Learning Objectives

1. Describe what is meant by anatomical barriers to infection.
2. List 4 ways in which the body can physically remove microorganisms or their products.
3. Briefly describe how intraepithelial T-lymphocytes and B-1 cells play a role in innate immunity.
4. Describe how bacterial antagonism by normal microbiota acts as a non-specific body defense mechanism and name 2 opportunistic microbes that may cause superinfection upon destruction of the normal microbiota.
5. Briefly describe the process involved in the development of antibiotic-associated colitis.

Anatomical barriers are tough, intact barriers that prevent the entry and colonization of many microbes. Examples include the skin, the mucous membranes, and bony encasements.

The skin

The skin, consisting of the epidermis and the dermis, is dry, acidic, and has a temperature lower than 37 degrees Celsius (body temperature). These conditions are not favorable to bacterial growth. Resident normal microbiota of the skin also inhibits potentially harmful microbes. In addition, the dead, keratinized cells that make up the surface of the skin are continuously being sloughed off so that microbes that do colonize these cells are constantly being removed. Hair follicles and sweat glands produce lysozyme and toxic lipids that can kill bacteria. Epithelial cells also produce defensins and cathelicidins to kill microbes. Beneath the epidermis of the skin are Langerhans’ cells - immature dendritic cells - that phagocytose and kill microbes, carry them to nearby lymph nodes, and present antigens of these microbes to T-lymphocytes to begin adaptive immune responses against them. Finally, intraepithelial T-lymphocytes and B-1 lymphocytes are associated with the epidermis and the mucosal epithelium. These cells recognize microbes common to...
the epidermis and mucous membranes and start immediate adaptive immune responses against these commonly encountered microbes.

The mucous membranes

Mucous membranes line body cavities that open to the exterior, such as the respiratory tract, the gastrointestinal tract, and the genitourinary tract. Mucous membranes are composed of an epithelial layer that secretes mucus, and a connective tissue layer. The mucus is a physical barrier that traps microbes. Mucus also contains lysozyme to degrade bacterial peptidoglycan, an antibody called secretory IgA that prevents microbes from attaching to mucosal cells and traps them in the mucus, lactoferrin to bind iron and keep it from being used by microbes, and lactoperoxidase to generate toxic superoxide radicals that kill microbes. Resident normal microbiota of the mucosa also inhibits potentially harmful microbes. In addition, the mucous membrane, like the skin, is constantly sloughing cells to remove microbes that have attached to the mucous membranes. Beneath the mucosal membrane is mucosa-associated lymphoid tissue (MALT) that contains Langerhans’ cells - immature dendritic cells - that phagocytose and kill microbes, carry them to nearby lymph nodes, and present antigens of these microbes to T-lymphocytes to begin adaptive immune responses against them. Intraepithelial T-lymphocytes and B-1 lymphocytes are associated with the epidermis and the mucosal epithelium. These cells recognize microbes common to the epidermis and mucous membranes and start immediate adaptive immune responses against these commonly encountered microbes.

Bony encasements

Bony encasements, such as the skull and the thoracic cage, protect vital organs from injury and entry of microbes.

Mechanical removal is the process of physically flushing microbes from the body. Methods include:

1. **Mucus and cilia**: Mucus traps microorganisms and prevents them from reaching and colonizing the mucosal epithelium. Mucus also contains lysozyme to degrade bacterial peptidoglycan, an antibody called secretory IgA that prevents microbes from attaching to mucosal cells and traps them in the mucus, lactoferrin to bind iron and keep it from being used by microbes, and lactoperoxidase to generate toxic superoxide radicals that kill microbes. Cilia on the surface of the epithelial cells propel mucus and trapped microbes upwards towards the throat where it is swallowed and the microbes are killed in the stomach. This is sometimes called the tracheal toilet.

2. **The cough and sneeze reflex**: Coughing and sneezing removes mucus and trapped microbes.

3. **Vomiting and diarrhea**: These processes remove pathogens and toxins in the gastrointestinal tract.

4. **The physical flushing action of body fluids**: Fluids such as urine, tears, saliva, perspiration, and blood from injured blood vessels also flush microbes from the body.

Bacterial Antagonism by Normal Microbiota

Approximately 100 trillion bacteria and other microorganisms reside in or on the human body. The normal body microbiota keeps potentially harmful opportunistic pathogens in check and also inhibits the colonization of pathogens by:
1. Producing metabolic products (fatty acids, bacteriocins, etc.) that inhibit the growth of many pathogens;
2. Adhering to target host cells so as to cover them and preventing pathogens from colonizing;
3. Depleting nutrients essential for the growth of pathogens; and
4. Non-specifically stimulating the immune system.

Destruction of normal bacterial microbiota by the use of broad spectrum antibiotics may result in superinfections or overgrowth by antibiotic-resistant opportunistic microbiota. For example, the yeast *Candida*, that causes infections such as vaginitis and thrush, and the bacterium *Clostridium difficile*, that causes potentially severe antibiotic-associated colitis, are opportunistic microorganisms normally held in check by the normal microbiota.

In the case of *Candida* infections, the *Candida* resists the antibacterial antibiotics because being a yeast, it is eukaryotic, not prokaryotic like the bacteria. Once the bacteria are eliminated by the antibiotics, the *Candida* has no competition and can overgrow the area.

*Clostridium difficile* is an opportunistic Gram-positive, endospore-producing bacillus transmitted by the fecal-oral route that causes severe antibiotic-associated colitis. *C. difficile* is a common healthcare-associated infection (HAIs) and is the most frequent cause of health-care-associated diarrhea. *C. difficile* infection often recurs and can progress to sepsis and death. CDC has estimated that there are about 500,000 *C. difficile* infections (CDI) in health-care associated patients each year and is linked to 15,000 American deaths each year.

Antibiotic-associated colitis is especially common in older adults. It is thought that *C. difficile* survives the exposure to the antibiotic by sporulation. After the antibiotic is no longer in the body, the endospores germinate and *C. difficile* overgrows the intestinal tract and secretes toxin A and toxin B that have a cytotoxic effect on the epithelial cells of the colon. *C. difficile* has become increasingly resistant to antibiotics in recent years making treatment often difficult. There has been a great deal of success in treating the infection with fecal transplants, still primarily an experimental procedure. Polymerase chain reaction (PCRs) assays, which test for the bacterial gene encoding toxin B, are highly sensitive and specific for the presence of a toxin-producing *Clostridium difficile* organism. The most successful technique in restricting *C. difficile* infections has been the restriction of the use of antimicrobial agents.

Think-Pair-Share Questions

1. A patient is given large doses of broad spectrum antibiotics and subsequently develops a *Candida albicans* infection of the vagina. Discuss why this might happen in terms of immediate innate immunity. Why didn't the antibiotic kill the *Candida albicans* too?
2. Often during intestinal infections drugs are given to suppress diarrhea. Discuss why this may not always be a good idea, especially with microbial infections that cause ulceration of the intestines.

Summary

Anatomical barriers such as the skin, the mucous membranes, and bony encasements are tough, intact barriers that prevent the entry and colonization of many microbes. Mechanical removal is the process of physically flushing microbes from the body. Examples include mucus and cilia, coughing and sneezing, vomiting and diarrhea, and the flushing action of bodily fluids. The normal microbiota keeps potentially harmful opportunistic pathogens in check and also inhibits the colonization of pathogens by producing metabolic products that inhibit the growth of many pathogens, adhering to target...
host cells so as to cover them and prevent pathogens from colonizing, depleting nutrients essential for the growth of pathogens, and non-specifically stimulating the immune system.

Destruction of normal bacterial microbiota by the use of broad spectrum antibiotics may result in superinfections or overgrowth by antibiotic-resistant opportunistic microbiota such as *Candida* and *Clostridium difficile*. 