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Host-Pathogen Interactions

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Interactions of Pathogens with the Host

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Glossary

Colonization The occupation of a normally nonsterile body surface such as the skin or mucosal membrane by bacteria in the absence of disease.

Communicable The property of an infectious agent of transmission from person to person.

Immunopathology Injury to the host that is mediated by the immune response to an agent.

Signs The objective manifestations of a disease that can be observed by one such as a physician.

Symptoms The subjective complaints of the clinical effects of any disease that are experienced and expressed by a patient.

Toxins Exogenous molecules that disrupt cell function.

Definitions Distinguishing the Key Concepts of Infectious Diseases

Infection is the presence of an organism in an ordinarily sterile body site or an organism other than normal flora for that location on a body surface. An infection may or may not cause illness of the patient. Infection that does not cause illness is called *subclinical*. Diseases cause *symptoms*, clinical manifestations that the patient describes such as pain, nausea, loss of appetite, or fatigue, and *signs*, objective observations such as fever, rash, paralysis, seizure, coma, or rapid breathing. The duration of infection may be *acute* (days or weeks) or *chronic* (months or years). If the pathogen is not cleared by the immune response, the infection is described as *persistent*. If an infectious agent persists without replicating, the infection is called *latent*. A latent infection can *reactivate*; the agent can replicate and cause illness if the immune system fails to keep it under control.

The presence of a pathogenic or nonpathogenic organism on a nonsterile body surface such as the skin or mucosa of the mouth, nasopharynx, gastrointestinal tract, or vagina in the absence of disease is defined as *colonization*. If such a pathogenic organism that has colonized a body surface begins to cause tissue damage as by production of a toxin, the condition has become an *infectious disease* even if only the toxin and not the microbe enters the circulation and the pathogen remains

on the mucosa or skin. *Invasion* of the microorganism beyond the body surface resulting in clinical signs and symptoms is also an *infectious disease*.

Pathogenesis of an infectious disease refers to two concepts: the sequence of events that occur in an infection and the mechanisms by which the pathogen causes cellular and tissue injury. The principal concepts related to the pathogenic sequence in infections are *transmission* of the agent, its *reservoir*, *portal of entry* into the body, *route of spread* in the body, and *target organs* of infection. The principal concepts related to pathogenic mechanisms are *toxins* (molecules that disrupt cell function); enzymes that damage molecules, cells, and tissue; and microbial interactions with the immune system including evasion of innate and adaptive immunity, *immunopathology* (injury caused by an immune response), clearance of the agent, and *resolution* of the infection.

Transmission and Portal of Entry

The mechanism by which an infectious agent enters the host is *transmission*. The organism is transmitted from its normal ecological niche, its *reservoir*, by ingestion, inhalation, mucosal contamination, or cutaneous inoculation. Infections that are transmitted from person to person are termed *communicable*. The reservoir of these infectious agents is infected or colonized persons who may be ill or asymptomatic carriers of the

pathogen. These persons shed the pathogens in their respiratory secretions, feces, or genital or cutaneous contact. Other reservoirs include animals, water, and soil.

Portals of entry are the upper respiratory tract, lungs, conjunctiva, gastrointestinal tract (mouth, esophagus, stomach, and large and small intestines), urethra, vagina, and skin. Droplets and aerosols (particles 5 μm in diameter or less) are generated by sneezing, coughing, and singing. Aerosols can remain suspended in the air for prolonged periods and inhaled deeply into the lungs, reaching the alveoli. Particles larger than 5 μm in diameter lodge in the nasopharynx, trachea, and bronchi. Infected nasal and respiratory secretions are frequently spread by hand-to-hand contact or hand-to-fomite (such as a doorknob) contact followed by transfer of the infected secretions from contaminated hand to the nose or conjunctival mucosa. Thus are the rhinoviruses that cause common colds and influenza viruses often transmitted. Aerosol particles inhaled into the alveoli initiate infection in the lung (e.g., tuberculosis).

Although ingestion of water or food contaminated by fecal organisms from another human or an animal enters the body via the mouth, the gastrointestinal tract is best considered to be a long extracorporeal tunnel that enters at the mouth and traverses the body exiting at the anus. Most enteric pathogens cause disease by either secreting toxins (e.g., enterotoxigenic *Escherichia coli*), infecting intestinal lining epithelium (e.g., rotavirus), or using the mucosa of the small intestine as the portal of entry into normally sterile tissue (e.g., *Salmonella typhi*). Sexually transmitted diseases involve transfer of microorganisms (e.g., herpes simplex virus type II) from infected genitalia to the partner's urogenital skin or mucosa. Urinary tract infections usually enter via the urethra (e.g., *E. coli*) from the contaminated perineal skin.

Infection of the skin can occur by contact with infected skin of another person (e.g., warts caused by human papillomaviruses) or via a wound that disrupts the anatomical integrity of the formidable cutaneous barrier. Wound infections range from a staphylococcal cutaneous abscess to life-threatening gas gangrene caused by *Clostridium perfringens*. Inoculation of pathogens through healthy skin can occur via a drug addict's contaminated needle (e.g., hepatitis C virus) or an arthropod bite (e.g., *Aedes aegypti* mosquito transmitting yellow fever virus). Indeed, pathogens are transmitted by saliva of feeding mosquitoes, ticks (e.g., Lyme disease), and mites (e.g., scrub typhus); regurgitation from fleas (e.g., plague); and feces of lice (e.g., epidemic typhus), fleas (e.g., murine typhus), and triatomid bugs (e.g., Chagas' disease).

Routes of Spread Within the Body

Some infectious agents replicate on or in epithelial cells at the portal of entry, spread to adjacent cells, and cause disease by damage to the tissue locally (e.g., coronaviruses in the upper respiratory tract) or produce toxins that are absorbed and disseminated systemically (e.g., *Corynebacterium diphtheriae*). Other pathogens invade at the portal of entry and produce enzymes that mediate spread directly through adjacent tissues (e.g., cellulitis caused by *Streptococcus pyogenes*).

However, most systemic infections spread through the body using the available anatomical avenues of the lymphatic vessels,

blood vessels, nerves, urinary tract, respiratory tract, female genital tract, mesothelial surfaces of the body cavities, and cerebrospinal fluid-containing subarachnoid space and cerebral ventricles. *Bartonella henselae* enter the skin via a scratch wound by a kitten and spread via cutaneous lymphatic vessels to the draining lymph nodes that become impressively enlarged in cat scratch disease. *Mycobacterium tuberculosis*, after establishing a primary lesion in the peripheral alveoli of the lung, spread via pulmonary lymphatic vessels to the hilar lymph nodes where immune-mediated pathology causes necrosis resulting in a classic Ghon complex (subpleural granuloma and hilar lymph node enlargement and cheese-like necrosis).

Spread by the bloodstream can disseminate infectious organisms to any organ in the body. Bacteremia, viremia, fungemia, and parasitemia may be an essential step in the natural history of the pathogen in a particular infectious disease such as measles or malaria. However, overwhelming bacteremia leading to sepsis is a severe life-threatening condition as is the parasitemia of falciparum malaria leading to fatal cerebral malaria with protozoa-laden infected erythrocytes impeding circulation in the brain.

Nerves are the route of spread of rabies virus from the portal of entry at the wound where a rabid dog's bite has inoculated virus-infected saliva to the central nervous system where cerebral neurons become infected. Conversely, after acute infection, latent herpes simplex virus infection in the trigeminal ganglion and sacral ganglia reactivates periodically and spreads via the trigeminal and sacral nerves to the lip and genitalia, respectively, causing the so-called fever blisters and genital herpes flares. Both types of lesions result in viral shedding potentially transmitting the infections to nonimmune contacts.

Urinary tract infections usually enter via the urethra and spread to the urinary bladder, causing acute bacterial cystitis, and pyelonephritis results from bacteria ascending the ureters and refluxing from the renal pelvis into the renal collecting ducts. Similarly, pathogens such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis* enter through the exocervical os and ascend via the endocervix and uterus to the fallopian tubes where they cause salpingitis.

Pathogens that establish infection in one part of the lung may spread via the lumens of the bronchioles and bronchi to other parts of the lung. Endobronchial spread is typical of common forms of tuberculosis and of bacterial bronchopneumonia.

It is a serious, often catastrophic situation when pathogens enter the peritoneal, pericardial, or pleural spaces. Spread of enteric bacteria over the peritoneal surface following a ruptured appendix results in life-threatening generalized acute peritonitis with fluid and pus flooding the peritoneal cavity. Bacterial pneumonia may penetrate the visceral pleura leading to spread over the pleural mesothelial surface leading to acute empyema, pus accumulating in the pleural cavity. Pathogens may also enter the pericardial sac by direct extension from adjacent infected lung or via spread through the bloodstream to the pericardium. Pericarditis, too, is usually a very serious condition.

Another space where spread is minimally impeded once organisms have entered it is that occupied by cerebrospinal fluid. A pathogen that enters the cerebral ventricles via the

choroid plexus can spread through the ventricles and via the foramina of the fourth ventricle into the subarachnoid space surrounding the brain. Organisms that enter the subarachnoid space readily spread over the surface of the brain and into its perivascular invaginations into the brain, the Virchow–Robin spaces. The result is meningitis or meningoencephalitis with severe neurological manifestations.

A special route of spread occurs in intrauterine infections of fetuses, namely, transplacental spread from the maternal blood. Infections of the mother that can spread transplacentally to the fetus are syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and human immunodeficiency virus. These congenital infections cause diseases varying from tissue-destructive fatality to congenital heart defects. It should be noted that intrauterine fetal infections can also occur by pathogens (e.g., *Streptococcus agalactiae*) entering via the cervix and ascending to the uterine cavity and traversing the amniotic sac, which may have ruptured prematurely.

Target Organ of the Infection

Many infectious agents have a tropism to infect a particular organ or portal of entry that leads to a particular organ. The organ or cell type that a pathogen infects is a major determinant of the clinical manifestations. Infection of the lungs frequently follows a pulmonary portal of entry and leads to pneumonia (e.g., *Streptococcus pneumoniae*). However, other serious pulmonary infections arrive in the lung through the bloodstream (e.g., secondary pneumonic plague). Often, pathogens are named by their characteristic target organ such as Japanese encephalitis virus, eastern equine encephalitis virus, and *Neisseria meningitidis* that often infect the brain and leptomeninges. Myocarditis is frequently caused by coxsackie B viruses, *Trypanosoma cruzi*, and *C. diphtheriae* toxin. Infections of the urinary tract also reflect the urethral portal of entry and ascending spread of enteric bacteria that contaminate the urethral meatus. Sexually transmitted pathogens (e.g.,

Treponema pallidum, *Trichomonas vaginalis*, and herpes simplex virus, type II) have evolved to adapt to the female and male genital tracts and to survive by transmission to new hosts. Enteric pathogens take advantage of poverty, poor hygiene, and failure to separate human fecal deposition from water supplies to maintain populations of persons continuously transmitting *Entamoeba histolytica*, *Vibrio cholerae*, *S. typhi*, enteroviruses, and pathogenic strains of *E. coli*. Tropism for the liver and inflammatory hepatic damage is characteristic of numerous viruses including yellow fever virus and hepatitis viruses A, B, C, delta, and E. *Rickettsia* target endothelial cells throughout the body; mononuclear phagocytes are host cells for *Ehrlichia chaffeensis*, *Listeria monocytogenes*, *Francisella tularensis*, *Coxiella burnetii*, and *Brucella*, and some obligately intracellular organisms such as *Anaplasma phagocytophilum* and *Ehrlichia ewingii* are even adapted to survive and replicate specifically in polymorphonuclear leukocytes. For some infections, microbial surface proteins called adhesins and host receptors for the adhesins have been identified to mediate the observed cellular and tissue tropism by determining which cell types are infected or to which body surface cells the organisms gain a firm foothold.

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