2 mm in diameter	10–100 mm in diameter

Figure 1.2

Comparison of prokaryotic and eukaryotic cells. ¹Some bacteria have more than one circular molecule as their genome. *Vibrios*, for example, have two circular chromosomes. *Borrellia* have linear chromosomes and a wide array of different sized plasmids.

A. Typical bacteria

Most bacteria have shapes that can be described as a rod, sphere, or corkscrew. Prokaryotic cells are smaller than eukaryotic cells (Figure 1.3). Nearly all bacteria, with the exception of the mycoplasma, have a rigid cell wall surrounding the cell membrane that determines the shape of the organism. The cell wall also determines whether the bacterium is classified as gram positive or gram negative (see p. 21). External to the cell wall may be flagella, pili, and/or a capsule. Bacterial cells divide by binary fission. However, many bacteria exchange genetic information carried on plasmids (small, specialized genetic elements capable of self-replication) including the information necessary for establishment of antibiotic resistance. Bacterial structure, metabolism, and genetics as well as the wide variety of human diseases caused by bacteria are described in detail in Unit II, beginning on p. 49.

B. Atypical bacteria

Atypical bacteria include groups of organisms such as *Mycoplasma*, *Chlamydia*, and *Rickettsia* that, although prokaryotic, lack significant characteristic structural components or metabolic capabilities that separate them from the larger group of typical bacteria.

III. FUNGI

Fungi are nonphotosynthetic, generally saprophytic, eukaryotic organisms. Some fungi are filamentous and are commonly called molds, whereas others (that is, the yeasts) are unicellular (see p. 203). Fungal reproduction may be asexual, sexual, or both, and all fungi produce spores. Pathogenic fungi can cause diseases, ranging from skin infections (superficial mycoses) to serious, systemic infections (deep mycoses).

IV. PROTOZOA

Protozoa are single-celled, nonphotosynthetic, eukaryotic organisms that come in various shapes and sizes. Many protozoa are free living, but oth-

ers are among the most clinically important parasites of humans. Members of this group infect all major tissues and organs of the body. They can be intracellular parasites, or extracellular parasites in the blood, urogenital region, or intestine. Transmission is generally by ingestion of an infective stage of the parasite or by insect bite. Protozoa cause a variety of diseases that are discussed in Chapter 21, p. 217.

V. HELMINTHS

Helminths are groups of worms that live as parasites. They are multicellular, eukaryotic organisms with complex body organization. They are divided into three main groups: tapeworms (cestodes), flukes (trematodes), and roundworms (nematodes). Helminths are parasitic, receiving nutrients by ingesting or absorbing digestive contents or ingesting or absorbing body fluids or tissues. Almost any organ in the body can be parasitized.

VI. VIRUSES

Viruses are obligate intracellular parasites that do not have a cellular structure. Rather, a virus consists of molecule(s) of DNA (DNA virus) or RNA (RNA virus), but not both, surrounded by a protein coat. A virus may also have an envelope derived from the plasma membrane of the host cell from which the virus is released. Viruses contain the genetic information necessary for directing their own replication but require the host's cellular structures and enzymatic machinery to complete the process of their own reproduction. The fate of the host cell following viral infection ranges from rapid lysis and release of many progeny virions to gradual, prolonged release of viral particles.

VII. ORGANIZING THE MICROORGANISMS

The authors have adopted two color-coded graphic formats: 1) an expanded hierarchical organization and 2) lists of clinically important bacteria and viruses.

A. Hierarchical organization

A hierarchical organization resembles a family tree. These graphs in Figures 1.4 and 1.5 divide bacteria and viruses into groups based on the characteristics of the microorganisms.

B. Lists of important bacteria and viruses

The hierarchical organizations described above are informative and useful as a study aids. However, they, at times, may provide the reader with too much information in a cumbersome configuration. The authors have thus adopted a second, simpler color-coded list format to represent the clinically important groups of bacteria and viruses. For example, bacteria are organized into eight groups according to Gram staining, morphology, and biochemical or other characteristics. The ninth item of the list, labeled "Other," is used to represent any organism not included in one of the other eight categories (Figure 1.6). In a similar way, viral pathogens are organized into seven groups based on the nature of their genome, symmetry of organization, and the presence or absence of a lipid envelope (Figure 1.7).

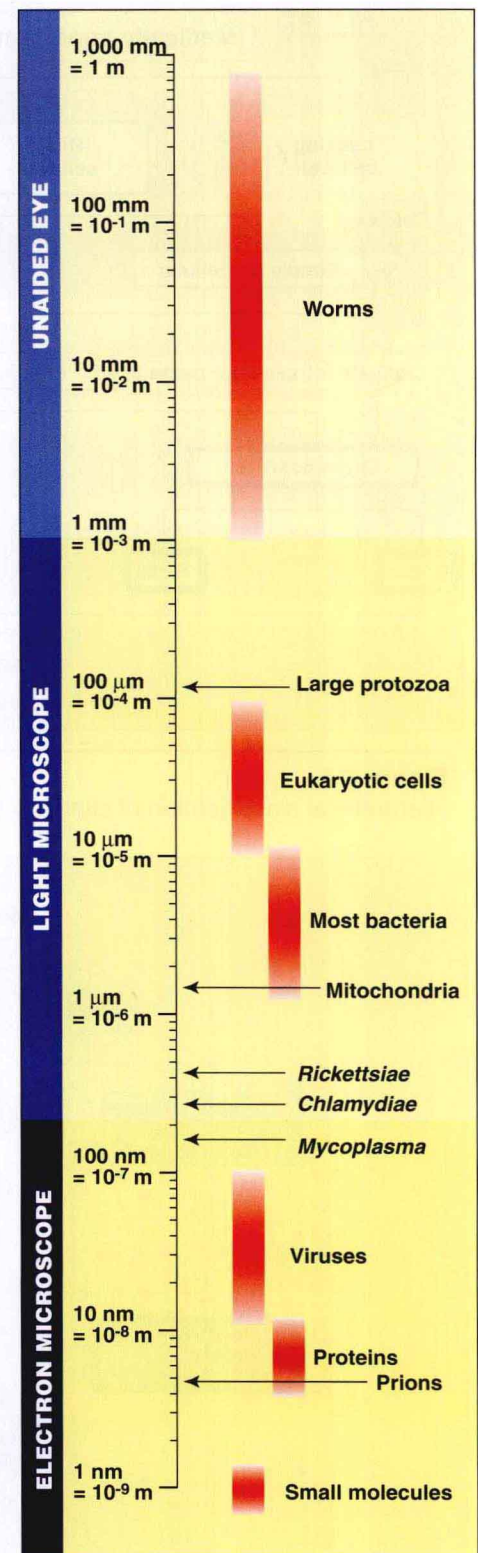


Figure 1.3
Relative size of organisms and molecules.

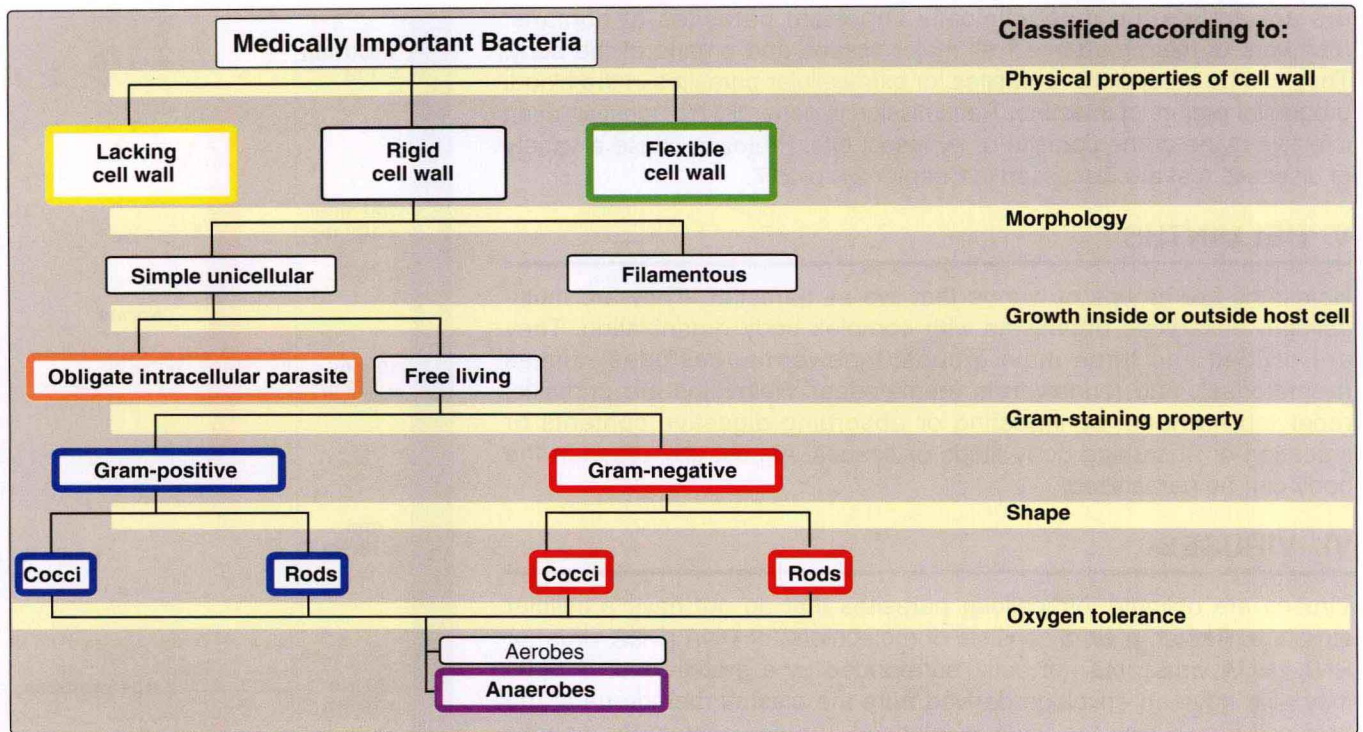


Figure 1.4

Hierarchical classification of clinically important bacteria according to six distinguishing characteristics.

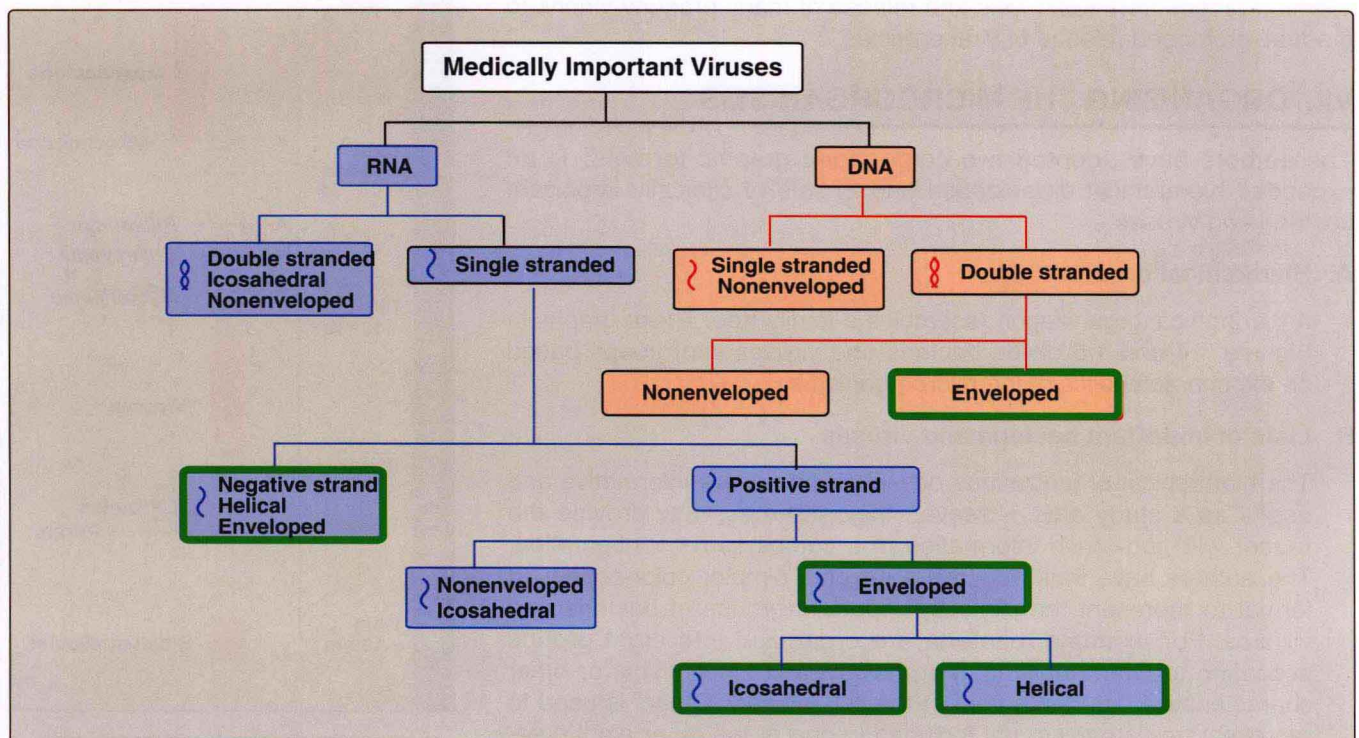
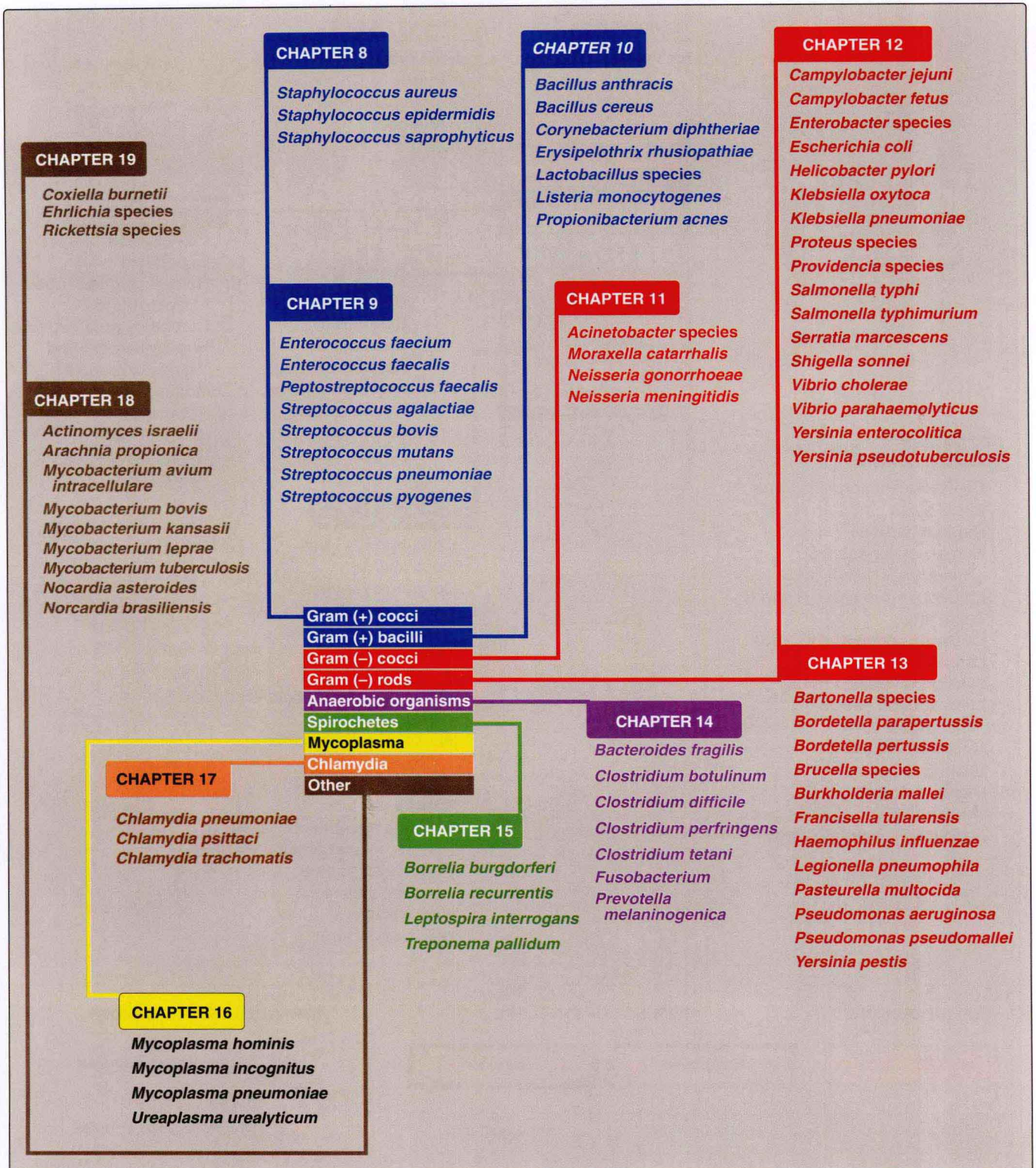


Figure 1.5

Classification of medically important virus families.

**Figure 1.6**

Medically important bacteria discussed in this book, organized into similar groups based on morphology, biochemistry, and/or staining properties.

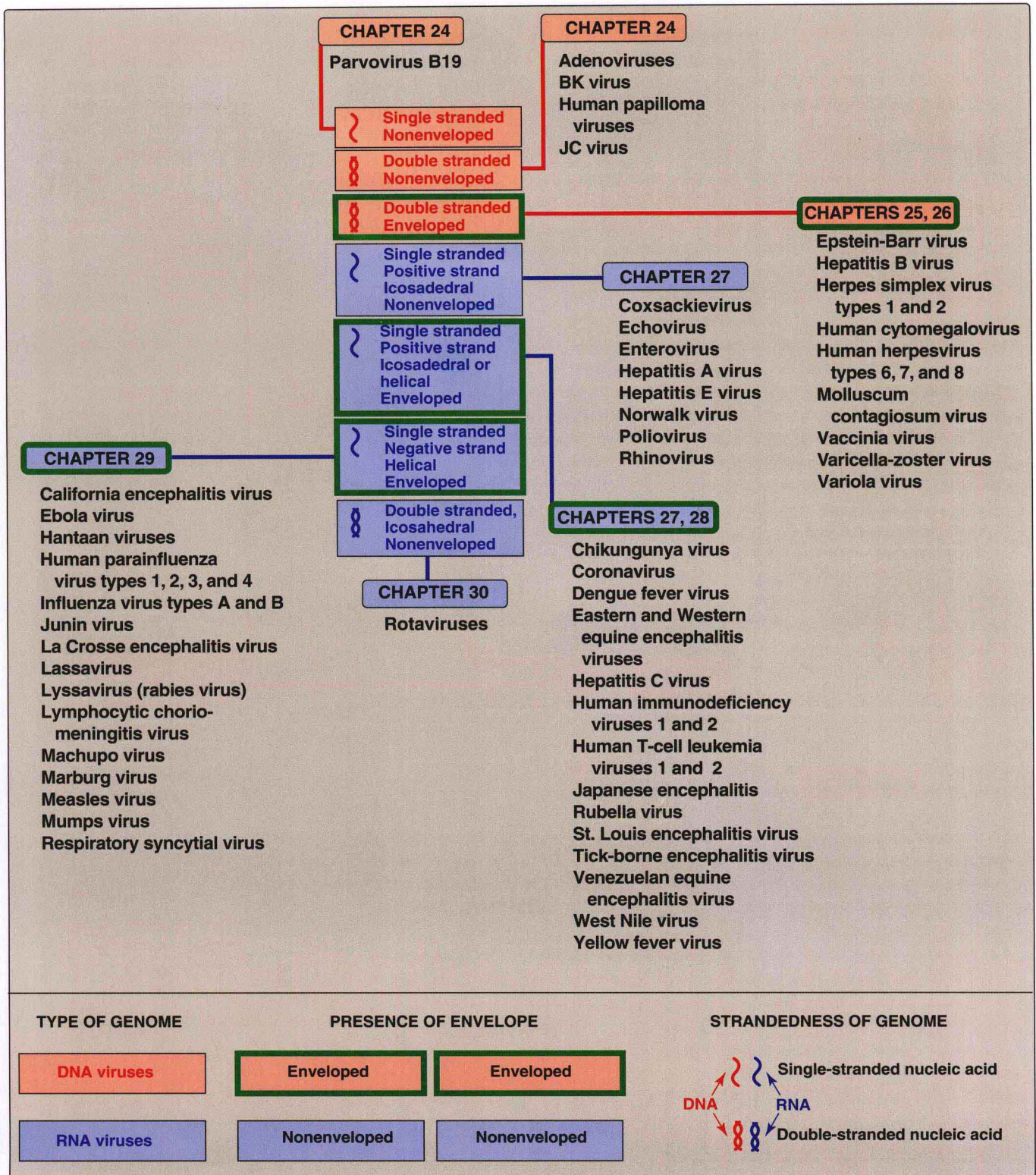


Figure 1.7

Medically important viruses discussed in this book, organized into similar groups based on the nature of the genome and the presence or absence of a lipid envelope.

Normal Flora

2

I. OVERVIEW

The human body is continuously inhabited by many different microorganisms (mostly bacteria, but also fungi and other microorganisms), which, under normal circumstances in a healthy individual, are harmless and may even be beneficial. These microorganisms are termed “normal flora.” The normal flora are also termed commensals, which literally means “organisms that dine together.” Except for occasional transient invaders, the internal organs and systems are sterile, including the spleen, pancreas, liver, bladder, central nervous system, and blood. A healthy newborn enters the world in essentially sterile condition, but, after birth, it rapidly acquires normal flora from food and the environment, including from other humans.

II. THE HUMAN MICROBIOME

The human microbiome is the total number and diversity of microbes found in and on the human body. In the past, the ability to cultivate organisms from tissues and clinical samples was the gold standard for identification of normal flora and bacterial pathogens. However, the recent application of culture-independent molecular detection methods based on DNA sequencing (see p. 28) indicates that the human body contains a far greater bacterial diversity than previously recognized. Unlike classic microbiologic culture methods, molecular detection requires neither prior knowledge of an organism nor the ability to culture it. Thus, molecular methods are capable of detecting fastidious and nonculturable species. Even using advanced molecular techniques, it is difficult to define the human microbiome because microbial species present vary from individual to individual as a result of physiologic differences, diet, age, and geographic habitat. Despite these limitations, it is useful to be aware of the dominant types and distribution of resident flora, because such knowledge provides an understanding of the possible infections that result from injury to a particular body site.

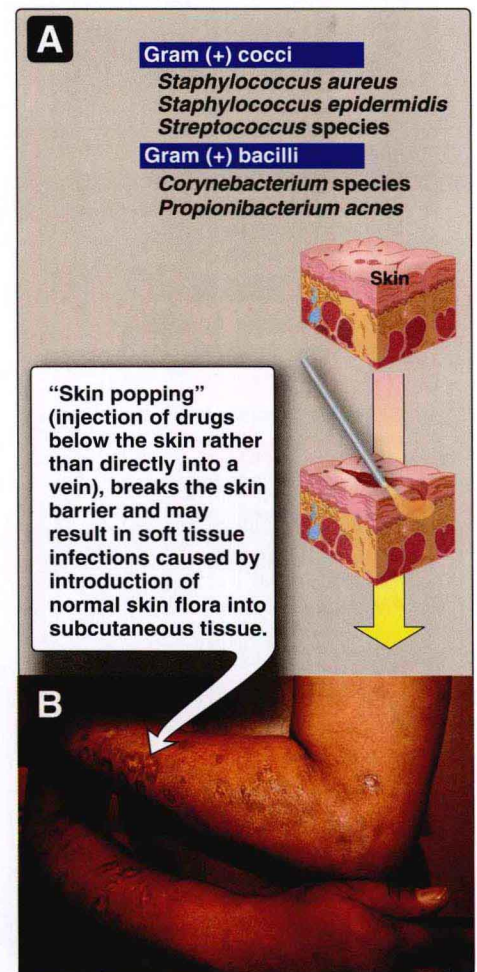


Figure 2.1

A. Examples of bacteria that inhabit the skin. B. Arm of individual who injects drugs by “skin popping.”

Gram (+) cocci
<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i> <i>Streptococcus</i> species
Gram (+) rods
<i>Corynebacterium</i> species <i>Propionibacterium acnes</i>
Gram (-) cocci
<i>Moraxella</i> <i>Neisseria</i> species

Figure 2.2

Examples of bacteria that inhabit the conjunctival sac. [Note: Tears, which contain the antimicrobial enzyme lysozyme, help limit the bacterial population of the conjunctiva.]

Gram (+) cocci
<i>Staphylococcus</i> species <i>Streptococcus sanguinis</i> <i>Streptococcus mutans</i>
Gram (+) rods
<i>Corynebacterium</i> species <i>Propionibacterium acnes</i>
Gram (-) cocci
<i>Neisseria</i> species
Gram (-) rods
<i>Haemophilus</i> species
Anaerobic organisms
<i>Bacteroides</i> species <i>Fusobacterium</i> <i>Prevotella</i> species
Spirochetes
<i>Borrelia</i> <i>Treponema</i>
Other
<i>Actinomyces</i>

The organism most often implicated in plaque formation is *Streptococcus mutans*, which produces the gelatinous glucans that constitute plaque material. *S. mutans*, accompanied by other acid-producing species, then adhere to the plaque and demineralize the tooth surface.

Figure 2.3

Examples of bacteria that inhabit the mouth.

III. DISTRIBUTION OF NORMAL FLORA IN THE BODY

The most common sites of the body inhabited by normal flora are, as might be expected, those in contact or communication with the outside world, namely, the skin, eye, and mouth as well as the upper respiratory, gastrointestinal, and urogenital tracts.

A. Skin

Skin can acquire any bacteria that happen to be in the immediate environment, but this transient flora either dies or is removable by washing. Nevertheless, the skin supports a permanent bacterial population (resident flora), residing in multiple layers of the skin (Figure 2.1). The resident flora regenerate even after vigorous scrubbing.

1. Estimate of the skin microbiome using classical culture techniques:

Staphylococcus epidermidis and other coagulase-negative staphylococci (see p. 76) that reside in the outer layers of the skin appear to account for some 90 percent of the skin aerobes. Anaerobic organisms, such as *Propionibacterium acnes*, reside in deeper skin layers, hair follicles, and sweat and sebaceous glands. Skin inhabitants are generally harmless, although *S. epidermidis* can attach to and colonize plastic catheters and medical devices that penetrate the skin, sometimes resulting in serious blood-stream infections.

2. Estimate of the skin microbiome using molecular sequencing techniques:

The estimate of the number of species present on skin bacteria has been radically changed by the use of the 16S ribosomal RNA gene sequence (see p. 28) to identify bacterial species present on skin samples directly from their genetic material. Previously, such identification had depended upon microbiological culture, upon which many varieties of bacteria did not grow and so were not detected. *Staphylococcus epidermidis* and *Staphylococcus aureus* were thought from culture-based research to be dominant. However DNA analysis research finds that, while common, these species make up only 5 percent of skin bacteria. The skin apparently provides a rich and diverse habitat for bacteria.

B. Eye

The conjunctiva of the eye is colonized primarily by *S. epidermidis*, followed by *S. aureus*, aerobic corynebacteria (diphtheroids), and *Streptococcus pneumoniae*. Other organisms that normally inhabit the skin are also present but at a lower frequency (Figure 2.2). Tears, which contain the antimicrobial enzyme lysozyme, help limit the bacterial population of the conjunctiva.

C. Mouth and nose

The mouth and nose harbor many microorganisms, both aerobic and anaerobic (Figure 2.3). Among the most common are diphtheroids (aerobic *Corynebacterium* species), *S. aureus*, and *S. epidermidis*. In

addition, the teeth and surrounding gingival tissue are colonized by their own particular species, such as *Streptococcus mutans*. [Note: *S. mutans* can enter the bloodstream following dental surgery and colonize damaged or prosthetic heart valves, leading to potentially fatal infective endocarditis.] Some normal residents of the nasopharynx can also cause disease. For example, *S. pneumoniae*, found in the nasopharynx of many healthy individuals, can cause acute bacterial pneumonia, especially in older adults and those whose resistance is impaired. [Note: Pneumonia is frequently preceded by an upper or middle respiratory viral infection, which predisposes the individual to *S. pneumoniae* infection of the pulmonary parenchyma.]

D. Intestinal tract

In an adult, the density of microorganisms in the stomach is relatively low (10^3 to 10^5 per gram of contents) due to gastric enzymes and acidic pH. The density of organisms increases along the alimentary canal, reaching 10^8 to 10^{10} bacteria per gram of contents in the ileum and 10^{11} per gram of contents in the large intestine. Some 20 percent of the fecal mass consists of many different species of bacteria, more than 99 percent of which are anaerobes (Figure 2.4). *Bacteroides* species constitute a significant percentage of bacteria in the large intestine. *Escherichia coli*, a facultatively anaerobic organism, constitutes less than 0.1 percent of the total population of bacteria in the intestinal tract. However, this endogenous *E. coli* is a major cause of urinary tract infections.

E. Urogenital tract

The low pH of the adult vagina is maintained by the presence of *Lactobacillus* species, which are the primary components of normal flora. If the *Lactobacillus* population in the vagina is decreased (for example, by antibiotic therapy), the pH rises, and potential pathogens can overgrow. The most common example of such overgrowth is the yeast-like fungus, *Candida albicans* (see p. 213), which itself is a minor member of the normal flora of the vagina, mouth, and small intestine. The urine in the kidney and bladder is sterile but can become contaminated in the lower urethra by the same organisms that inhabit the outer layer of the skin and perineum (Figure 2.5).

IV. BENEFICIAL FUNCTIONS OF NORMAL FLORA

Normal flora can provide some definite benefits to the host. First, the sheer number of harmless bacteria in the lower bowel and mouth make it unlikely that, in a healthy person, an invading pathogen could compete for nutrients and receptor sites. Second, some bacteria of the bowel produce antimicrobial substances to which the producers themselves are not susceptible. Third, bacterial colonization of a newborn infant acts as a powerful stimulus for the development of the immune system. Fourth, bacteria of the gut provide important nutrients, such as vitamin K, and aid in digestion and absorption of nutrients. [Note: Although humans can obtain vitamin K from food sources, bacteria can be an important supplemental source if nutrition is impaired.]

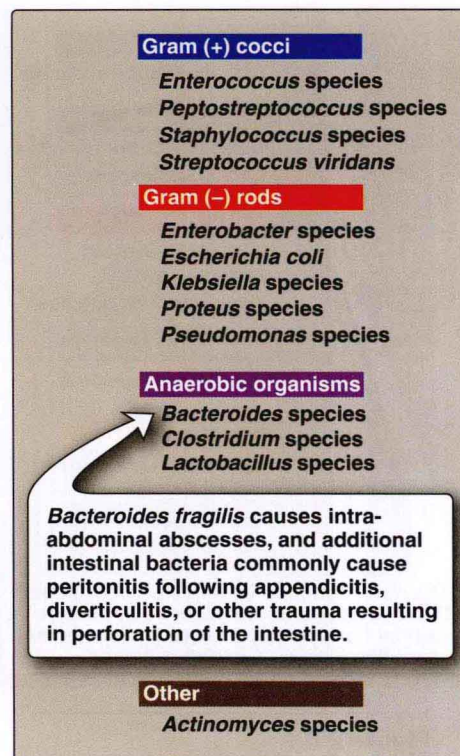


Figure 2.4

Examples of bacteria that inhabit the gastrointestinal tract.

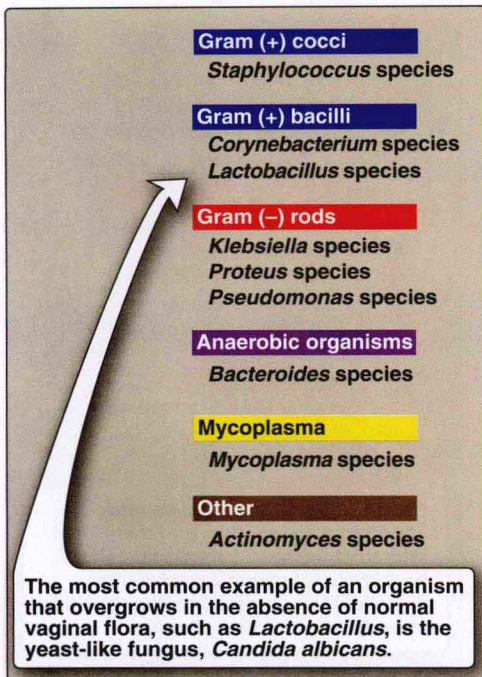


Figure 2.5

Examples of bacteria that inhabit the vagina.

V. HARMFUL EFFECTS OF NORMAL FLORA

Clinical problems caused by normal flora arise in the following ways: 1) The organisms are displaced from their normal site in the body to an abnormal site. An example already mentioned is the introduction of the normal skin bacterium, *S. epidermidis*, into the bloodstream where it can colonize catheters and heart valves, resulting in bacterial endocarditis. 2) Potential pathogens gain a competitive advantage due to diminished populations of harmless competitors. For example, when normal bowel flora are depleted by antibiotic therapy leading to overgrowth by the resistant *Clostridium difficile*, which can cause severe colitis. 3) Harmless, commonly ingested food substances are converted into carcinogenic derivatives by bacteria in the colon. A well-known example is the conversion by bacterial sulfatases of the sweetener cyclamate into the bladder carcinogen cyclohexamine. 4) When individuals are immunocompromised, normal flora can overgrow and become pathogenic. [Note: Colonization by normal, but potentially harmful, flora should be distinguished from the carrier state in which a true pathogen is carried by a healthy (asymptomatic) individual and passed to other individuals where it results in disease. Typhoid fever is an example of a disease that can be acquired from a carrier (see p. 116).]

Study Questions

Choose the ONE correct answer

2.1 The primary effect of lactobacilli in the adult vagina is to

- A. maintain an alkaline environment.
- B. maintain an acidic environment.
- C. produce a protective mucus layer.
- D. increase fertility.
- E. keep the menstrual cycle regular.

Correct answer = B. Lactobacilli produce acid that, in turn, inhibits the growth of potential pathogenic bacteria and fungi. None of the other answers are known to be attributed to lactobacilli.

2.2 A patient presents with severe colitis associated with an overgrowth of *Clostridium difficile* in the lower bowel. The most likely cause of this condition is

- A. botulinum food poisoning.
- B. a stomach ulcer.
- C. a compromised immune system.
- D. antibiotic therapy.
- E. mechanical blockage of the large intestine.

Correct answer = D. Antibiotic therapy can reduce normal flora in the bowel, allowing pathogenic organisms normally present in low numbers to overgrow. None of the other answers explains the overgrowth of *Clostridium difficile*.

2.3 The predominant bacterial species that colonizes the human skin is

- A. *Lactobacillus*.
- B. *Candida albicans*.
- C. *Streptococcus pneumoniae*.
- D. *Staphylococcus epidermidis*.
- E. *Bacterioides fragilis*.

Correct answer = D. Human skin normally contains up to 10,000 *Staphylococcus epidermidis* per cm². Other colonizing bacteria may be present but in much lower numbers. *Candida albicans* is a yeast-like fungus, not a bacterium.