

# Human Susceptibility and Pathobiology

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Susceptibility generally is defined as the inability of the host's body to prevent or overcome invasion by pathogenic microorganisms. The physiologic basis for resistance resides in the defense mechanisms that decrease susceptibility. These factors are categorized into three broad groups: 1) nonspecific mechanical and chemical factors, such as the epithelial mucosal lining of the gastrointestinal tract, 2) an army of defensive cells, including lymphocytes and neutrophils, and 3) antibodies that provide specific immunity.

Resistance to infection by foodborne pathogens within the population of consumers varies, such that some subgroups are at a low risk of illness (and a very low risk of serious illness or death), most are at a moderate risk of illness (and a low risk of serious illness or death), and still others are at high risk of illness (and a moderate risk of serious illness or death) when exposed to the same level of pathogens in the same food vehicle. The shape of the distribution and the scale are determined by characteristics of the population, microorganism, food and process.

As stated in the CAST document *Foodborne Pathogens: Risks and Consequences*,<sup>1</sup> the GI tract serves as the first line of defense against the actions of potential foodborne pathogenic microorganisms. To cause illness, these microorganisms first must be present in the food ingested by the host, and second must be able to overcome the host's defense mechanisms. Chapter 3 of *Foodborne Pathogens: Risks and Consequences* is a clear, concise description of body defenses and what happens when these barriers are breached. I will follow the logic flow of that document in this presentation to facilitate the combined use of these two information sources.

## THE STOMACH

Because of the hydrochloric acid produced by parietal cells in the stomach, gastric juices of the healthy adult normally are quite acidic with a pH of less than 2.<sup>1</sup> Low gastric pH is an important defense against ingested pathogens in

foods because most foodborne pathogens are pH labile.<sup>2</sup> Anything that increases the stomach's pH, like the buffering effect of some foods or antacids or decreased production of gastric acid in response to drugs or disease, will increase the risk of sufficient numbers of pathogens surviving the stomach and entering the friendlier environment of the small intestine.

Basal gastric acid output is low at birth (and even lower in preterm infants), but generally reaches adult levels by 1 month of age.<sup>3</sup> With advancing age, however, an overall decline in gastric acid output occurs, probably due to a reduction in parietal cell mass.<sup>4</sup> The incidence of achlorhydria reaches a prevalence of 30% in those over the age of 60 years. This is important because achlorhydria decreases the number of ingested pathogens like *Salmonella* necessary to cause infection.<sup>5</sup> Age greater than 60 years has an effect similar to that of antacid use on increasing the rate of salmonellosis.<sup>6</sup> Persons with diabetes mellitus appear to have lower basal and lower augmented acid secretion than do euglycemic persons; thus, they assume a level of risk of foodborne disease similar to that of the elderly population at an earlier age.<sup>7</sup> Chronic atrophic gastritis is a fairly common complication of diabetes. Therefore, on the basis of gastric pH, one would expect infants less than 1 month old, persons with diabetes or other disorders that lower parietal cell output, and adults more than 60 years old to be at increased risk of foodborne disease.

## GENERAL IMMUNOLOGY AND THE INTESTINAL IMMUNE SYSTEM

The gastrointestinal tract is a unique and complex immunologic organ.<sup>2,3</sup> Gut-associated lymphoid tissue (GALT) consists of aggregated lymphoid cells in Peyer's patches and nodules, and diffusely scattered lymphoid cells throughout the gastrointestinal tract. The M-cell epithelial layer which overlies the lymphoid aggregates binds to microbial antigens in the lumen of the gut, transports them through the epithelial barrier, and presents them to the lymphoid cells below. There, several T-cell subpopulations and T-cell derived growth and differentiation factors induce proliferation and differentiation of immature B-cells into plasma cells that produce immunoglobulin A (IgA) and reside in the lamina propria of the intestinal wall. Local production of IgA oc-

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curs when these immunocompetent cells are stimulated by contact with their specific antigen in the gut. Secretory IgA neutralizes viruses and enterotoxins, prevents the attachment of bacterial pathogens to intestinal cell surfaces, and inhibits bacterial motility.

The development of the immune system begins early in fetal development, but children are not immunologically mature until puberty. Probably because of the lack of intestinal microflora during fetal life, Peyer's patches are small at birth, and later become larger and richer in B-cells. Deficiencies of cell-mediated immune response of infants are related to the immaturity of cellular interactions, Neonates in general also have decreased B-cell differentiation and reduced immunoglobulin production.<sup>8</sup> The concentration of IgA in saliva, stool and serum of infants is low.<sup>3</sup>

A noticeable decline in cell-mediated immunity occurs between age 60 and 70 years.<sup>5,9,10</sup> Antibody production also diminishes in the elderly, primarily because of decreased helper T-cell activity, increased suppressor T-cell activity, and other changes associated with the involution of the thymus. Peak antibody levels occur in childhood, declining by 50% by the age of 50 years and by 75% by 90 years of age.

In 1980, approximately 25 million people in the United States were over age 65. By 2020, this number is expected to double. Within this group, the most rapidly growing segment is individuals over age 85. In 1980, about 2.3 million people were older than age 85; this number is expected to triple by 2020 to about 7.3 million persons. Therefore, not only is the population as a whole aging, but the "very old" population—that part of the population that is at greatest risk of foodborne infections and of severe illness and death is the most rapidly growing segment. By the year 2040, 22% (approximately 67 million persons) of the population of the United States—and everyone in this meeting who is still alive—will be aged 65 and over.

In addition to T-cell and B-cell lymphocytes, an adequate number of properly functioning neutrophils also is an important component of the resistance to foodborne infections in the normal adult population. In premature infants, neutrophils have decreased adherence and bacteriocidal function. Neutrophils in the elderly have diminished chemotaxis and reduced intracellular killing of microorganisms.<sup>5</sup> In addition, the elderly's bone marrow produces fewer new neutrophils. Decreased neutrophil function becomes especially pronounced over 80 years of age, but occurs earlier in the elderly with debilitating conditions. The annual death rates in the United States for septicemia are 22/100,000 in the 65-74 year age group, 62/100,000 in the 75-84 year age group, and 160/100,000 for those at least 85 years old.<sup>10</sup> Atherosclerosis can decrease the blood supply of the GI tract of the elderly, further decreasing the gut's ability to defend itself. Therefore, persons over 50 years of age with atherosclerosis have a four-fold increase in risk of invasive salmonellosis and other septicemic disease.<sup>9</sup>

Adherence of neutrophils to endothelium is an integral component of neutrophil function, and the recurrent severe bacterial infections that sometimes occur in persons with diabetes is due in part to defective neutrophil adherence.<sup>7,11</sup> Low neutrophil counts (neutropenia), as well as numbers of other granulocytes (granulocytopenia), are commonly seen in cancer patients as a result of underlying disease chemotherapy radiation therapy.<sup>12</sup> While disruption of immunity, the intestinal mucosal lining, and the normal intestinal microflora also increase the risk of foodborne infection in cancer patients, the incidence of serious infections is most closely linked to the degree and duration of neutropenia.

Approximately 1 million persons in the United States are infected with HIV. Although the rapid upward trend in AIDS incidence slowed in 1987, we continue to add 40,000 to 50,000 new HIV infections each year. Persons infected by HIV are at increased risk of *Salmonella* gastroenteritis.<sup>13</sup> In addition, the epidemiology of *Salmonella* bacteria in the United States has changed since the onset of the HIV epidemic, with marked increases in the proportion of isolates that are from blood in states and demographic groups with the highest AIDS incidence.<sup>14</sup>

Malnutrition has a broad range of deleterious effects on nearly all of the host's defense mechanisms.<sup>2,12</sup> Infectious diarrhea can cause malnutrition by decreasing gut dwell time, promoting bacterial overgrowth, direct toxic effects, and by damaging villi and microvilli. Malnutrition impairs cell-mediated immunity, but must be severe before it increases susceptibility to bacterial colonization by decreasing production of IgA. Malnutrition also decreases phagocytosis, chemotaxis and bacterial killing by neutrophils. In addition to the impact of foodborne disease on nutritional status, some superantigens like the enterotoxins of *Staphylococcus aureus* stimulate suppressor T-cells in the gut, causing a general decrease in GALT activity against foodborne bacteria. Thus, foodborne disease itself can increase susceptibility to other foodborne infections.

## RESIDENT INTESTINAL MICROFLORA

More than 400 species of bacteria live in the normal adult human GI tract.<sup>1</sup> The normal resident intestinal microflora protects against colonization by foodborne pathogens by the elaboration of antimicrobial substances, production of inhibitory short-chain fatty acids, and the creation of an unfavorable oxidation-reduction potential.<sup>12</sup> The GI tract of a newborn is sterile at birth and normally becomes colonized by bacteria within a few days. By one year of age, the GI tract populations of indigenous microorganisms have reached adult levels. With time, however, fecal microflora change, and older persons have smaller populations of intestinal anaerobic lactobacilli and larger numbers of coliforms and fungi than younger persons.<sup>5</sup>

Events that alter the resident microflora can increase susceptibility to infectious foodborne disease. For example, taking penicillin-derivative antimicrobial drugs in the month

before exposure to *Salmonella* increases the risk of salmonellosis caused by multiple-drug resistant *Salmonella*.<sup>6</sup> Colonization of the intestinal tract by potential pathogens in cancer patients is promoted by reduced normal flora from administration of broad spectrum antimicrobial agents and other causes, and by mucosal damage and narcotic-induced reduction in gut motility.<sup>12</sup> The disrupted mucosa, immunologic deficits, and the cytotoxic effects on the intestinal epithelium of transplanted T-cells in bone marrow recipients increase the risk of systemic invasion by enteric pathogens.

## INTESTINAL MUCUS AND MUCOSA

The gastrointestinal tract serves as an important interface between ingested materials and the body's internal environment. In this critical position, the intestinal surface serves as a major barrier to the entry of noxious substances like bacteria, viruses, protozoa, and their toxins.<sup>3</sup>

The mucosal surface is composed of mucus and a single layer of epithelial cells, and acts as a physical barrier to the attachment, uptake and penetration of pathogens in the gut lumen. The small intestine has a vast absorptive surface because of its length (20 feet long in the average adult), folds (plicae), and villi.<sup>1</sup> Masses of tiny projections that extend from the villous surfaces further expand the area of contact between the mucosal surface and the contents of the lumen, and give the absorptive epithelial cells a fuzzy appearance under the microscope; this is called the brush border (or the microvillus membrane), and is the location damaged by attaching and effacing *E. coli*.

The mucous blanket overlying the epithelial cell layer is formed by large glycoproteins produced by goblet cells and mucous glands located in the mucosa.<sup>2</sup> The mucus protects the mucosa from digestive enzymes and penetration by microorganisms. It also acts as a binding matrix for secretory IgA, countering the effects of normal peristalsis. The composition of carbohydrate side chains on glycoproteins and glycolipids in mucus and the brush border may influence the specific adherence of bacteria and their toxins, and adherence is a prerequisite to bacterial colonization and toxin production.<sup>3</sup> The carbohydrates of mucus are binding sites for bacteria and their toxins, and intestinal mucus in infants has lower quantities of carbohydrate than mucus in adults. Non-steroidal anti-inflammatory drug use in adults can alter the composition of intestinal mucus and reduce its protective effectiveness. In addition, some pathogens, like *Campylobacter*, can penetrate intestinal mucus because of their motility and can metabolize mucus as a source of nutrition.

## PERISTALTIC ACTION

Normal intestinal peristalsis is another important factor for limiting bacterial proliferation and overgrowth.<sup>2</sup> Intestinal peristalsis serves as a defense mechanism of the host by sweeping away foodborne pathogens and their toxins. Duodenal peristalsis increases to adult levels at approximately 2 months of age.<sup>3</sup> At the other end of the age scale,

reduced epithelial turnover and degenerative changes in connective tissue and innervation reduce the defensive efficiency of peristalsis in the elderly.<sup>5</sup> Disturbances in gastric and intestinal motility also occur in persons with diabetes and are thought to be secondary to an autonomic neuropathy.<sup>7</sup> Reduced intestinal motility and prolonged gastrointestinal transit time increase the opportunity for foodborne pathogens to adhere to intestinal epithelium and increase susceptibility to enteric pathogens.

In summary, the body has a number of defenses that protect us from pathogens in the foods we consume. When these barriers are lowered by age, disease or other factors, or when they are simply overwhelmed by the level of contamination or the virulence of the microorganism, foodborne disease occurs. As the distribution of population characteristics shifts toward a larger group of highly susceptible consumers, the risk of foodborne disease will rise. This population is susceptible to a greater range of microorganisms and becomes ill when exposed to smaller doses. Because of the general decline in "herd immunity" within the population, foodborne infections have increased opportunity to spread person-to-person after their introduction, making their public health impact even greater.<sup>15</sup>

Summing across all of the body's defenses against foodborne infections, everything works pretty well from our first birthday until our fiftieth if we are otherwise healthy and prudent. Our risk of foodborne illness is very high at birth and drops rapidly during the first couple of months. It starts to slowly rise around age 50 and reaches very high levels beyond 80 years. This roughly parallels our observations on rates of *Salmonella* gastroenteritis by age, and we may be able to use salmonellosis as a general predictor of consumer susceptibility.

Elderly persons are more vulnerable to sepsis than are young people, and are at greater risk of death from such infections. While the elderly as a group are at increased risk of illness and death from foodborne infections, the risk for the elderly who are also debilitated by other diseases is especially high. In a study of foodborne disease outbreaks in nursing homes, where the highest proportion of debilitated elderly reside, Levine et al.<sup>16</sup> found a ten-fold higher case fatality rate for elderly patients in institutions compared with non-institutionalized patients. Approximately 5% of persons over the age of 65 years now live in nursing homes. Again, rates of invasive salmonellosis may be a useful guide for the likelihood of serious foodborne illnesses in the population that consumes a food product of interest.

At the other end of the age scale, an increasing number of children in the United States are cared for in day care centers. These children, whose immune response to foodborne pathogens is curtailed by the immaturity of their immune system and its lack of prior exposure to foodborne pathogens, and whose gastric environment is not as hostile to foodborne pathogens as an adult's would be, can rapidly spread from person to person pathogens that were originally introduced on contaminated food.

Malnutrition, HIV infection, cancer, diabetes mellitus, and other health problems that decrease the effectiveness of one of these defensive factors keep people out of the maximally protected phase longer and remove them from it sooner. States of elevated risk may be age-related or acquired secondary to various pathological states and associated therapeutics. Progress in therapeutics, medicine and surgery have expanded the population of compromised persons who are at elevated risk for developing infectious diseases. These immunocompromised consumers become ill when exposed to lower doses, are more likely to suffer invasive disease, and are susceptible to infection by opportunistic pathogens.<sup>8</sup>

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