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Lung immune defences in the immunosuppressed patient

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1.1 Introduction

The respiratory tract is constantly exposed to environmental elements and potential pathogens on a daily basis during the obligatory process of breathing or through subclinical aspiration. To avoid infectious disease pathogenesis in the respiratory tract, a number of elegant, complex and interdependent systems of host defence mechanisms are in place to prevent microorganism colonization of the respiratory epithelium, promote efficient microbe elimination, and maintain sterility of the lower respiratory tract in the healthy host. The layers of host defence mechanisms include physical barriers and secreted chemical factors (operant immediately), innate immune system (operant within minutes to hours), and the adaptive immune system (operant within days). Disruption of any of these components of lung host defence may lower critical threshold for microbial invasion and promote disease pathogenesis. Several acquired immunodeficiency states are associated with frequent and severe respiratory tract infections, and lung infections with opportunistic pathogens. This chapter will review the components of lung host defences in health with particular focus on human data, and discuss perturbations of host defences associated with select specific immunodeficiency states that may promote susceptibility and contribute to pathogenesis of respiratory tract infections.

1.2 Host defence function in health

In health, host defence function is provided by three critical integrated components, including (1) physical (or mechanical) and chemical mechanisms; (2) innate immunity; and (3) adaptive immunity. Physical and chemical mechanisms are present and operate continuously and serve as an immediate protective function to microbial challenge. For microbes that circumvent or bypass physical and chemical mechanisms, the innate

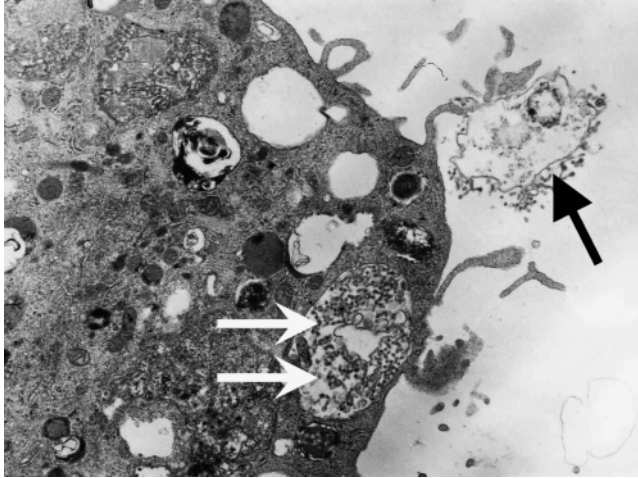


Figure 1.1 Electron micrograph of human alveolar macrophage engaging pneumocystis organisms. Alveolar macrophages represent the predominant immune cells in the alveolar airspace, and critical effector cells in pathogen recognition and elimination. Pneumocystis trophic forms are seen in the process of engagement by macrophage pseudopodia (arrow) and ingested in the macrophage (arrows). *Pneumocystis* is a major opportunistic pathogen responsible for severe pneumonia in the immunocompromised host. (Electronmicrograph courtesy of Angeline Warner, Harvard School of Public Health, Boston, MA).

immune system represents another layer of the host defence response. Cellular and soluble components of innate immunity are constantly present, and are capable of recognizing, engaging and eliminating a broad array of microbes (through molecular recognition of conserved molecular patterns expressed by pathogens but not host cells) within minutes to hours of microbial challenge (Figure 1.1). Through a relatively limited number of secreted and host-cell associated recognition molecules, innate immunity can detect and generate an appropriate antimicrobial response to a broad range of bacteria, fungi and viruses. In health, the majority of daily microbial challenges are likely effectively cleared by these first two layers of host defences, as the majority of living creatures have only mechanical and chemical defences, and innate immunity. If clearance of microbes is not achieved despite activation of innate immune mechanisms, the adaptive immune system can be activated within days to provide an amplified and specific immune response. The adaptive immune response is composed predominantly of B-lymphocytes and T-lymphocytes that recognize specific antigen determinants on pathogens, and ultimately provide lifelong memory against repeated challenges with the same pathogen.

Physical (mechanical) and chemical mechanisms of host defence

Physical barrier and mechanical host defence mechanisms, and chemical host defence mechanisms are constantly available for immediate action in the healthy host. Particle size in part determines fate, as particles and microbes generally exceeding $5\ \mu\text{m}$ can be entrapped as air flows through the tortuous channels of the nasopharynx and by nasal

hairs, and through inertial forces are impacted along the tonsillar pillars, glottis, trachea and branching bronchi and bronchioles. Entrapped particles and microbes may be expelled through coughing and sneezing mechanisms. The complex glycoprotein mucins lining the airway epithelial surfaces facilitate particle entrapment, and promote elimination by the cephalad respiratory epithelial cell ciliary movement that allows expectoration or swallowing of mucin-entrapped pathogens. In general, particles and potential pathogens smaller than 5 μm can bypass these mechanical obstacles and gain access to the terminal bronchioles and alveoli. In addition, the respiratory epithelium serves as a critical barrier function. Similar to the function of the skin, the integrity of the mucosal surfaces including the respiratory epithelial cells and associated tight junctions remains critical to protective host defence function. The importance of these mechanisms, which operate constantly, is underscored by conditions that interfere with proper function such as mucociliary disease (dynein arm dyskinesia), bronchiectasis (anatomical distortion and scarring of epithelium), and neurological disorders or pharmacological agents that prevent effective cough reflexes.

A number of secreted airway products also contribute to antimicrobial functions by several mechanisms including direct antimicrobial activity, opsonization and agglutination (Table 1.1). Microbes that pass the physical and mechanical barriers may be eliminated by a range of chemical mediators that are constantly expressed and may be further induced. These mediators include molecules capable of direct antimicrobial effect (ex. lysozyme, lactoferrin, SLPI, complement, α -, β - and θ -defensins and cathelicidins), agents that inhibit microbial growth (ex. transferrin), and molecules that serve as opsonins that facilitate host cell recognition (ex. complement, fibronectin, collectins, SP-A, SP-D, IgA and IgG) or modulate host cell response to pathogens (ex. LPS-binding protein) (Crouch, 1998; Shepherd, 2002; Zhang and Koziel, 2002; McCormack and Whitsett, 2002). Lung collectins, such as surfactant components

Table 1.1 Secreted antimicrobial factors in the airways.

Cathelicidin
Collectins
SP-A
SP-D
mannose binding protein (MBP), or mannose binding lectin (MBL)
Complement
Defensins (α and β)
Fibronectin, vitronectin
Ficolins
Immunoglobulins
IgA (predominant in upper airways)
IgG (predominant in lower airways)
Lactoferrin
LPS binding protein (LBP)
Lysozyme
Transferrin

SP-A and SP-D can serve as opsonins and enhanced phagocytosis, agglutination of microbes, and increased bacterial membrane permeability promoting pathogen elimination (Shepherd, 2002). Classical pathway complement proteins C3, C4, C1q and alternative complement pathway component factor B are expressed in the lung alveolar fluid (Watford, Ghio and Wright, 2000), and can provide opsonization of microbes in the respiratory tract.

Innate immunity in the lungs

Innate immunity is an evolutionarily conserved ancient defence mechanism that comprised components that are constantly expressed and available, can be activated within minutes to hours, and can engage potential pathogens upon initial encounter (Martin and Frevert, 2005; Zaas and Schwartz, 2005). The principal cellular components of lung innate immunity include alveolar macrophages, neutrophils, NK cells, dendritic cells and eosinophils. Alveolar macrophages represent the predominant immune cell in the alveolar airspace, accounting for >85% of mobile cells in the alveoli. Neutrophils and eosinophils are generally not present in the alveoli but are recruited in response to chemotactic signals. Natural killer (NK) cells participate in early innate defence through cytotoxic activity against pathogen-infected cells and secretion of cytokines and chemokines that modulate subsequent steps in the adaptive immune response (Biron *et al.*, 1999). Recognition of microbial products by dendritic cells triggers functional dendritic cell maturation and leads to initiation of antigen-specific adaptive immune responses.

The innate immune response is mediated through interactions of microbes or microbial products with the germline-encoded host cell receptors. Innate immune cells such as alveolar macrophages recognize potential pathogens through surface recognition receptors such as mannose receptors, β -glucan receptors, scavenger receptors and Toll-like receptors (TLRs). The family of mammalian TLRs serves a critical role in the early host defence response through recognition of conserved molecules derived from microbial pathogens (Imler and Hossmann, 2001), leading to activation of NF- κ B (Beutler, 2000) and MAP kinases (Barton and Medzhitov, 2003), and subsequent transcription and translation of host defence genes (Medzhitov, 2001; Aggarwal, 2003). Expressed on cells near mucosal portals of entry including macrophages (Jones *et al.*, 2001) dendritic cells (Muzio *et al.*, 2000) and lung epithelial cells (Armstrong *et al.*, 2004), mammalian TLR1 through TLR9 represent critical molecules in the first line of host defence to microbes in the lungs. Functional deficiency or genetic deletion of TLR4 increase susceptibility to *H. Influenza*, *S. pneumoniae*, and *K. pneumoniae* respiratory tract infection in murine models (Wang *et al.*, 2002; Branger *et al.*, 2004). Humans with TLR4 mutations are hyporesponsive to inhaled LPS (Arbour *et al.*, 2000). Alveolar macrophage and alveolar epithelial cells exhibit limited responsiveness to TLR4 stimulation due to relatively low membrane expression of the adaptor molecule MD-2 (Jia *et al.*, 2004; Kajikawa *et al.*, 2005). TLR5 polymorphism (TLR5^{392stop}) in the ligand binding domain increases susceptibility of humans to *Legionella pneumonia* (Hawn *et al.*, 2003).

Regulation of activating pattern recognition receptors

Control of inflammatory responses to infectious challenge is of particular importance for the continued normal gas exchange function of the lungs. In general innate receptor activation promotes proinflammatory responses, and cellular innate immune responses (such as macrophages) to antigenic challenge can result in enhanced innate immune response upon future rechallenge by the same antigen (Bowdish *et al.*, 2007). However, concurrent with innate surface membrane and intracellular receptor activation to promote proinflammatory responses, a number of counter regulatory molecules are also activated that likely limit the proinflammatory response to maintain homeostasis and limit collateral damage. Examples of these regulatory molecules for TLRs include: TOLLIP, IRAK-M, sMyD88, ST2, SIGIRR, SOCS-1, NOD2, MIF, PR105 and TAM receptor family (TYRO3, AXL and MER) (Rothlin *et al.*, 2007; Liew *et al.*, 2005). Whether these molecules are modulated by immunosuppressive agents or medical conditions associated with immune suppression is not completely understood.

Regulation of innate immunity by secreted products

In addition to serving antimicrobial functions, soluble products can also serve to modulate cellular innate immune response in the lungs. For example, lung collectins such as SP-A can modulate the innate immune response, such as regulating macrophage pattern recognition receptor expression (Beharka *et al.*, 2002) and regulating the generation of macrophage reactive oxygen species (Crowther *et al.*, 2004). SP-A and SP-D bind LPS and prevent interaction with LBP and TLR4-CD14 complex on alveolar macrophages (Borron *et al.*, 2000; Sano *et al.*, 2000) and thus limit activating responses. In addition to hepatic production as an acute phase reactant, LBP is expressed by pulmonary artery smooth muscle cells (Wong *et al.*, 1995) and type-II alveolar epithelial cells (Wong *et al.*, 1995; Dentener *et al.*, 2000). Alveolar lining fluids contain high concentrations of sCD14 and LBP (Martin *et al.*, 1992; Martin *et al.*, 1997b) and thus can modulate TLR4-mediated signaling.

Epithelial cells

Alveolar epithelial cells, in addition to providing a physical barrier function, also contribute to the innate immune response in the lungs. Epithelial cells express defensins HBD-1 and HBD-2 (McCray and Bentley, 1997; Hiratsuka and Al, 1998), and defensins also stimulate IL-8 production by epithelial cells (van Wetering *et al.*, 1997). Epithelial cells express TLRs and CD14, and can thus respond to microbial products analogous to TLR signaling in leukocytes, with release of IL-1 β , IL-6, TNF- α , IL-8 and RANTES, GM-CSF, and TGF- β (Diamond, Legarda and Ryan, 2000). Microbes and microbial components (such as lipopolysaccharide, peptidoglycan and flagella) can interact with innate receptors (such as TLR2) expressed on the apical surface of epithelial cells (often in the context of lipid rafts) (Soong *et al.*, 2004), which in turn can promote Ca²⁺ release (Chun, Soong and Prince, 2006) and activate epithelial cell transcription factors such as

NF- κ B, AP-1, C/EBP and CREB to promote host defence gene activation. In a murine model, targeted disruption of respiratory epithelial cell NF- κ B results in blunted neutrophil recruitment in response to LPS inhalational challenge (Skerrett *et al.*, 2004), suggesting a significant contribution of chemotactic signals by respiratory epithelial cells in the context of TLR stimulation.

Adaptive immunity in the lungs

Generation of adaptive immunity requires the somatic rearrangement of lymphocyte receptors (including B-lymphocyte and T-lymphocyte receptors) that confers antigen specificity directed against specific epitopes expressed by pathogens, amplifying the immune response against pathogens expressing the specific antigen or epitope, and promotes immune memory that allows enhanced immune response upon future rechallenge with the pathogen expressing the same antigen or epitope. Therefore, in contrast to innate immunity, which represents preprogrammed expression of molecules and receptors present at birth, the adaptive immune system is acquired throughout life as a consequence of cumulative challenges with infectious agents.

For persistent infectious challenge, antigens are presented to lymphocytes by lung dendritic cells in regional lymph nodes. As alveolar macrophages are poor antigen-presenting cells, alveolar macrophages may transport antigen to interstitium and/or regional lymph nodes where antigen can be processed by dendritic cells, or perhaps antigen may be processed by alveolar dendritic cells that then may be transported to the regional lymph nodes. Once in the regional lymph nodes, dendritic cells present antigen to responsive T- and B-lymphocytes in the context of MCH molecules to activate the adaptive immune response. B-lymphocytes are activated to produce antibodies directed against specific epitopes, and CD8⁺ T-lymphocytes target infected cells expressing specific epitopes on the cell surface. Whereas T-lymphocyte receptors can interact with processed or cleaved foreign antigens, B-lymphocyte receptors can interact directly with intact foreign antigens.

Innate immunity regulated by adaptive immunity

Traditionally, innate immunity provided the initial response to contain newly encountered infectious challenge, and with continued activation or overwhelming infection the adaptive immune response is triggered (instructed in part by specific receptors and particular signals generated by the innate immune response). Consequently, the adaptive immune response provided critical regulatory signals that amplified the innate immune effector cells. In this model, the innate immune system provides the initial first line of host defence within minutes and hours of infectious challenge, whereas the regulatory influence of the adaptive immune response occurred within days of the initial infectious challenge (and thought that the adaptive response was able to modulate or regulate the innate response following antigen processing and development of antigen-specific T-lymphocytes and B-lymphocytes). However, recent data suggest that components of the adaptive immune system may regulate the initial innate immune

response. In a MHV model of infection, regulation of the host cytokine response to MHV infection was modulated by T-lymphocytes, which required cell–cell contact and was in part MHC-II dependent (Kim *et al.*, 2007). Importantly, this T-lymphocyte-regulated influence of innate immune cell proinflammatory cytokine release (to avoid a ‘cytokine storm’-mediated lethality) occurred within 24 hours of new infectious challenge, well in advance of traditional adaptive immune responses.

1.3 Host defence function in select immunocompromised patients

Immunocompromised patients represent a heterogeneous population with genetic or acquired conditions that predispose to infectious complications, including pneumonia. Although immunocompromised patients may share common deficiencies in some components of immunity, certain medical conditions or the use of specific immune modulatory agents target specific components of innate or adaptive immunity, and result in relatively specific functional or quantitative defects in immunity. Recognizing that elimination of certain pathogens or opportunistic microbes may rely predominantly on specific components of innate or adaptive immunity, unique immunodeficiencies associated with certain conditions predispose individuals to certain types of infectious complications (Figure 1.2). The remainder of the chapter will review current understanding of the mechanisms underlying immunocompromised states in select patient groups, and serves as the basis for discussions in subsequent chapters that focus on specific conditions in greater detail.

HIV infection

HIV is the causative agent of AIDS. As of 2006 more than 30 million people worldwide were living with AIDS, with 4.3 million newly infected with HIV and 2.9 million deaths due to AIDS (Prevention, 2006). Opportunistic infections including tuberculosis remain the major cause of mortality in HIV+ patients worldwide, with more than 60% of deaths in HIV caused by secondary infections (Organization, 2007). The dramatic loss of CD4+ T-lymphocytes accounts for many of the manifestations of AIDS (Douek, Picker and Koup, 2003). Even in the presence of antiretroviral therapy, peripheral CD4+ T-lymphocyte count remains the best factor for predicting the risk of opportunistic infection, although peripheral viral load remains an independent risk factor (Ledergerber *et al.*, 1999). However, in addition to T-lymphocytes, evidence suggests HIV infection is associated with dysfunction of several other types of immune cells.

CD4+ T-lymphocyte dysfunction

HIV infection is associated with a number of specific quantitative and qualitative abnormalities of CD4+ T-lymphocytes. Progressive depletion of peripheral CD4+

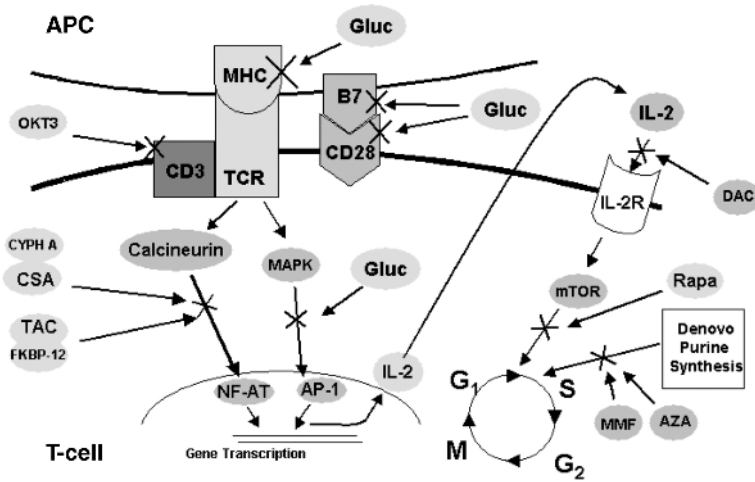


Figure 1.2 Pathways influenced by immune modulating agents: Transplant graft rejection occurs when recipient antigen presenting cells (APC) present alloantigens from the graft to recipient T-cells via MHC Class II. T-cells recognize these antigens via the CD3-T-cell receptor (TCR) complex. This interaction when coupled with co-stimulatory signals such as B7-CD28 results in the activation of calcineurin and mitogen activated protein kinases (MAPK) eventually resulting in T-cell activation. Calcineurin accomplishes this by dephosphorylating, thus activating, the transcriptions factor nuclear factor of activated T-cells (NF-AT), while MAPK activated the transcription factor AP-1. These transcriptions factors stimulate the production of a variety of immune activating cytokines including IL-2. Released IL-2 binds to IL-2 receptor on helper T-cells activating the protein mTOR which results in T-cell expansion by stimulating T-cells to enter the S phase of the cell cycle. Glucocorticoids (Gluc) inhibit expression of MHC and co-stimulatory molecules on APCs and T-cells. Gluc also inhibit MAPK activation. Cyclosporine (CSA) forms a complex with cyclophilin A (CYPH A) and tacrolimus (TAC) after binding to FK-binding protein 12 (FKBP12), and each inactivate calcineurin. Daclizumab (DAC) blocks the IL-2 receptor, while rapamycin (RAPA) inhibits mTOR. Azathioprine (AZA) and mycophenolate mofetil (MMF), both inhibit denova purine synthesis which inhibits DNA synthesis during the S phase in lymphocytes.

T-lymphocytes remains the hallmark of HIV infection, especially advanced AIDS. Current concepts suggest that the CD4+ T-lymphocyte depletion is a consequence of chronic immune activation and not by direct virus-mediated cell death (Brenchley, Price and Douek, 2006). Massive mucosal CD4+ memory T-lymphocyte depletion from the gut lamina propria may lead to increased bacterial translocation, chronically activating innate and adaptive immunity (Brenchley, Price and Douek, 2006; Centlivre *et al.*, 2007; Veazey *et al.*, 1998; Guadalupe *et al.*, 2003; Brenchley *et al.*, 2004). Chronic T-lymphocyte activation generates a continuous supply of HIV targets which eventually surpasses the ability to produce new T-lymphocytes and leads to systemic T-lymphocyte depletion (Brenchley, Price and Douek, 2006). This early preferential loss of CD4+ T-lymphocytes at mucosal sites may also play a role in increasing incidence of infections at these mucosal sites independent of changes in peripheral CD4+ T-cell count (Veazey and Lackner, 2003), as peripheral CD4+ T-lymphocyte counts do not

predict local T-lymphocyte responses to microbes such as Hepatitis C virus (Koziel, 2006) or *Mycobacterium tuberculosis* (Breen *et al.*, 2006).

CD4+ T-lymphocyte depletion is also associated with abnormal lymphocyte proliferative responses to CMV and HSV in AIDS patients with serologic evidence of prior exposure to these viruses (Sheridan *et al.*, 1984), and decreased proliferative response and IFN- γ secretion to *M. tuberculosis* despite clinical response to highly-active antiretroviral therapy (HAART) (Schluger, Perez and Liu, 2002; Sutherland *et al.*, 2006). Although the ability of T-lymphocytes to produce IFN- γ in response to mitogens or antigens correlates with HIV clinical status, peripheral CD4+ T-lymphocyte count, and predict progression to AIDS (Murray *et al.*, 1985), the above data suggest the abnormalities of T-lymphocyte function may occur early in HIV disease and may not reverse with HAART.

CD8+ T-lymphocyte dysfunction

The absolute numbers of peripheral blood CD8+ T-cells increases rapidly with acute HIV infection and continue to increase with disease progression (Lang *et al.*, 1989; Margolick *et al.*, 1993), a pattern similar to that observed in lungs (Twigg *et al.*, 1999). The intensity of CD8+ T-lymphocyte infiltration of lungs depends on HIV viral load and may portend a poor prognosis (Twigg *et al.*, 1999). CD8+ T-lymphocytes can be infected with HIV, especially in late-stage HIV infection (Livingstone *et al.*, 1996). Similar to CD4+ T-lymphocytes, HIV infects predominantly activated CD8+ T-lymphocytes, which express high levels of CD4 (Kitchen *et al.*, 1998), although the frequency of CD8+ T-lymphocyte infection is low (Brenchley *et al.*, 2004) and the significance is unclear. Evidence, however, suggests functional impairment of CD8+ T-lymphocytes in HIV infection, as CD8+ T-lymphocyte-mediated cytotoxicity in response to influenza virus is reduced in HIV (Shearer *et al.*, 1985), and progressive HIV infection is associated with a loss of IFN- γ producing CD8+ T-lymphocytes specific to CMV (Bronke *et al.*, 2005). CD8+ T-lymphocytes may control HIV replication (Benito, Lopez and Soriano, 2004) and functional impairment in cytokine production, perforin expression, phenotypic maturation, and low proliferation may contribute both to disease pathogenesis and susceptibility to opportunistic infections (Benito, Lopez and Soriano, 2004).

B-lymphocyte dysfunction

HIV infection is characterized by elevated numbers of polyclonal B-cells that spontaneously secrete immunoglobulins (De Milito, 2004), and patients with AIDS have increases in serum IgA, IgG and IgM (Shirai *et al.*, 1992). Evidence for B-cell dysfunction includes abnormal proliferation (Lane *et al.*, 1983), abnormal differentiation (Conge *et al.*, 1998), increased apoptosis (Muro-Cacho, Pantaleo and Fauci, 1995), and reduced capacity to co-stimulate CD4+ T-lymphocytes (Malaspina *et al.*, 2003). HIV infected persons demonstrate abnormal antibody response to pneumococcal vaccine (Ballet *et al.*, 1987) especially in subjects with CD4+ T-lymphocyte count

<500 cells/mm³ (Rodriguez-Barradas *et al.*, 1992). These abnormalities are associated with specific loss of memory B cell subsets (D'Orsogna *et al.*, 2007) similar to that seen in other immunodeficiencies such as common variable immunodeficiency (Hart *et al.*, 2007). Many B-lymphocyte abnormalities are related to plasma viremia and can be rescued by HAART (Morris *et al.*, 1998; Notermans *et al.*, 2001; Malaspina *et al.*, 2003). The lungs of HIV infected individuals demonstrate elevated B-lymphocytes and immunoglobulin levels (Young *et al.*, 1985; Fahy *et al.*, 2001), although opsonic activity of lung immunoglobulins, specifically to *Pneumococcus*, may be impaired in HIV (Eagan *et al.*, 2007).

Macrophage dysfunction

HIV can infect macrophages by interaction of the HIV gp120 envelope glycoprotein V3 hypervariable loop and macrophage CCR5 [Zhang, 1996 #19] *in vitro* and *in vivo* [Koziel, 1999:23]. Unlike CD4+ T-lymphocytes, HIV infection of macrophages leads to persistent infection with low-level viral replication [Fauci, 1988:20]. The role of macrophages as a reservoir for HIV persistence and the role in HIV pathogenesis remains controversial [Stebbing, 2004:#21] although macrophages may be a major source of HIV replication during opportunistic infections [Orenstein, 1997:22].

Although only 1–10% of alveolar macrophages are infected with HIV [Koziel, 1999:23], these cells demonstrate impaired phagocytosis (Koziel *et al.*, 1998), NF- κ B nuclear translocation (Zhang *et al.*, 2004), and respiratory burst response (Koziel *et al.*, 2000) to *Pneumocystis*. Alveolar macrophage functional abnormalities may be specific as phagocytosis of Ig-opsonized erythrocytes (Koziel *et al.*, 1998), opsonized *S. pneumonia* (Gordon *et al.*, 2001), and unopsonized *E. coli* (Elssner *et al.*, 2004) remain intact, whereas phagocytosis of the intracellular pathogen, *M. tuberculosis*, is enhanced (Day *et al.*, 2004; Patel *et al.*, 2007). Alveolar macrophages from asymptomatic HIV+ individuals demonstrate impaired TLR4 signaling (Tachado *et al.*, 2005), and impaired apoptotic response (Patel *et al.*, 2007), β -chemokine and TNF α secretion in response to *M. tuberculosis* (Patel *et al.*, 2007; Saukkonen *et al.*, 2002). Taken together, these studies suggest that HIV is associated with targeted and pathogen-specific alterations in macrophage responses.

Dendritic cell dysfunction

Both myeloid and plasmacytoid dendritic cells (DC) are susceptible to HIV infection, with 1–3% of DCs infected *in vivo* (Wu and KewalRamani, 2006). Both infected DC and uninfected DC that can bind HIV through C-type lectin receptors such as DC-SIGN and mannose receptor (Turville *et al.*, 2002) and are capable of transmitting HIV to T-lymphocytes, a mechanism by which initial infection may be established and by which HIV infection may be maintained and spread in tissues and lymph organs (Wu and KewalRamani, 2006). HIV-mediated modulation of antigen-presenting function of DC may be a key aspect of viral pathogenesis and contributes to viral immune evasion (Wu and KewalRamani, 2006). DC infected *in vitro* or taken from

the peripheral blood of HIV+ subjects less efficiently stimulate T-lymphocytes (Macatonia *et al.*, 1990; Knight, Patterson and Macatonia, 1991), and total DCs are decreased in chronic HIV infection (Macatonia *et al.*, 1990). Although total DCs are increased in acute HIV infection, costimulatory receptor expression is decreased (Lore *et al.*, 2002). HIV selectively infects immature DCs, although, unlike with DC infection from other viruses, HIV-infected DC fail to mature in culture and instead stimulate T-lymphocytes to produce an immunosuppressive response with increased levels of IL-10 (Granelli-Piperno *et al.*, 1998; Granelli-Piperno *et al.*, 2004; Granelli-Piperno *et al.*, 2006).

Neutrophil dysfunction

A number of abnormalities of neutrophil function have been observed in HIV infected individuals. Neutrophils are vital for the host defence of both bacterial and fungal organisms (Kuritzkes, 2000). Neutropenia may occur in up to one-third of HIV infected individuals (Kuritzkes, 2000). The expression of CD88, the ligand for complement 5a (C5a), is reduced in neutrophils from HIV+ individuals with corresponding decreases in C5a-mediated neutrophil chemotactic responses (Monari *et al.*, 1999; Meddows-Taylor, Pendle and Tiemessen, 2001). A reduction in neutrophil IL-8 receptor expression and IL-8 mediated chemotaxis has been described in HIV+ individuals (Meddows-Taylor, Martin and Tiemessen, 1998). Additional neutrophil defects include reduced IL-8 production in response to *Cryptococcus* in late stage AIDS (Monari *et al.*, 1999), impaired bacterial killing (Ellis *et al.*, 1988), impaired phagocytosis of *Candida* (Ellis *et al.*, 1988), impaired adhesion molecule expression (Ellis *et al.*, 1988) and impaired respiratory burst activity (Ellis *et al.*, 1988; Elbim *et al.*, 1994).

Organ transplant recipients

Pulmonary complications, especially infectious complications are among the most common in transplant recipients (Kotloff, Ahya and Crawford, 2004). Infections in the transplant patient may increase risk of graft rejection (Hartmann, Sagedal and Hjelmessaeth, 2006; Potena and Valantine, 2007) and conversely graft rejection may increase risk of infection (Hamadani *et al.*, 2007). Allograft rejection is mediated predominantly by CD4+ T-lymphocytes which are activated by either recipient or donor antigen presenting cells (APC) which present both alloantigens and costimulatory molecules (Lindenfeld *et al.*, 2004). This, in turn, leads to T-lymphocyte activation and proliferation, with subsequent activation of immune cells such as B-lymphocytes, CD8+ cytotoxic T-lymphocytes, macrophages and NK cells (Lindenfeld *et al.*, 2004). Immunosuppressive agents administered to organ transplant recipients aim to prevent allograft rejection by inhibiting specific steps in this process. Novel immunotherapy agents have contributed to improved survival in organ transplant patients, although the mechanism of immune suppression can increase susceptibility to infectious complications. Select agents used in organ transplant recipients are discussed below and the modes of action are summarized in Figure 1.2.

Glucocorticoids

Glucocorticoids are potent immunosuppressive agents that inhibit a broad array of cellular processes involved in both allograft rejection and host defence. Glucocorticoids cross the cell membrane, bind to the cytoplasmic glucocorticoid receptor and translocate to the nucleus where the receptor-steroid complex increases expression of specific responsive genes while inhibiting others (Morand, 2007). In T- and B-lymphocytes, major effects are mediated by inhibition of the transcription factors activator protein-1 (AP-1) (Jonat *et al.*, 1990), in part through the induction of MAP kinase phosphatase 1 (MKP-1) (Clark, 2003), and inhibition of nuclear factor kappa-B (NF- κ B) (Auphan *et al.*, 1995). These factors modulate the expression of costimulatory molecules, growth factors and cytokines such as IL-2 which inhibit T- and B-lymphocyte proliferation (Morand, 2007). In monocytes, glucocorticoids target cytokine production through a similar mechanism (Lindenfeld *et al.*, 2004), and reduce MHC class II expression (Duncan and Wilkes, 2005). In addition, glucocorticoids retard inflammatory responses by decreasing the production of vasoactive and chemoattractive factors, and decrease neutrophil adherence and migration by inhibiting endothelial expression of adhesion molecules in part by inhibiting phospholipase A₂ (an early enzyme required for the production of leukotrienes and prostaglandins) (Lindenfeld *et al.*, 2004; Duncan and Wilkes, 2005).

Calcineurin inhibitors

Tacrolimus and cyclosporine represent mainstays of transplant immunosuppression therapy allowing the sparing of the more toxic corticosteroids (Haberal *et al.*, 2004). Both agents inhibit the calcium-activated/calmodulin dependent serine threonine phosphatase calcineurin which is found predominantly in T-lymphocytes (Kahan, 1989; Ho *et al.*, 1996). Cyclosporine binds an immunophilin called cyclophilin A, while tacrolimus (FK506) binds FK-binding protein 12. In each case the drug-immunophilin complex binds and inactivates calcineurin. Active calcineurin dephosphorylates (thus activates) the transcription factor family nuclear factor of T-lymphocytes (NFAT) (Kapturczak, Meier-Kriesche and Kaplan, 2004), which results in IL-2, IL-4, and CD40 ligand expression (cytokines and surface proteins vital for T-lymphocyte proliferation and activation). In addition, calcineurin inhibition also interferes with NF- κ B activation, Na-K-ATPase, IL-3, GM-CSF and nitric oxide synthase while upregulating the immunosuppressive cytokine transforming growth factor- β production (TGF- β) (Kapturczak, Meier-Kriesche and Kaplan, 2004). Upregulation of TGF- β may also be responsible for the fibrosis that occurs in chronic organ rejection (Kapturczak, Meier-Kriesche and Kaplan, 2004). In addition, both drugs inhibit MAP kinase/AP-1 activation (Matsuda *et al.*, 2000) and antigen presentation by dendritic cells (Lee *et al.*, 2005) in a calcineurin-independent manner.

mTOR inhibitors

Rapamycin (sirolimus) is structurally related to FK506 and binds to FK-binding proteins, but does not inhibit calcineurin, and instead binds the kinase mammalian

target of rapamycin (mTOR) (Easton and Houghton, 2006). mTOR phosphorylates a variety of proteins important for regulating the cell cycle, and thus mediates the signaling for a variety of growth factor receptors that stimulate the growth and proliferation of T- and B-lymphocytes (Heitman, Movva and Hall, 1991; Ingle, Sievers and Holt, 2000). Rapamycin effectively inhibits lymphocyte proliferation by preventing IL-2 receptor mediated activation of cell cycle progression from G1 to S phase via inhibition of mTOR. In addition, rapamycin inhibits proliferation of smooth muscle, fibroblasts, endothelial cells and a variety of other cell types which gives it potential in both cancer therapy (Easton and Houghton, 2006) and drug eluting stents (Wessely, Schomig and Kastrati, 2006), but may increase the likelihood of complications such as anastomotic dehiscence post-lung transplantation (King-Biggs *et al.*, 2003).

Antimetabolites

Azathioprine (AZA) is a pro-drug of 6-mercaptopurine (6-MP) developed in the 1950s (Duncan and Wilkes, 2005), while Mycophenolate mofetil (MMF) was developed as a more potent and selective replacement for AZA (Duncan and Wilkes, 2005). Both drugs inhibit *de novo* purine synthesis, inhibiting DNA and RNA production, and are considered antimetabolites. Unlike other cell types, lymphocytes depend on both the *de novo* and salvage pathways for purine biosynthesis making these drugs relatively specific for inhibiting T- and B-lymphocyte proliferation (Gummert, Ikonen and Morris, 1999). AZA is metabolized to 6-MP by glutathione (Taylor, Watson and Bradley, 2005), then metabolized to purine analogs 6-thiouric acid, 6-methyl-MP, and 6-thioguanine triphosphate (6-thio-GTP) which upon incorporation into DNA halts DNA synthesis. This mode of action activity is not specific for lymphocytes which accounts, in part, for decreased specificity of AZA for lymphocytes compared to MMF (Gummert, Ikonen and Morris, 1999). 6-MP is also converted into thioinosinic mercaptopurine, which inhibits *de novo* pathway enzymes phosphoribosyl pyrophosphatase synthase and inosinate monophosphate dehydrongenase (IMPDH), inhibiting synthesis of adenosine monophosphate (AMP), and guanosine monophosphate (GMP). In addition, 6-thio-GTP can inhibit the rhoGTPase rac1 in place of GTP, blocking CD28 costimulation pathways and preferentially causing apoptosis of activated lymphocytes (Tiede *et al.*, 2003).

MMF, a pro-drug of mycophenolic acid (MPA), is a more potent and selective inhibitor of *de novo* purine synthesis with less effect on hematopoietic cells and neutrophils (Duncan, 2005:76). MPA is not a purine analog, but instead inhibits IMPDH by reversibly binding the cofactor site (NAD/H₂O), preventing a critical enzyme in GMP production (Sintchak, 1996:92), and leads to the accumulation of AMP over GMP which feedbacks negatively on proximal enzymes within the *de novo* pathway, and potently inhibits T- and B-lymphocyte proliferation, antibody production, NK cell generation and delayed-type hypersensitivity response (Gummert, Ikonen and Morris, 1999). As guanosine nucleotides are also required for glycosylation of proteins (Laurent *et al.*, 1996), MPA inhibits glycosylation of adhesion molecules, decreasing recruitment of leukocytes to areas of inflammation (Gummert, Ikonen and Morris, 1999).

Antilymphocyte antibodies

Polyclonal antithymocyte globulin (ATG) are purified monomeric anti-human gamma globulins created by immunizing rabbits, horses, or goats with human thymocytes or T cell lines (Haidinger *et al.*, 2007). These agents are typically used for induction or to treat acute rejection (Beiras-Fernandez, Thein and Hammer, 2003). They bind to cell surface receptors, thereby opsonizing lymphocytes for complement-mediated lysis or reticuloendothelial cell-dependant phagocytosis (Beiras-Fernandez, Thein and Hammer, 2003). ATG recognize most molecules involved in the T-lymphocyte activation cascade such as CD2, CD3, CD4, CD8, CD11a, CD18, CD25, HLA DR and HLA class I (Beiras-Fernandez, Thein and Hammer, 2003). Although T cell depletion is the major mechanism of action, additional effects include modulating key cell surface molecules that mediate leukocyte-endothelium interactions, induce B-lymphocyte apoptosis, interfere with DC functional properties and induce regulatory T- and natural killer T-lymphocytes (Mohty, 2007).

Monoclonal antibodies

The first monoclonal antibody used in organ transplantation was OKT3 or Muromonab-CD3, a murine IgG2a monoclonal antibody directed against the human T-lymphocyte surface protein CD3 (Renders and Valerius, 2003). CD3, when complexed with the T cell receptor (TcR), is critical to CD4+ T-lymphocyte activation and to CD8+ T-lymphocyte to binding and lysis of target cells (Chatenoud and Bluestone, 2007). T-lymphocytes exposed to OKT3 subsequently internalize the TcR-CD3 complex, which induce immunosuppressive mechanisms, including: 1) Cell coating preventing T-lymphocyte-cell interactions; 2) T-lymphocyte depletion via destruction of Ab-coated T-lymphocytes; 3) T-lymphocyte anergy via internalization of TcR-CD3 complex (thus low expression of TCR); and 4) upregulation of immune modulating T-regulatory cells (Chatenoud, 2003). The mechanism of T-lymphocyte depletion includes complement mediated cell lysis, antibody dependent cell killing by NK cells or macrophages, and apoptosis via ligation of CD95 (Fas) which occurs in activated T-lymphocytes (Chatenoud, 2003). The latter effect on T regulatory cells may in part account for prolonged OKT3 effects following antibody clearance (Chatenoud and Bluestone, 2007).

Antireceptor antibodies

Daclizumab is a humanized monoclonal antibody directed against the CD25 molecule, a key component of the IL-2 receptor (IL-2R) (Waldmann, 2007), central in promoting T-lymphocyte activation, differentiation and proliferation (Duncan and Wilkes, 2005). The main mechanism of action of daclizumab is to inhibit IL-2 induced T-lymphocyte proliferation. Importantly, daclizumab does not deplete non-CD25+ T-lymphocytes, and thus affords higher specificity than OKT3 or ATG (Duncan and Wilkes, 2005). Other effects include inhibition of CD8+ T-lymphocyte production, immunoglobulin production, and suppression of IL-15 dependant T-lymphocyte proliferation (Waldmann, 2007).

IL-2 is also important in immune regulatory functions such as IL-2 activation-induced cell death and the maintenance and fitness of T-regulatory cells, although the clinical significance in patients treated with Daclizumab is uncertain (Waldmann, 2007). Alemtuzumab (anti-CD52 monoclonal antibody, or Campath) was initially used for the treatment of chronic lymphocytic leukemia, now with increasing off-label use for transplantation induction (Magliocca and Knechtle, 2006). CD52 is a glycoprotein expressed on approximately 95% of peripheral blood lymphocytes, natural killer cells, monocytes, macrophages and thymocytes (almost all mononuclear cells) (Hale, 1990:103). The biological effects may be prolonged, with reduction of T- and B-lymphocytes observed for greater than one year after a single dose (Magliocca and Knechtle, 2006).

Immunodeficiency associated with cancer patients

In patients with malignancy, infections (including pneumonia) are a significant cause of morbidity and mortality (Joos and Tamm, 2005). Neutropenia associated with chemotherapy or hematologic malignancies is the strongest factor for infection risk (Joos and Tamm, 2005). The duration of neutropenia (absolute granulocyte count of ≤ 500 cells/mm³), is strongly linked to incidence of infections including bacterial and fungal pneumonias (Viscoli, Varnier and Machetti, 2005). Neutrophils are important in the control of *Aspergillus*, in particular killing of hyphae forms (Feldmesser, 2006). Platelets, which are also typically low in neutropenic patients, may also have antimicrobial properties against *Staphylococcus*, *Candida* and *Aspergillus* (Yeaman *et al.*, 1992; Yeaman *et al.*, 1996; Christin *et al.*, 1998). Monoclonal antibody therapies, such as Alemtuzumab (used to treat T-lymphocyte lymphomas or leukemias) cause profound cytopenias. Rituximab, a monoclonal antibody to CD20, specifically targets B-lymphocytes (used to treat B-cell lymphomas) but does not induce as profound immunosuppression as alemtuzumab or other chemotherapy agents (Plosker and Figgitt, 2003).

Numerous immune defects have been described in patients with solid and hematologic cancers. Hematologic malignancies, specifically acute leukemias, are associated with neutropenia, impaired neutrophil function (Hubel *et al.*, 1999), and impaired T-lymphocyte activation (Scrivener *et al.*, 2003). Defects in T-lymphocytes function in solid organ malignancies including abnormalities in interferon signaling in T-lymphocytes from melanoma patients (Critchley-Thorne *et al.*, 2007), increased expression of immunosuppressive TGF- β -secreting T-regulatory cells in patients with non-small cell lung cancer and ovarian cancer, and defects in NK cells, cytotoxic T cells, and macrophages in select solid tumours (Elgert, Alleva and Mullins, 1998; Kiessling *et al.*, 1999). In addition to increasing infection risk, tumour-induced immune dysfunction may also contribute to tumour progression (Elgert, Alleva and Mullins, 1998; Kiessling *et al.*, 1999).

Chemotherapy-induced defects in immune function are the major factors in the susceptibility of cancer patients to infection (Joos and Tamm, 2005). Cancer therapy may contribute to structural defects in the lungs, independent of impaired immune cells.

Direct pulmonary toxicity from bleomycin (Sleijfer, 2001), busulfan (Oliner *et al.*, 1961), cyclophosphamide (Malik *et al.*, 1996), methotrexate (Cannon, 1997) and radiotherapy (Abratt *et al.*, 2004) are clinically appreciated. Although the mechanism of drug-induced and radiation-induced lung injury is not well understood, epithelial injury is believed to play a central role (Higenbottam *et al.*, 2004). Lung epithelial injury may increase risk of pulmonary infection due to breakdown of mucosal barriers and impairing lung clearance mechanisms (Blijlevens, Donnelly and de Pauw, 2005), such as impaired respiratory ciliary function described in bone marrow transplant recipients (Au *et al.*, 2001). In addition, breakdown of gastrointestinal mucosal barriers with chemotherapy is believed to be responsible for increased incidence of gram-negative infections (including pneumonia) through hematogenous spread (Viscoli, Varnier and Machetti, 2005).

Immunodeficiency associated with collagen vascular disease

Infections associated with collagen vascular disease are common and can result in high morbidity and mortality (Noel *et al.*, 2001). Immunodeficiency in subjects with collagen vascular disease are attributed to agents used in treatment (Hamilton, 2005) although some immune defects have been attributed directly to collagen vascular diseases. For example, systemic lupus erythematosus (SLE) is associated with a relative T- and B-cell lymphopenia (Banchereau and Pascual, 2006), reduced T-lymphocyte activation (Kytaris and Tsokos, 2004), and SLE acute exacerbations ('flares') are independent risk factors for infection (Noel *et al.*, 2001).

Various pharmacological agents are used to treat this group of diseases. In addition to immunosuppressive agents such as corticosteroids, AZA, MMF and cyclosporine (described above), other agents include cyclophosphamide and methotrexate (Ponticelli, 2006). Cyclophosphamide is an alkylating agent that inhibits DNA replication (Martin *et al.*, 1997a), and can induce neutropenia (Martin *et al.*, 1997a), generalized lymphopenia (Cupps and Fauci, 1982), and can impair B-lymphocyte activation, proliferation and differentiation (Zhu *et al.*, 1987). Methotrexate interferes with folate metabolism, and consequently purine and pyridine synthesis (Genestier *et al.*, 2000), and results in decreased T- and B-lymphocyte replication, activation and differentiation (Quemeneur *et al.*, 2004). Methotrexate also interferes with neutrophil migration and may decrease leukocyte phagocytic function (Genestier *et al.*, 2000).

A number of monoclonal antibody or soluble receptor antagonists are used to treat Crohn's disease, rheumatoid arthritis and sarcoidosis including rituximab, TNF- α inhibitors, and IL-1 receptor antagonist (Hamilton, 2005; Ponticelli, 2006). These agents are used to neutralize the effects of TNF- α , a critical protein in mediating inflammation (Clark, 2007). The TNF- α inhibitors include infliximab, a chimeric monoclonal antibody, and adalimumab, a fully human monoclonal body, that bind and neutralize both soluble and surface bound TNF- α . Etanercept is a soluble receptor fusion protein that binds to soluble TNF- α less avidly than infliximab (Hamilton, 2005), but also binds lymphotoxin which infliximab does not. TNF- α is particularly important in mediating host-defence against specific organisms such as *M. tuberculosis*

(Patel *et al.*, 2007). In particular, TNF- α is vital to the formation and maintenance of granulomas to destroy pathogens, limit generalized inflammation, and prevent dissemination of pathogens (Algood, Lin and Flynn, 2005). The use of TNF- α inhibitors can be associated with the development of life-threatening disseminated infections that are typically controlled by granulomas, including tuberculosis, histoplasmosis, aspergillosis, *Cryptococcus* infection, and listeriosis (Hamilton, 2005).

The immunocompromised critically ill patient

Burns, trauma, sepsis and other critical illness place patients at increased risk of nosocomial pneumonias with attendant high mortality (Wunderink, 2005; Church *et al.*, 2006). A number of factors contribute to infection susceptibility, especially mechanical factors including reduced cough and decreased airway protection from delirium, sedatives, analgesics, or pain, supine positioning that may impair mucociliary clearance or increases aspiration risk, direct thoracic wall or pulmonary injury due to chest wall trauma, pulmonary contusion, or smoke inhalation, all of which may also impair cough or mucociliary clearance. The presence of an endotracheal tube bypasses critical upper respiratory tract mechanisms, and provides a direct conduit for microbes into the lower respiratory tract. Furthermore, the normal host bacterial flora is altered due to colonization with ICU-associated microbes and the use of multiple antibiotics (Wunderink, 2005).

Other factors that contribute to infection risk include immunoparalysis associated with critical illness (Wunderink, 2005). Burn trauma patients have decreased expression of HLA-DR in peripheral blood monocytes and elevated expression of IL-10 suggesting decreased immune activation and relative immunosuppression (Sachse *et al.*, 1999), with similar findings noted in patients with other forms of trauma, major surgery, and sepsis (Monneret *et al.*, 2003). These findings correlate with reduced LPS responsiveness (Wolk *et al.*, 1999), increased levels of regulatory T-lymphocytes (Monneret *et al.*, 2003), and increased risk of nosocomial infection (Sachse *et al.*, 1999). There is also evidence for decreased opsonic activity (Saba *et al.*, 1986) and decreased respiratory burst activity in critically ill patients (Zapata-Sirvent and Hansbrough, 1993). Lymphopenia and increased lymphocyte apoptosis also correlates with mortality in sepsis (Hotchkiss *et al.*, 2001) and inhibitors of apoptosis may improve outcomes in sepsis (Hotchkiss *et al.*, 2001). Agents targeted to counteract immunoparalysis in the critically ill may improve outcomes by reducing risks for serious infections.

1.4 Summary and future directions for this field

As our understanding of the barrier and pharmacological defences, the innate immune and adaptive immune systems (and the instructive bidirectional interaction of these systems) in health improves through continued scientific research, an improved understanding of the factors that predispose immunocompromised patients to various infections may be identified as targeted or specific deficiencies in innate or adaptive

Table 1.2 Summary of immunocompromised host populations.

Immunocompromised host	Mechanism(s) of immunocompromise	Predominant area(s) of immune dysfunction	Common infectious organisms
HIV+ Individuals	(1) Direct HIV-mediated effects causing cytotoxicity and dysfunction. (2) Indirect effects through alterations of mucosal immunity	(1) T-cell depletion and dysfunction (2) B-cell dysfunction (3) Macrophage dysfunction (4) Neutrophil depletions and dysfunction	Community-Acquired Bacterial organisms, <i>Pneumocystis</i> , <i>Mycobacterium tuberculosis</i>
Transplant Patient	(1) Medication-related immunosuppression	(1) T-cell dysfunction (2) B-cell dysfunction	Community-acquired bacterial organisms, CMV, <i>Pneumocystis</i>
Cancer Patient	(1) Chemotherapy related immunosuppression (2) Direct cancer-induced immunosuppression	(1) Neutropenia (2) barrier dysfunction from chemotherapeutic/radiation injury	Gram-negative bacteria, <i>Candida</i> infection, <i>Aspergillus</i> infection
Collagen Vascular Disease	(1) Steroids and pharmacologic immunosuppressives (2) Anti-cytokine therapy	(1) T-cells/B-cells dysfunction (2) Granuloma Formation (anti-TNF)	Bacterial Infections Mycobacterium tuberculosis, Histoplasma
Critically Ill Patient	(1) Impaired mucosal barrier function (2) immunoparalysis due to critical illness	(1) impaired ciliary function due to direct lung injury (2) impaired clearance due to intubation, sedation and positioning. (3) impaired T-cell/B-cell function	Bacterial infections, <i>Candida</i> infections

immune systems. Understanding the underlying basic mechanisms that contribute to the pathogenesis of infectious diseases will allow development of targeted and novel therapeutic agents for use in immunocompromised hosts for the purpose of augmenting or rescuing immune function and controlling infectious disease in vulnerable patients (Table 1.2).

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