How Microorganisms Cause Disease

Over the past few years, it has become evident that humans and other animals harbor a complex ecosystem of microbial flora (the *microbiome*) that has important roles in health and disease. It is estimated that the normal human body harbors 10 times more microbial cells than human cells! Most of these commensal organisms coexist happily with their human hosts, occupying microenvironmental niches that might otherwise be filled by potential pathogens, and in doing so help to prevent infectious disease. However, under conditions where normal host defenses are breached or attenuated (described below), even "healthy" microbial flora may cause symptomatic infections and can even be fatal.

Most infectious diseases are caused by pathogenic, noncommensal organisms, which exhibit a wide range of virulence. Highly infectious microbes produce disease in a high fraction of healthy individuals, sometimes at "doses" of only a few organisms. Other microbes are minimally pathogenic, requiring large exposures and concomitant breaches of host defenses to cause disease. We will start our review of infectious disease at the beginning of the process, the establishment of a "beachhead" in the host, and then discuss dissemination and transmission of infection, before turning to specific infectious diseases.

Routes of Entry of Microbes

Microbes can enter the host by breaching epithelial surfaces, inhalation, ingestion, or sexual transmission (Table 8-1)**.** In general, respiratory, gastrointestinal, and genitourinary tract infections in otherwise healthy persons are caused by virulent microorganisms with the ability to damage or penetrate the epidermis or mucosal epithelium. By contrast, skin infections in healthy persons are mainly caused by less virulent organisms that enter the skin through superficial injuries.

Skin

The intact keratinized epidermis protects against infection by serving as a strong mechanical barrier and by producing antimicrobial *fatty acids* and *defensins*, small peptides that are toxic to bacteria. These and other substances secreted by the skin create an environmental niche that is occupied by potential opportunistic organisms. Certain fungi (*dermatophytes*) can cause superficial infections of the intact stratum corneum, hair, and nails, but **most skin infections are initiated by mechanical injury of the epidermis**. The injury may range from minor trauma (superficial pricks and abrasions), to large wounds, burns, and pressure-related ulcers, particularly in diabetics. In the hospital setting, infections may stem from intravenous catheters in patients or needle sticks in healthcare workers. Some pathogens penetrate the skin via an insect or animal bite; vectors for such infections include a wide range of unpleasant characters, such as fleas, ticks, mosquitoes, mites, lice, and rabid animals. In general, microorganisms can not traverse the unbroken skin; exceptions include the larvae of *Schistosoma*, which release enzymes that dissolve the adhesive proteins that hold keratinocytes together.

Gastrointestinal Tract

Most gastrointestinal pathogens are transmitted by food or drink contaminated with fecal material. When hygiene fails, diarrheal disease becomes rampant. The gastrointestinal tract has several local defenses. Of these, *acidic gastric secretions* are particularly important since they are highly effective at killing certain organisms. Healthy volunteers do not become infected with *Vibrio cholerae* unless they are fed 10^{11} organisms, but neutralizing stomach acid reduces the necessary infectious dose by 10,000-fold. A *viscous layer of mucus* covers the gut throughout its length, protecting the surface epithelium. *Pancreatic enzymes* and

Table 8-1 Routes of Microbial Infecton

Site	Major Local Defense(s)	Basis for Failure of Local Defense	Pathogens (examples)
Skin	Epidermal barrier	Mechanical defects (punctures, burns, ulcers)	*S. aureus*, *Candida albicans*, *Pseudomonas aeuginosa*
		Needle sticks	HIV, hepatitis viruses
		Arthropod and animal bites	Yellow fever, plague, Lyme disease, malaria, rabies
		Direct penetration	Schistosoma
GI Tract	Epithelial barrier	Attachment and local proliferation of microbes	*Vibrio cholerae*, *Giardia*
		Attachment and local invasion of microbes	*Shigella*, *Salmonella*, *Campylobacter*
		Uptake through M cells	Poliovirus, certain pathogenic bacteria
	Acidic secretions	Acid-resistant cysts and eggs	Many protozoa and helminths
	Bile and pancreatic enzymes	Resistant microbial external coats	Hepatitis A, rotavirus, Norovirus
	Normal protective flora	Broad spectrum antibiotic use	*Clostridium difficile*
Respiratory Tract	Mucociliary clearance	Attachment and local proliferation of microbes	Influenza viruses
		Ciliary paralysis by toxins	*Haemophilus influenzae*, *M. pneumoniae*, *Bordtella pertusis*
	Resident alveolar macrophages	Resistance to killing by phagocytes	*M. tuberculosis*
Urogenital Tract	Urination	Obstruction, microbial attachment and local proliferation	*E. coli*
	Normal vaginal flora	Antibiotic use	*Candida albicans*
	Intact epidermal/epithelial barrier	Microbial attachment and local proliferation	*N. gonococcus*
		Direct infection/local invasion	Herpes viruses, syphilis
		Local trauma	Various sexually transmitted diseases, e.g., human papilloma virus