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Concepts of Infectious Diseases

Aim: The purpose of this lecture is to introduce some of the basic concepts and terms used in the discussion of infectious diseases. These concepts are needed for the subsequent discussions of the different pathogens, bacterial, fungal and viral, that will be presented during the course.

Subjects to be Discussed: The lecture will review several of the classic epidemiologic studies in Infectious diseases and provide some more recent clinical correlates. The Infectious Disease cycle -- pathogen, pathogen reservoirs, means and vectors of transmission and susceptibility to infection -- will be reviewed. The standard terminology to discuss infections will be presented and finally concepts of bacterial virulence will be discussed.

Historical Perspective: The concept of disease transmission and contagion was well established before microorganisms were identified. John Snow was one of the first to apply epidemiologic methodology to infectious diseases with his classic investigation of the Broad Street cholera epidemic in 1854.

Ignaz Semmelweiss demonstrated in 1846 the importance of handwashing using antiseptics in the prevention of puerperal sepsis.

In the 1860's, John Lister proved the importance of aseptic technique and disinfection in reducing the incidence of infections following surgery.

In 1890 Robert Koch theorized that certain diseases were caused by particular pathogens and established postulates for proving the etiologic role of these pathogens. The Henle-Koch postulates stated that: 1) the bacteria should be identified in the lesions of the infection; 2) the bacteria could be isolated in pure culture on artificial media; 3) the disease was reproduced when inoculated into a susceptible animal: and 4) the bacteria was then recoverable from the infected animal.

These early investigators were among the first to advance the "germ theory" of disease by recognizing that some infectious diseases were contagious – *i.e.* transmitted by contact, while others were communicable – transmitted indirectly by water or insects. This was in conflict with the current theory that diseases were spread by "miasmas" – poisonous vapors.

Epidemics: The above descriptions are classic examples of **epidemics.** These are outbreaks of infections that are in excess of the normal "endemic" incidence of a particular type of infection. There are 2 types of epidemics. A **Common Source Outbreak** is represented by a sharp curve. It is a point source outbreak with a single site or agent (*e.g.,* food) causing infection. Eliminate the source and eliminate the epidemic. (*i.e.,* removing the handle during the Broad Street Pump epidemic). A **Propagated Epidemic** is when secondary cases are involved such as chicken pox affecting a large community. A wave of individuals acquires the infection and because of the presence of susceptible subjects secondary cases occur. This continues until a sufficient amount of community members develop immunity and are protected from subsequent infection.

Terminology

Pathogen: A pathogen is any microorganism that is capable of causing disease in a susceptible host. Pathogens are often described as primary, capable of causing disease in normal hosts, or opportunists, primarily causing disease in immunocompromised individuals. Some microorganisms are highly pathogenic, *e.g., Shigella spp*., and a relatively small number are

capable of causing disease while others, *e.g.*, *Staphylococcus epidermidis*, require special settings or a relatively high bacterial inoculum.

Infection: Infection refers to the ability of microorganisms to invade tissue and find conditions that are suitable for growth and replication. It should be noted that it is, in general, not in the interests of the organism to destroy the host; rather it is preferable to find an ecological niche that will allow tissue colonization with perhaps some replication, but without the risks of invasion. It is the exception for microorganisms to cause infection rather than the rule (See Lewis Thomas – Lives of a Cell - Essay "Germs"). Alterations in the site of colonization, the bacterial density or level of host immunocompetence will alter the likelihood of infection. Infection is also sometimes a function of the host's response to microorganisms. Infections may cause either clinical or subclinical illness *i.e.* apparent versus inapparent illness. Many individuals develop an immune response to a pathogen without manifesting any signs of illness.

Intoxication: Some pathogens can cause disease by the elaboration of a toxin. This can occur in the absence of viable bacteria. One example of this is certain types of food poisoning.

Carrier: An individual with asymptomatic colonization or infection who is capable of transmitting infection to others. They may or may not be ill themselves (*e.g.*, hepatitis C). Historically, "Typhoid Mary" a cook was responsible for several outbreaks of *Salmonella typhi* infections in the Northeast.
See: http://www.history1900s.about.com/homework/history1900s/library/weekly/aa062900a.htm

Latency: The pathogen remains viable but is dormant within the host. It however remains capable of causing disease at a later date (*e.g., Mycobacterium tuberculosis* or herpes viruses).

The Infectious Disease Cycle:
Reservoirs: Reservoirs for bacterial pathogens are generally divided into the following: humans (the most common animate reservoir), animals, soil and water. Knowing the reservoir and the exposure history of the patient is often helpful in establishing the likely pathogen. For example a farmer with a puncture wound from a stray nail is more likely to have an infection caused by a soil pathogen such as clostridia than a pathogen carried by water (*e.g.*, legionella)

Patterns of transmission: Infections can be acquired from within the host (endogenous infection) or from without (exogenous infection). Endogenous infections usually result from an alteration in the equilibrium between the host and the pathogen. The host may become immunocompromised, a commensal may be inoculated into a sterile site, or antibiotics may alter the "normal" or indigenous microbial flora. Exogenous infections may spread by horizontal transmission *i.e.* spread to unrelated individuals or by vertical transmission *i.e.* spread from parent to offspring. Examples of horizontal transmission include sexual or water-borne.

There are several means of microbial transmission including person-person (respiratory secretions, fecal-oral contamination), vector-borne (mosquitoes, ticks), animals (dogs, cats) or environmental (food, water).

Portals of Entry: There are numerous means of inoculation, including through breaks in the skin, inhalation, ingestion, *etc*. Each organ system has its own unique host defense mechanisms that must be bypassed in order for an infection to be established.

Response to infection: There is a varied response to infection ranging from subclinical illness to full-blown, life-threatening disease. As clinicians we are most familiar with the extreme

presentations of illness – witness the first presentations of AIDS, West Nile virus or Legionnaire's Disease. Most infections are, however, subclinical and are detected only when serologic or other sensitive assays become available for recognition of past exposure. This concept is often referred to as the "Iceberg Model of Infection." There are exceptions such as Rabies and HIV infection which cause overt disease in virtually everyone infected.

The Nature of Infections

Infectious disease syndromes: It is important to keep in mind that many different bacterial species may cause the same syndrome. For example both Gram positive and negative bacteria can cause the sepsis syndrome characterized by fever, disorientation and shock. In addition, the same bacterial species is capable of causing multiple different syndromes. For example *Streptococcus pyogenes* causes impetigo as well as toxic shock.

Pathogenesis of host damage: Pathogens cause damage in a number of different ways. They may: 1) directly cause tissue damage by the elaboration of proteolytic enzymes that destroy or damage tissue; 2) induce an excessive immune response resulting in damage *e.g., endotoxin* induction of cytokines; 3) cause a hypersensitivity reaction as may be seen in endocarditis with immune complex glomerulonephritis ; or 4) may cause malignant transformation of host cells as is seen in hepatitis B or with helicobacter.

Host susceptibility to infection: There are a number of host factors that increase susceptibility to infection such as the extremes of age, malnutrition, congenital or acquired defects in immunity and various forms of medical treatment.

Sequence of Steps Necessary for Infection

Adherence and colonization: adherence may be the result of specific (adhesin-receptor) or nonspecific (e.g. hydrophobic) interactions.

Evasion of host defense: Bacteria utilize a variety of mechanisms to evade the host immune response. One example is the presence of a bacterial capsule that helps prevent phagocytosis by polymorphonuclear leukocytes. Other examples include the capacity of bacterial pathogens such as salmonella, listeria and *M. tuberculosis* for prolonged intracellular survival. Bacteria can also express surface molecules mimicking host molecules – e.g. staphylococci express protein A, an Fc receptor.

Invasion: the ability to invade tissue or cells. There are different pathways of invasion. Some bacteria may spread as the result of the elaboration of proteolytic enzymes. Other spread by surviving intracellularly and spreading with host cells to other tissue sites. Invasion sometimes involves the subversion of host enzymes or pathways to facilitate survival and spread.

Interference with the host response: some pathogens mimic or co-opt host defense mechanisms and utilize them to invade tissue.

Host tissue damage: much of the damage resulting from infection is the result of the host immune response rather than the pathogen itself. One example of this is bacterial meningitis.

Virulence: Virulence (from the Latin virulentus – full of poison) refers to the ability of an organism to cause disease. This is often dependent on the possession of factors such as surface adhesins that enable the microorganism to colonize host tissue, toxins that can cause cellular damage or capsules that interfere with phagocytosis. These virulence determinants may be found on the chromosome, on a plasmid or on a bacteriophage. They are transmissible from strain to

strain or species to species and the genes for different virulence factors may be genetically linked. Some investigators would include antimicrobial resistance as virulence determinants.

Falkow described criteria to demonstrate that a particular bacterial component functioned as a virulence determinant. He called this the molecular equivalent of Koch's postulates for pathogenicity. They include the following: 1) the property under study should be found in the pathogenic members of the species; 2) inactivation of the gene is associated with decreased virulence; and 3) reversion of the gene restores the pathogen's virulence. Pili found on *E. coli* are examples of virulence genes that confer the ability to certain strains to cause urinary tract infections because of their ability to adhere to uroepithelial cells.