Biology for Physicians: The Basics of Medical Microbiology

See online here

Microorganisms play a significant role in the pathogenesis of diseases in human beings. Prophylaxis and treatment are only possible if you have an exact understanding of the structure and metabolism of bacteria, viruses, and fungi. This article outlines the different morphological criteria and important facts about the structure, reproduction, and growth of the most important microorganisms.

Bacteria

All living organisms are divided into three domains:

- Eukaryotes (living organisms with a nucleus): humans, animals, plants, fungi
- Prokaryotes (living organisms without a nucleus): bacteria
- Archaea: formerly called archaebacteria

Not all unicellular pathogens are bacteria. Protists combine the groups of unicellular pathogens with a nucleus (i.e., eukaryotes). Protists include:

- Protozoa (important pathogens in malaria, sleeping sickness)

- Unicellular algae
- Certain fungi

Morphology and structure of bacteria

Bacteria are prokaryotes: They do not have an enveloped nucleus. Instead, the DNA is compressed into a nucleus-like body, the nucleoid, without being limited by a membrane. There are also no other organelles, as there are in eukaryotes (no endoplasmic reticulum, mitochondria, etc.): The entire metabolism of the bacterium takes place in the cytoplasm.

The two most important characteristics that identify bacteria microscopically are the external appearance of the bacterium, the Gram stain, as well as the type of flagellation (if any).

The following table provides an overview of the morphological classification of bacteria.

Cocci	Spherical, immobile, single or paired (**diplococci**), as twisted chains (**streptococci**) or as clusters (**staphylococci**)
Bacilli	Elongated shape (rods)
Spirilla	Helical shape (twisted)
Spirochetes	Helical, long, flagella-like filaments, corkscrew-like movements, their subgroup are the **treponema**
Vibrions	Gram-negative, round comma-shaped bacteria, flagellated

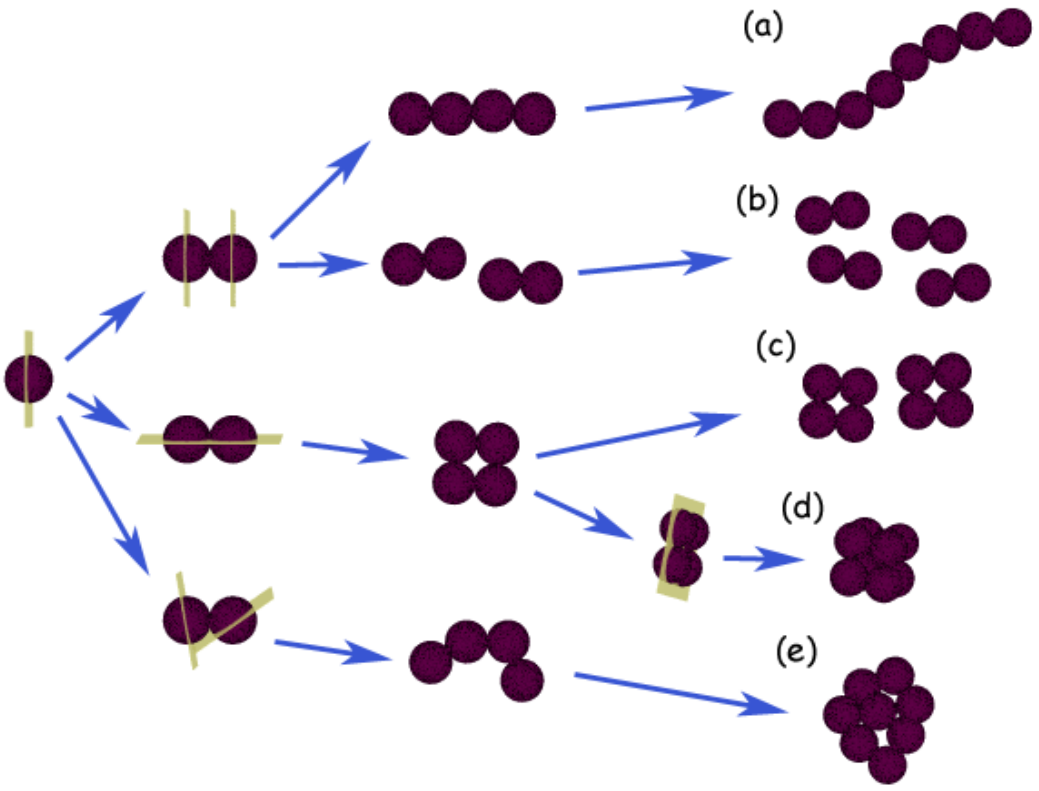

Image: “Arrangements of cocci. (a) streptococcus, divide along the same plane. (b) diplococcus, make pairs of two cocci after division. (c) tetrad, divide along two planes regularly. (d) sarcina, divide along three planes regularly. (e) staphylococcus, divide along planes irregularly.” by Y tambe. License: CC BY-SA 3.0

Bacterial cell walls

The bacterial cell wall attaches to the outside of the cell membrane. It provides mechanical stability and allows for the exchange of nutrients and waste. The

peptidoglycan murein is part of almost all bacterial walls. Murein consists of N-acetyl glucosamine and N-acetylmuramic acid cross-linked through oligopeptides. A murein sacculus develops from this linkage, which protects the cell and acts against osmotic pressure.

Mycoplasmas are bacteria that lack a cell wall.

Classification of bacteria according to Gram staining

Gram staining, a method named after the Danish bacteriologist Hans Christian Joachim Gram (1853–1938) is used to classify bacteria. It plays an important role in diagnostics because gram-negative bacteria are less sensitive to penicillin due to their additional lipid bilayer membrane.

The process of Gram staining includes:

- Administering the violet dye to the cells
- Washing off the stain with alcohol
- Red counter-staining of cells

Gram-positive bacteria show up as a violet stain; Gram-negative bacteria show up as a red stain.

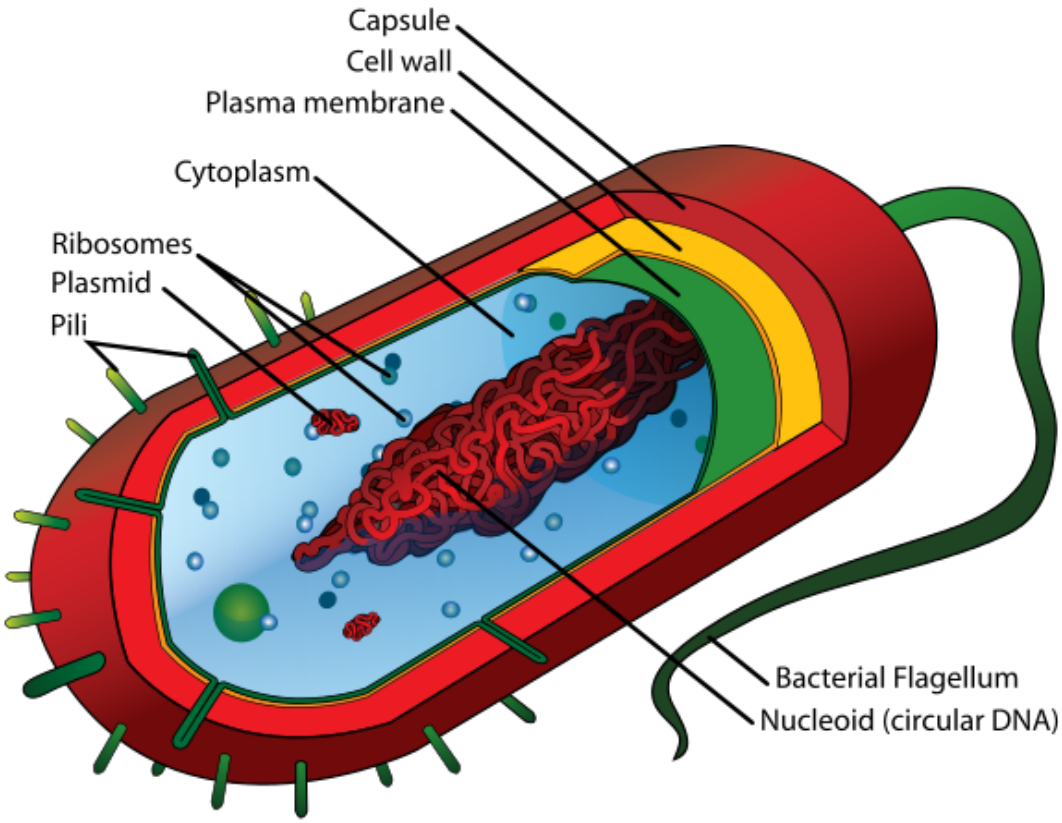

Image: “The cell envelope comprises a plasma membrane, seen here in green, and a thick peptidoglycan-containing cell wall (the yellow layer). No outer lipid membrane is present, as would be the case in Gram-negative bacteria. The red layer, known as the capsule, is distinct from the cell envelope.” License: CC0 1.0

Gram-positive bacteria have a thicker murein layer, while gram-negative bacteria have a thinner murein layer but a second membrane in the form of a lipid bilayer.

For the hosts themselves, an infection with gram-negative bacteria is more critical. Upon decomposition, the lipopolysaccharides of the second membrane layer can be released by the host body as endotoxins. Endotoxins act as pyogenes and cause high fever and chills.

Overview of gram-positive and gram-negative bacteria and diseases

Bacterium	Disease
Gram-positive	
Bacillus anthracis	Splenic fever (anthrax)
Corynebacterium diphtheriae	Diphtheria
Clostridium perfringens	Gas gangrene
Staphylococcus aureus	Nosocomial infections, impetigo
Streptococcus pneumoniae	Pneumonia, other infections
Mycobacterium tuberculosis	Tuberculosis
Gram-negative	
Haemophilus influenzae	Sinusitis, bronchitis, meningitis
Escheria coli	Urinary tract infections, neonatal meningitis
Chlamydophila pneumoniae	Pneumonia
Mycoplasma pneumoniae	Atypical pneumonia
Neisseria meningitidis	Meningitis

Bacterial flagella and pili

Approximately 50% of prokaryotes move with the help of flagella. Flagella can either be monotrich, meaning one single flagellum or polytrich, meaning more than one flagellum on the bacterium. Bacterial flagella consist of the protein flagellin and are not covered by the cell membrane. The placement of the flagella is either monopolar (at one end of the cell), bipolar (on both ends of the cell), or peritrich (all over the bacterium).

Sometimes, the proteins of the flagella are species-specific and thus work as antigens, which can be identified in serology (e.g., in salmonella or *E. coli*).

Pili are similar in structure to flagella but are much smaller. Pili (or fimbria) help the bacterium better adhere to surfaces and other bacteria. This adherence of the bacterium to a potential host is made possible by the fimbria. Therefore, they represent a virulence factor.

The purpose of flagella is movement. Pili adhere to surfaces.

Bacterial metabolism

Almost all bacteria need organic substances in order to survive; they, therefore, belong to the heterotrophic organisms. Bacteria are further classified according to their relationship to oxygen.

Obligate aerobe (aerophilic)	Oxygen is needed in order to maintain the metabolism.
Obligate anaerobe	There are no respiratory enzymes present; energy is generated via anaerobic glycolysis; oxygen has a toxic effect.
Microaerophilic	Oxygen is needed for growth; however, if the level is too high, growth will stop.
Facultative anaerobe	Growth is possible with or without oxygen.

Bacterial genetics

Bacteria are capable of exchanging genetic material with other bacteria. Because bacteria can integrate foreign DNA into their own genome, they can recombine their existing gene pool. In this way, different bacteria strains can transfer genetic properties among each other.

The three mechanisms of gene transfer are:

- Conjugation: parasexual transfer through contact via F pili
- Transduction: gene transfer through bacteriophages (viruses that infect bacteria)
- Transformation: the introduction of free, isolated, foreign DNA into the bacterial genome

The cause of the pathogenic effect of bacteria

Different factors have an influence on the virulence (strength of pathogenicity) of bacteria:

- The number of infecting bacteria
- Adhesions
- Invasion factors
- Replication rate
- Formation of endo- and exotoxins
- The ability to avoid the immune system

Endotoxins: Endotoxins are created during the breakdown of parts of the bacterial cell wall (see above) when bacteria die. Through cytokines, endotoxins activate the complement cascade as well as the coagulation cascade in the host, resulting in septic shock. Non-disease-specific symptoms caused by endotoxins include fever, pain, shock, fatigue, and discomfort.

Exotoxins: Some bacteria can produce toxins on their own and also secrete them. If they target a host, this can result in very severe disease-specific symptoms. Examples include cholera, botulinum, diphtheria, and tetanus toxins.

Antibacterial substances: Antibiotics and chemotherapeutics

Bactericidal substances kill bacteria, but bacteriostatic substances simply inhibit their growth. Antibiotics are substances synthesized from bacteria and fungi that work against other microorganisms. Antibiotics and chemotherapeutics interfere in certain steps of bacterial cell metabolism. They inhibit replication, transcription, and translation, or damage the bacterial cell wall or cell membrane. Penicillins, for example, inhibit murein synthesis.

Fungi

Fungi belong to the eukaryote domain and, like plants, have cell walls and vacuoles, exhibit cytoplasmic streaming, and are immobile. Almost all fungi cell walls are composed of chitin, however, not cellulose. Fungi do not carry out photosynthesis but get their substrates for metabolism because they are saprophytes (i.e., they obtain their food from

dead matter).

Fungal growth forms and reproduction

Fungi are mostly composed of thread-like hyphae. The organism of a fungus consists of a tubular system in which the hyphae form a strongly branching net, the mycelium. Yeasts are the exception: they do not form any hyphae or a mycelium.

Fungi can reproduce either sexually or asexually. Asexual reproduction takes place through binary fission, the breakdown of hyphae, budding (in yeasts), or the formation of conidia (containing asexual, mitotic spores). Sexual reproduction occurs through the merging of two physiologically different cells. The emerging diploid cell can now bud out and form diploid cells. If reduction division does not occur until the zygote stage, haploid spores form.

Fungi have the ability to switch between diploid and haploid forms.

Toxic synthesis products of fungi

Some fungi can produce toxic substances, which pose a threat to humans. The following overview summarizes the most important fungi and the toxic substances they produce, as well as their effect.

Toxin	Fungus	Effect
Aflatoxin	Aspergillus flavus, Aspergillus parasiticus	Highly carcinogenic, often the cause of food poisonings (traces on nuts, grain, spices)
Amanitin	Death cap mushroom	Inhibition of RNA polymerase II, lethal even in small doses
Muscarine	Toadstool (fly agaric mushroom)	Impacts the parasympathetic regulation of the nervous system
Ergotamine	Ergot fungus (Clavizeps purpurea)	Impacts the autonomic nervous system, hallucinogenic effect, effects uterine contraction
Cyclosporine A	Cylindrocarpon, Tolypocladium	Immunosuppressive effect (clinical use after organ transplants)

The pathogenic effect of fungi

Infectious diseases caused by fungi are called mycoses. In a healthy individual, they usually do not pose a problem. If the immune system is compromised, however, they will break out as opportunistic infections.

- Dermatophytes are keratinophilic fungi that affect human skin, hair, and nails
- Yeast and mold fungi affect the gastrointestinal and respiratory mucous membranes (high risk after treatment with antibiotics!)
- Systemic mycoses develop when fungi spores are inhaled; they can then manifest in different inner organs, resulting in severe infections that can be lethal. (HIV-positive patients are susceptible to these infections.)

Synthesis of antibiotics

Alexander Fleming determined in 1928 that some fungi are capable of producing

substances that are effective as antibiotics, including penicillin from *Penicillium notatum*, cephalosporin from *Acremonium,* and griseofulvin from *Penicillium griseofulvum*. Fifty of these approximately 2,000 substances characterized as antibiotics are used as chemotherapeutics.

Viruses

Viruses are infectious particles that are between 20 nm and 300 nm in size. Viruses cannot grow on their own or reproduce; they use host cells instead. They invade the host cells and use the host metabolism for their own reproduction. Bacteriophages are a particular type of virus: They use bacteria as their hosts by injecting their genome into the bacterium and integrating it into the genome.

Structure and classification of viruses

The genetic information of the virus exists in the form of a nucleoid from DNA or RNA. The nucleoid is surrounded by capsid, a protein layer, and partially by an additional layer of lipids and glycoproteins. Some viruses have enzymes; for example, reverse transcriptase (RT).

Viruses are classified according to the following characteristics:

- RNA or DNA
- Single- or double-stranded genome
- Naked or enveloped (additional envelope)
- Cube-based, helical, or complex capsid symmetry
- Animals, plants, or humans as a host
- Immunological characteristics
- Sensitive toward chemical or physical properties

Viral replication

With regard to the type of replication, it is important to differentiate between bacteriophages and eukaryotic viruses.

The replication cycle of bacteriophages

Phages are composed of a single- or double-stranded head and a tail, which serves to adhere to the host bacterium. After penetrating the cell wall, this hollow tail injects its genome into the bacterium. Afterward, 2 different cycles can follow the lytic replication cycle or the temperate/lysogenic cycle.

During the lytic replication cycle, DNA is transcribed immediately. The protein structures and the envelopes of the phage are replicated by the host, as is the DNA later on. The bacterium dies off in the process. Approximately 100–200 new infectious phages are released per host cell.

The temperate cycle is also referred to as the lysogenic cycle. The term ‘lysogenic’ describes the integration of the phage DNA into the bacterial chromosome. Prophages are created, which are first replicated together with the bacteria DNA and inherited.

The replication cycle of viruses infecting eukaryotic cells

In this case, the viruses completely invade the host cell. The genome is released inside the infected cell.

The 6 steps of viral replication are:

- Attachment: using specialized proteins to attach to the host cell
- Penetration: invading the cell
- Uncoating: the capsid is dismantled and genetic material is made available
- Replication: the viral nucleic acid and viral proteins are synthesized
- Maturation: synthesis components form new viruses
- Liberation/release: new viruses exit the cell via membrane lysis or pinching of the cell membrane

Special case: Retroviruses

In retroviruses, the genetic information is present in the form of RNA rather than DNA. Retroviruses possess a special enzyme, the RT. The RT transcribes the RNA into DNA before releasing it into the host cell. The most prominent example of a retrovirus is HIV, which causes AIDS.

Prions

The term ‘prions’ is derived from the term ‘proteinaceous infectious particle’: Prions are very small, pathogenic infectious, proteins. Prions are associated with several degenerative diseases, including bovine spongiform encephalopathy, commonly known as ‘mad cow disease.’

Other diseases include scrapie in sheep, Creutzfeldt-Jakob disease, and kuru (found exclusively in a tribe practicing cannibalistic rites). The transfer mechanism of prions has not yet been determined.

Parasites

Parasites are organisms that take metabolic advantage of another organism. They can be classified as viruses, bacteria, fungi, protozoa, helminths, or arthropods. Zoonoses are human diseases that are transmitted via animals.

Protozoa

Protozoa are basic single-celled eukaryotes consisting of genetic material and a single-layer lipid membrane. They use arthropod vectors to infect species and can exist in two forms: an active trophozoite and a dormant cyst.

Classification

Class	Species
Amoebas	Entamoeba histolytica
Flagellates	Giardia lambia
Cillates	Balantidium coli
Apicomplexans	Plasmodium spp.

Helminths (worms)

Helminths are multi-celled organisms that can reproduce sexually or are hermaphroditic. They have the ability to develop into dormant cysts. Helminths live complex lives

involving animal and environmental reservoirs. They can be transmitted via fecal-oral or fecal-skin contact, or through ingestion. The disease burden is directly related to the number of worms that are in the host.

Nematodes (roundworms)

Roundworms are non-segmented worms that can infect the intestine, blood, or skin.

Transmission Route	Species
Intestine	Ascaris Lumbricoides, Strongyloides stercoralis
Blood	Onchocerca volvulus, Wuchereria bancrofti
Tissue	Ancylostoma brazilense (hookworm)

Flatworms (Platyhelminthes)

Flatworms are a primitive worm that is asymmetrical in shape. They are divided into trematodes (Schistosoma) and cestodes (tapeworms).

Trematodes

Trematodes are a common water-borne parasite. It is estimated that between 200 and 300 million people worldwide are infested with trematodes. They are laid as eggs in fresh water. These parasites cannot swim and need to mature in freshwater snails. Once matured, the Schistosoma penetrate through exposed human skin into the bloodstream. The trematodes enter the venous system and lay eggs in the intestinal tract. The eggs are released with human feces into the environment.

Species	Egg laying location
Schistosoma japonicum	Intestine
Schistosoma masoni	Intestine
Schistosoma haematobium	Bladder
Schistosoma mekongi	Intestine

Cestodes

Cestodes are a segmented worm that lives in the digestive tract of their host and absorbs nutrients as they pass through the intestine. The parasite’s eggs are ingested through undercooked food.

Prevalence of parasitic infections

The majority of parasitic infections occur in tropical regions and in developing countries. Hosts may not show any symptoms of infestation until immunosuppression occurs.

Infection	Prevalence
Toxoplasmosis	1–2 billion
Ascariasis	1 billion
Hookworm disease	800–900 million
Amebiasis	200–400 million
Schistosomiasis	200–300 million
Malaria	200–300 million

Filariasis	250 million
Giardiasis	200 million
Pinworm infection	60–100 million
Strongyloides	50–80 million
Guinea Worm Disease	Nearly eradicated
Typanosomiasis	15–20 million
Leishmaniasis	1–2 million

Review Questions

The correct answers can be found below the references.

1. Over the course of an infectious disease, an endotoxin shock can occur as a result of the release of lipopolysaccharides. During which kind of infection is this most likely to occur?

A. Retroviruses
B. Gram-negative rods
C. Gram-positive rods
D. Gram-positive diplococci
E. Facultative anaerobes

2. A 13-year-old boy who has never been seriously ill before is taken to the hospital with a fever, difficulty breathing, and increasing suspicion of pneumonia. Four days early, his family physician had prescribed a broad-spectrum antibiotic (penicillin with gram-negative and gram-positive efficacy spectrum) without any improvement. The failure of this therapy as well as the clinical symptoms the boy is experiencing point to which most likely original pathogen?

A. *Staphylococci*
B. *Enterobacteriaceae*
C. Viruses
D. Mycoplasmas
E. *Streptococci*

3. Retroviridae represents a certain group of viruses. Which stage of the replication cycle of viruses was the determining factor for the name of these special viruses?

A. Penetration
B. Transcription
C. Maturation
D. Uncoating
E. Liberation/Release

References

Wenisch (2013): mediscript Kurzlehrbuch Biologie – Elsevier Verlag.

Poeggel (2009): Kurzlehrbuch Biologie – Thieme Verlag.

Carrol, K.C., et al., *Medical Microbiology*. 27th ed. New York: McGraw-Hill. 2013. Print

Ryan, K.J., Ray, C.G. *Sherris Medical Microbiology.* 6th ed. New York: Mcgraw-Hill, 2014. Print

Gladwin, M., Trattler, B. *Clinical Microbiology made Rediculously Simple.* 5th ed. Miami: MedMaster 2011. Print.

Correct anwers: 1B, 2D, 3B

Notes