Factors Predisposing to Infection

Dean C. Norman

It is well established that the elderly are at both increased risk for acquiring many types of infections and for increased severity of illness when an infection occurs (1). Predisposing factors, which in part account for this phenomenon, include decrements in host defenses with age that are made worse by chronic disease, undernutrition, and certain medications that are commonly prescribed to older persons. Some of these factors are organ specific. For example, the increased prevalence of urinary tract infection in the elderly is due in part to age-related changes in the urinary tract, which include anatomic changes (e.g., prostatic hypertrophy) and altered physiology (e.g., increased bladder residual volume). Furthermore, the elderly are more likely to be hospitalized, undergo invasive procedures, and suffer procedure-associated complications that compromise mucocutaneous and other barriers to infection. Moreover, hospitalization and chronic illness increase the risk of colonization and subsequent infection with virulent nosocomial flora (2). This chapter further identifies and summarizes factors that increase infection risk in elderly persons. Fever, as a host defense, is not covered here because it is discussed in detail in Chapter 3.

1. INFECTION RISK

The risk for developing an infection and to some extent its severity is directly proportional to the inoculum and virulence of the pathogen(s) and inversely proportional to the integrity of the host defenses. Aging and comorbidities associated with aging affect all three of these factors. It is the interplay of these three variables that account for the increased susceptibility to and severity of infections in the geriatric population.

1.1 Virulence

The virulence of a pathogen is dependent on its ability to attach to and penetrate the host and its ability to successful replicate in the host environment. Virulence factors are properties that enable a pathogen to establish itself in the host and cause disease (3). For example, for certain uropathogenic strains of *Escherichia coli*, virulence is determined by the presence of P-fimbriae, which are surface structures known as
adhesins. Adhesins attach to receptors on uroepithelial cells and facilitate attachment to and colonization of uroepithelial cells (4). Virulence is also dependent on the pathogen’s ability to avoid being overwhelmed by the host’s defenses and its ability to damage the host. In the case of Streptococcus pneumoniae, a common pneumonia pathogen in elderly persons, virulence is determined by pneumococcal capsular polysaccharide, which allows the bacterium to resist phagocytosis by host cells. This virulence factor is overcome if capsular-specific antibodies are present to facilitate opsonization.

The elderly are more likely to be colonized with virulent bacteria, especially those elderly who are exposed to nosocomial flora and have major breaches in barriers to infection (e.g., presence of an indwelling bladder catheter). Furthermore, for reasons that are unclear, the risk for colonization of the oropharynx by potentially virulent Gram-negative bacilli or Staphylococcus aureus is increased in elderly patients, and this risk increases with increasing dependence and acuity of illness (2). Therefore, hospitalized elderly are at greatest risk for oropharyngeal colonization with these pathogens. Drying of upper airway secretions with age, exposure to antibiotics, and changes in local immunity may all be contributing factors.

Resistance of bacteria to antibiotics, although technically not a virulence factor, potentially increases morbidity and mortality related to infections. Frail, institutionalized elderly may suffer repeated hospitalizations and undernutrition as well as undergo repeated courses of antimicrobial therapy. Normal bacterial flora may be altered in these cases and will increase the risk for colonization by resistant bacteria.

1.2. Inoculum

The inoculum is an important determinant of risk of infection and plays a significant role in the increased risk of infection in the elderly. For example, even young, healthy individuals aspirate small amounts of oropharyngeal secretions (5). However, the elderly are more likely to have neurovascular disease with resultant swallowing disorders and also at more risk to undergo tube feedings, both of which dramatically increase the risk of aspiration of copious amounts of oral secretions. Furthermore, in the elderly, the adverse effects of alcohol, long-acting benzodiazepines, and other sedating agents increase the risk for aspiration. Given the loss or alteration with age of important pulmonary host defenses including cough reflex, mucociliary clearance and changes in immune function it is not surprising that elderly patients have a markedly higher incidence of pneumonia. Endotracheal intubation and prolonged mechanical ventilation further compromise host defenses; these interventions increase the risk of aspiration of large inocula of bacteria. Such macroaspiration dramatically raises the probability for development of severe respiratory infection. Finally, the elderly are more likely to undergo intravascular catheterization and the placement of chronic dwelling bladder catheters. These catheters, even when meticulously maintained, can serve as a conduit for inocula of bacteria, thus bypassing basic host barriers to infection.

1.3. Host Defenses

Host defenses can be separated into two major divisions: nonspecific (natural) and specific (adaptive) defenses. Specific immune defenses are discussed in the fol-
Predisposing Factors

following paragraphs. Nonspecific defenses include mucocutaneous barriers, complement and certain effector cells such as macrophages, neutrophils and natural killer (NK) cells.

1.3.1. Mucosal Defenses

Mucocutaneous tissues are more than simple mechanical barriers. The skin has antibacterial properties including a relatively low pH and glandular secretions, which have an antibacterial effect. Aging results in significant changes such as loss of dermal thickness and subcutaneous tissue as well as reduced glandular secretion, which makes the skin less capable of withstanding shearing forces. Furthermore, with age, the skin become relatively avascular, which also increases the susceptibility to injury. Also, there is a loss of Langerhans cells, and cytokine dysregulation occurs, both of which decrease the specific immune response (6). Loss of mobility resulting from coexisting diseases may lead to increased pressure and shearing forces. Edema and vascular diseases may further compromise the integrity of this important barrier. This will facilitate colonization and invasion with virulent bacteria.

The mucosal host defense system, like the skin, is a first-line defense against invading pathogens. Mucus secretions and ciliary action continuously trap and remove bacteria, thus preventing microbes from gaining access to deeper, normally sterile tissues. Furthermore, Peyer’s patches contain T and B cells, which are capable of processing bacterial antigen necessary for the specific immune response (7). Immunoglobulin A antibody is the predominant immunoglobulin of the mucosal immune system and does not appear to be reduced with age. However, it is not clear whether or not aging reduces the ability of the mucosa to perform as a host defense. Nevertheless, xerostomia from all causes, periodontal disease, and certain gastrointestinal disorders, such as diverticulitis and ischemic bowel disease, occur commonly in geriatric patients and potentially damage mucosal defenses.

1.3.2. Immune Responses

The immune response is made up of two interdependent entities. These are the various components of nonspecific or natural immunity (e.g., neutrophils, macrophages, NK cells, and complement cells mentioned earlier) and specific immune responses (cellular and humoral immunity). Natural immunity is immediate and does not require prior sensitization to particular foreign antigen, does not discriminate between different antigens, and is not enhanced by repeated exposure to a particular antigen. In contrast, the specific immune response is usually initiated by a specific foreign antigen and involves cells of lymphoid lineage including T cells (cellular immunity) and B cells (humoral immunity). Stimulus from a foreign antigen results in the generation of specific molecules, which, in effect, modulate responses among the effector cells of the immune response. Repeated exposure to the specific antigen enhances the response, and this is the basis of what is an essential host defense against a wide variety of microbial pathogens. It should be mentioned that NK cells are presumably of lymphoid lineage and are an important host defense against tumor cells and possibly virus-infected cells. However, NK cells do not require prior sensitization to become cytotoxic and are considered to be an effector of natural immunity.

A summary of the specific immune response is as follows: Each mature T cell has a unique receptor that is specific for a certain antigen (epitope), and the total T-cell popu-
lation provides an extensive capacity to bind with a multitude of different antigens. The T-cell receptor (TCR) does not bind directly to antigen but requires processing of the antigen by antigen-presenting cells (APC). After phagocytosis, APCs break the antigen into polypeptide components, which are complexed on the cell’s surface with molecules that are coded within the major histocompatibility complex. The TCR in concert with another T-cell marker, CD3, can then initiate the cascade of signal transduction resulting in cytokine secretion, clonal expansion, and differentiation of T cells necessary for the specific T-cell response (8–10).

T cells have been extensively studied in animal models and humans including aging populations. T cells are composed of two distinct cell types: T helper cells that express the CD4 marker and cytotoxic T cells that express the CD8 marker. T helper cells are further subdivided into Th1 and Th2 cells; Th1 cells secrete interleukin 2 (IL-2) and gamma interferon. Th1 cells are the major effector cells for cytotoxic activity (including killing of cells infected with intracellular pathogens such as viruses) and the inflammatory response. Th2 cells secrete IL 4, 5, 6, and 10 and have a major role modulating B-cell proliferation, differentiation, and antibody production. T cells that have not yet responded to a specific antigen are referred to as naive T cells that express the marker CD45RA and are relatively short lived. T cells, which, after clonal expansion and differentiation, have a TCR with high avidity for antigen may become long-lived memory cells. Memory T cells express the marker CD45RO.

1.4. Changes with Age

The components of natural immunity (e.g., phagocytosis by macrophages, neutrophils, complement activity, and NK activity) do not appear to be greatly affected by aging in healthy elderly patients. Although NK cellular function does not appear to be changed with age, the response of NK cells to cytokine signals may be altered (11). However, there are consistent changes observed with age in the cellular and humoral components of specific immunity. First, it is firmly established that there is a shift from naive T cells to memory T cells with age and that both T-cell proliferation and IL-2 production are reduced (8,9). Although IL-6 has been found to be increased with age in some studies, this is not a consistent finding. One study did find that elderly caregivers had increased levels of IL-6 during periods of stress (12). Some studies have demonstrated alterations in cytokine production and increased cytokine dysregulation with age, but thus far studies in humans are inconclusive (13,14). A recent study comparing infected elderly with younger patients confirmed that blood levels of certain cytokines remain elevated for prolonged periods of time in old compared with young patients. This finding may indicate prolonged inflammation response to infections in old compared with the younger patients (15).

T-cell proliferation in response to mitogens and specific antigens is decreased with aging and is not explained entirely by reductions in IL-2 production (8,9). Although studies consistently demonstrate reduced T-cell proliferation with age, there is wide interindividual and population variability. State of health, exercise, and nutritional status will influence measures of specific immunity (16–18). Finally, B-cell production of specific, high-affinity antibodies is reduced with age. This is not simply an in vitro observation because even relatively healthy elderly persons as a population do not mount as great an antibody response to T-cell-dependent antigens such as influenza
It also appears that cytotoxic T-cell functions are reduced somewhat with aging. Finally, alterations of apoptosis (programmed cell death) with age have been postulated to explain some of the age-related changes in immune function; however, this theory is under active investigation (19). Table 1 summarizes the foregoing discussion.

**REFERENCES**


---

**Table 1**

**Effect of Aging on Immune Function**

<table>
<thead>
<tr>
<th></th>
<th>Decrease</th>
<th>Increase</th>
<th>No change or inconclusive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T cells:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cell number</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thymus gland X (Involutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory T cells</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Naive T cells</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTH^a</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proliferation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin 2</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin 4</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Interleukin 6</td>
<td></td>
<td>X^b</td>
<td></td>
</tr>
<tr>
<td>Interleukin 10</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Interferon-gamma</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B cells:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell number</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>High-affinity antibodies</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonspecific antibodies</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>NK^c cells:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^aDelayed type hypersensitivity reaction.

^bSee Subheading 1.3.

^cNatural killer.


