Chapter 49

Infections that cause secondary immune deficiency

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Introduction

Immune deficiencies can be subdivided into two categories: primary or secondary. This chapter describes secondary defects related to infection, and other forms of secondary immunodeficiency are described elsewhere in this book. Some microbes manipulate or exhaust effector immune responses, leading to secondary infections by other microbes. While the manipulation or exhaustion of immune responses is an important defense mechanism of some microbes to evade effective immune clearance, it is also likely that the genetic immune response repertoire that programs how an infected individual will respond to these microbes contributes significantly to whether the resulting immune responses will protect against, or facilitate, superinfection by other microbes. In this chapter, we discuss how some microbes manipulate or, in the case of the human immune deficiency virus (HIV), exhaust protective innate and/or adaptive immunity, ultimately leading to severe microbial superinfections by other infectious organisms that cause significant morbidity and, on occasion, mortality from secondary infections.

A critical component of host defense includes the expression of immunosuppressive cytokines. IL-10, and TGF-β, and the generation of regulatory T cells that can express these cytokines serve to limit the immune-mediated damage related to host defense. These same elements also cause secondary immune deficiency by suppressing or blocking effector Th1-like responses. These immunoregulatory elements, generated in response to the original infection, as a consequence, can lead to secondary immune deficiency and the development of severe or fatal infection with other microbes. Some of the microbes that cause temporary or permanent changes in immune responses to other organisms are shown in Table 49.1 (see below). In addition, Fig. 49.1 shows the functional diversity of CD4$^+$ T cells that has evolved to control the microbiome present on mucosal surfaces. In concert with the repertoire of these T cells, and the cytokines and chemokines that they express, the continuum of macrophages (Fig. 49.2)[1] and their respective cytokine/chemokine repertoires expressed in response to microbial infection, form the critical immune response elements that are required to mount and maintain an effective immune response against these microbes.

The amount of immunomodulatory cytokines, such as IL-10, expressed during infection contributes to the development of secondary infections during and after recovery from the primary infection. Alteration in the balance between immunity and immune suppression is in part, based on how much IL-10 is expressed during a given infection. IL-10 promoter polymorphisms that control high, intermediate, or low expression of IL-10[2–4] during and after microbial infection may influence the development of resistance or susceptibility to secondary microbial infection. Excessive IL-10 levels defined by a given host's IL-10 genotype could predispose an individual to develop secondary infections by blocking appropriate pro-inflammatory responses. In contrast, low IL-10 levels, also defined by a given host's genotype, could protect against secondary infection, at the expense of limiting collateral tissue damage and T cell memory that higher IL-10 expression would support.[5] Taken together, the successful balance of cellular innate and adaptive immune responses, and the cytokine/chemokine repertoires that they express during a primary infection to an infectious microbe, can temporarily or permanently "hijack" effective immune responses that are necessary to prevent other infections by microbes

TABLE 49.1 Microbes that cause secondary immune deficiency states.

Microbe	Affected immunocyte	Immune dysregulation phenotype	Pathogens causing secondary infection	Abnormal lab tests associated with microbe infection
Viruses:				
Measles	T Cells Dendritic cells	(1) Diminished lymphocyte proliferation (2) Decreased antibody production (3) Increased susceptibility to co-infection or super-infection with viral, bacterial or fungal pathogens	(1) Viral: Herpes simplex, cytomegalovirus, parainfluenza, adenovirus, coxsackie, respiratory syncytial virus (2) Bacteria: *S. aureus*, S. pneumonia, Klebsiella, Pseudomonas, mycobacteria, Acinetobacter (3) fungal: Candida	(1) Anti-measles IgM (2) Mitogen/Lymphocyte Proliferation Assay (3) Lymphocyte profile (T/B/NK cell immunocyte counts)
Influenza A Virus	Neutrophils	(1) Deactivation of chemotaxis, respiratory burst, degranulation, and bacterial killing (2) IFNs-γ, -α, -β triggered by IAV depresses macrophage function and macrophage scavenger receptor (MARCO) (3) Impaired murine chemokine recruitment of neutrophils to the lung	(1) Bacteria: Streptococcal pneumoniae, Staphylococcal (MRSA), Haemophilus influenzae pneumonia post Influenza A Virus infection	(1) PCR-based influenza assay (2) complete blood count with manual differential
Human Immune deficiency Virus (HIV)	CD4$^+$ cells (T cells, macrophages)	Depletion of CD4$^+$ T cells over time	Opportunistic infections: Bacteria, fungi, parasites	(1) 4th generation HIV-1/2 Ag/Ab Assay (2) Lymphocyte count (T/B/NK immunophenotype)
Human T cell Lymphotropic Virus (HTLV)	T cells, NK cells	(1) induces cytotoxic T cells to kill virus-infected cells, (2) alter CD4$^+$ T cell function and cytokine production (3) decreases NK cell activation	Strongyloides schistosomiasis	(1) HTLV-1 and HTLV-2 IgG/IgM (2) Lymphocyte count (T/B/NK immunophenotype)
Cytomegalovirus	T Cells	(1) lower frequency of naïve T cells and accumulation of memory T cells (2) immune senescence	Rare secondary bacterial/viral super infection	(1) CMV PCR (2) CMV IgG (3) Lymphocyte count (T/B/NK immunophenotype)

TABLE 49.1 Microbes that cause secondary immune deficiency states.—cont'd

| Microbe	Affected immunocyte	Immune dysregulation phenotype	Pathogens causing secondary infection	Abnormal lab tests associated with microbe infection
Epstein-Barr Virus	B Cells	(1) Depletion of B cells (X-linked lymphoproliferative syndrome (XLP)) (2) Monoclonal/polyclonal gammopathy (3) Autoimmunity (4) Cancer	Parvoviridae, Streptococcus group A.	(1) EBV DNA by PCR (2) Heterphile Ab (3) EBV Serology (EBV Viral capsid IgG/IgM, EBV early Antigen, EBV Nuclear Antigen) 4) Lymphocyte count (T/B/NK immunophenotype)
Parasites:				
Leishmania	Macrophages	(1) Decreased MHC class II expression (2) Decreased IL-1 production	Bacteria that cause infection in patients with chronic granulomatous disease.	(1) Visualization of amastigote in smears or tissue (histopathology) (2) parasite isolation by *in vitro* culture (3) molecular detection of parasite DNA (4) serologic testing
Malaria	T Cells Dendritic cells	(1) Impaired dendritic cell maturation and activation (2) Increased susceptibility to co-infection with viral and bacterial pathogens (3) Decreased efficacy of heterologous vaccines (4) Reactivation of existing Epstein-Barr infection, with increased susceptibility to develop lymphoma	(1) viral: Herpes zoster, hepatitis B, Moloney leukemia virus, Epstein-Barr virus (2) bacterial: Salmonella	(1) Light microscopy - Giemsa stained blood smears (2) Rapid diagnostic test — antigen based assay (HRP2, pLDH, aldolase) (3) PCR based confirmation for research and epidemiological uses (4) Lymphocyte count (T/B/NK immunophenotype)
Bacteria:				
Bordetella Pertussis	Airway macrophages, neutrophils	(1) Delay of neutrophil recruitment and influx into airways (2) Depletion of airway neutrophils	Pyogenic bacterial and mycoplasma pneumonia	(1) culture - ciliated respiratory epithelium posterior nasopharynx (2) polymerase chain reaction (PCR) — polyester/ rayon swab - ciliated respiratory epithelium of posterior nasopharynx (3) Serology of pertussis antibodies (IgA or IgG to pertussis toxin, filamentous hemagglutinin, pertactin, fimbriae, or sonicated whole organism) acutely versus 4 weeks later
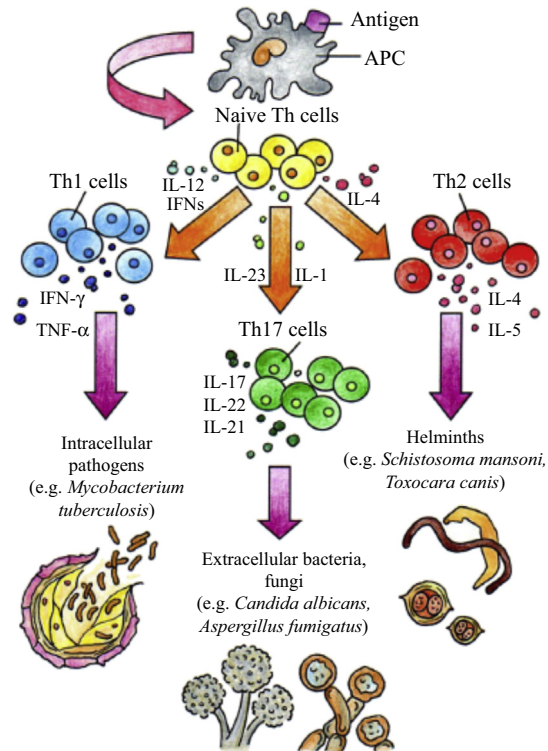
FIG. 49.1   Adaptive T cell responses to microbes. T helper (T$_H$) cell responses to microbial antigens presented by antigen-presenting cells (APCs), their cytokine milieu and role in driving the subsequent T-cell responses that are involved in protection against bacteria, fungi and parasites. *Figure from D'Elios MM, Benagiano M, Della Bella C, Amedei A. T-cell response to bacterial agents. J Infect Dev Ctries 2011;5(9):640—5. Reprinted under https://creativecommons.org/licenses/by/4.0/.*

that are commonly found in the environment. Thus, an imbalance in the immune responses made during a primary infection can have devastating consequences on the ability of an individual to generate effective immune responses to prevent or survive secondary infections caused by different microbes. Failure to establish an appropriate innate/adaptive immune balance can lead to persistent, severe, or fatal infections cause by secondary infections.

Distinguishing secondary immune deficiency from primary immune deficiency

It is often difficult to distinguish secondary immune deficiency in a normal individual with a significant initial primary infection, where the offending microbe temporarily subverts or paralyzes the adaptive immune response to other microbes, from a patient with primary immune deficiency disease (PIDD) who presents with a serious initial infection (Box 49.1). Several clues help distinguish between an initial infection in these different patient populations.[6–8] Among these clues that patients with PIDD are more likely to have are:

- a family history of recurrent infections that persist despite optimal medical management
- evidence of neonatal/early childhood demise secondary to infection
- bloodline relatives who have had frequent miscarriages
- unusual infections, such as meningitis or deep seeded organ abscesses
- relatives with repetitive infections with unusual organisms especially in male relatives
- multiple microbes causing an infection at the same time.

Patients with normal immune systems who become infected with viruses, bacteria, or parasites known to temporarily subvert or paralyze adaptive immunity without the above history are more likely to have secondary immune defects caused by microbes that prevent appropriate immunity to other organisms. Thus, the challenge for clinicians is to distinguish between patients with PID versus those with microbe-induced, secondary immune deficiency at the time of first presentation of a serious infection. In this review, we address the patient population with secondary, infection driven immune compromise, in contrast to patients with PIDD who are the focus of the remainder of this textbook.
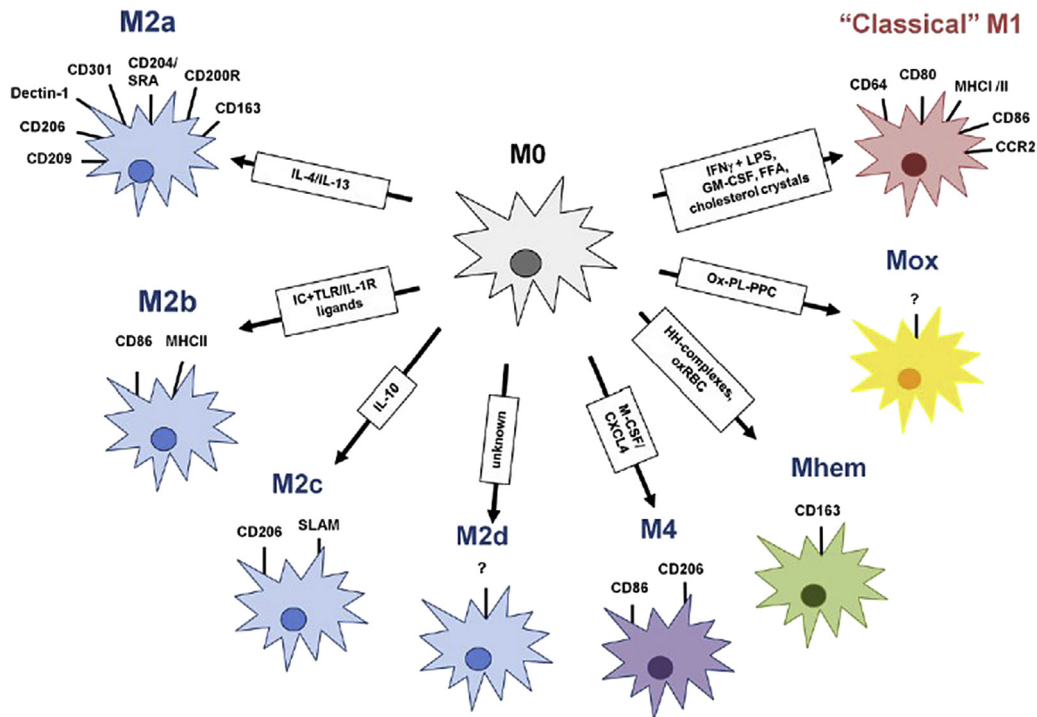
FIG. 49.2 **General concepts and properties of polarized macrophages**. Classically activated macrophages (M1) are induced through LPS and/or microbial product stimulation. Their inflammatory repertoire is characterized by the secretion of pro-inflammatory mediators and the release of reactive oxygen and nitrogen intermediates. In contrast, alternative activation of macrophages (M2) covers a continuum of functional states classified as M2a, induced by IL-4/IL-13; M2b, induced by immune complexes and TLR agonists; and M2c, induced by IL-10 and glucocorticoid hormones. *From Labonte AC, Tosello-Trampont AC, Hahn YS. The role of macrophage polarization in infectious and inflammatory diseases. Mol Cells. 2014 Apr 30; 37(4): 275−285.*

Sepsis

Sepsis with a wide variety of organisms causes a profound secondary immune deficiency. It is not an uncommon scenario to have to rule out a PIDD in the intensive care setting where both the underlying disease and medications may alter the immunologic findings. Sepsis is one of the more common causes of secondary lymphopenia (Box 49.1). Furthermore, there are both acute disruptions of immunologic function and longer term findings that are poorly characterized that are seen after trauma and burn injuries as well. In fact, increased mortality persists for years after an episode of sepsis. Immunologic findings occurring with acute sepsis include:

- Decreased CD4$^+$ T cells (apoptosis)
- Decreased γδ T cells
- Decreased NK cells
- Decreased B cells
- Diminished neutrophil oxidative burst
- Diminished TLR responses from monocytes
- Diminished monocyte HLA-DR expression
- Diminished NK cytotoxicity

Thus, findings of altered immune function during sepsis require confirmation after clinical recovery. When immediate action is required, interpretation of results requires placing the laboratory results in the context of recognized secondary immunologic effects.

BOX 49.1 Causes of lymphopenia

Primary immune deficiencies
Infections
- Brucellosis
- Cytomegalovirus (CMV)
- Epstein Barr Virus (EBV)
- Human immunodeficiency virus (HIV)
- Histoplasmosis
- Human lymphotropic virus (HTLV)
- Influenza
- Leishmania
- Malaria
- Measles
- Pertussis
- Parvovirus B19
- Viral hepatitis
- Tuberculosis
- Typhoid fever
- Rickettsia
- Varicella zoster virus

Autoimmunity
- Sarcoidosis
- Sjögren's syndrome
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Myasthenia gravis

Medications
- Chemotherapy (most)
- Anti-lymphocyte globulin
- Alemtuzumab
- Azathioprine
- Bisphosphonates (some)
- Carbamazepine
- Cimetidine
- Corticosteroids
- Dimethyl fumarate
- Imidazoles
- Interferons
- Methotrexate
- Opioids
- Psoralen
- Rituximab

Gastrointestinal/nutritional conditions
- Celiac disease
- Ethanol Abuse
- Inflammatory bowel disease
- Lymphangiectasia
- Malnutrition
- Protein loosing enteropathy
- Zinc deficiency

Hematology/Oncology conditions
- Bone marrow failure
- Hodgkin's disease
- Aplastic anemia

Radiation
- Radiation therapy
- Radiation injury
- Thermal energy (burn)
- Ultraviolet A irradiation

Other conditions
- Cushing Syndrome
- Exercise
- Idiopathic CD4$^+$ lymphocytopenia
- Lymphocyte loss conditions
- Renal failure
- Sepsis/Severe Acute Respiratory Syndrome (SARS)
- Stress
- Thoracic duct drainage, leak, rupture, diversion
- Trauma

Examples of microbes that cause temporary or long-term secondary immune deficiency

Table 49.1 [9] shows some of the microbes that are known to induce secondary immune deficiency, the cells that they affect, and the pathogens causing secondary infection. In some cases, secondary immune deficiency occurs as a result of a cytokine storm. Some infections known to cause a cytokine storm are shown in Box 49.2. Below, we describe examples of how some of these microbes suppress immunity and thereby cause secondary immune deficiency, predisposing patients to secondary microbial infections.

Viruses that hijack immune responses to other microbes

Measles virus: temporary immunosuppression

Measles virus (MV) continues to cause child morbidity and mortality worldwide, despite the availability and use of an effective live attenuated measles vaccine.[10–14] Part of the reason why control of MV continues to be elusive is that it is

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BOX 49.2 Select Infections causing cytokine storm[224–233]

- *Anaplasma phagocytophilum*
- *Burkholderia pseudomallei*
- Crimean-Congo hemorrhagic fever virus
- Dengue virus
- Ebola virus
- *Ehrlichia chaffeensis*
- *Francisella tularensis*
- Influenza (H5N1, H7N9 more than H1N1, H3N2)
- Junin virus
- Lassa virus
- Marburgvirus
- *Puumala orthohantavirus*
- Middle East respiratory syndrome CoV (MERS-CoV)
- Severe acute respiratory syndrome CoV (SARS-CoV)
- Visceral Leishmaniasis
- Yellow fever virus

highly contagious for susceptible individuals and there are difficulties with vaccine delivery. MV infection begins in the respiratory tract, spreads systemically in lymphoid, epithelial and endothelial cells, and ultimately infects multiple organs,[15] causing a characteristic fever, rash, and conjunctivitis 10−14 days after respiratory infection (Fig. 49.3A and B). High fever, rhinorrhea and conjunctivitis typically precede the rash and the rash migrates from the head and neck to the hands and feet over 3−4 days. Many of these manifestations are caused by the immune response made to MV, and commonly this response clears MV in infected tissues and prevents re-infection for life (Fig. 49.3C and D). However, MV infection can cause several weeks of immune suppression after resolution in select individuals. This is the primary cause of measles-associated deaths: MV-induced secondary infection.[16] Although vaccination against measles is very high in the United States, 92.7% of children aged 19−35 months were vaccinated in 2017,[17] there are pockets of unvaccinated people who are susceptible to local outbreaks of measles. Since "herd immunity" is primarily effective when the vaccination rate is around 96%,[18] vaccination levels below this level leave children and adults at risk for primary MV infection and secondary microbial infections.
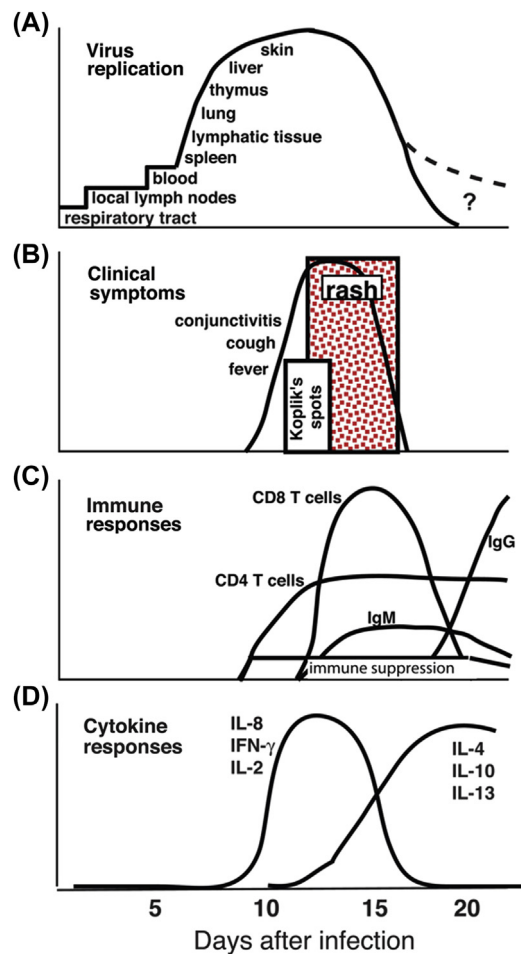

FIG. 49.3 **Outline of the pathogenesis of measles virus (MV) from the time of infection through recovery**. (A) MV infection is initiated in the respiratory tract and spreads systemically to infect multiple organs, including lymphoid tissue, liver, lungs, and skin. Epithelial cells, endothelial cells, B and T cells, monocytes/macrophages, and dendritic cells can be infected. MV clearance begins with the onset of the rash. Clearance of MV is complete 20 days after infection; however, viral RNA (dashed line) persists at multiple sites. (B) Clinical signs and symptoms begin approximately 10 days after infection, with prodromal symptoms of fever, conjunctivitis, and oral Koplik's spots, followed by a maculopapular rash for 3−5 days. (C) The rash represents adaptive immune responses with infiltration of $CD4^+$ and $CD8^+$ T cells into sites of MV replication and clearance. There is a rapid activation, expansion, and then contraction of MV-specific $CD8^+$ T cells. $CD4^+$ T cell responses appear at the same time, but activation is prolonged. MV-specific IgM appears with the rash, and this is commonly used for diagnostic purposes. This is followed by the sustained MV-specific IgG synthesis. Immune suppression is evident during acute disease and for many weeks after recovery. (D) Cytokines and chemokines produced during infection are found in plasma in elevated amounts. Early, IL-8 is increased. During the rash, IFN-γ and IL-2 are γ and IL-2 are produced by activated T_H1-like, $CD4^+$ and $CD8^+$ T cells. After rash resolution, T_H2-like T cells and regulatory $CD4^+$ T cells produce IL-4, IL-10, and IL-13. *Figure reproduced from Griffin DE. Measles virus-induced suppression of immune responses. Immunol Rev 2010;236:176−89 ©2010 John Wiley & Sons A/S.*

Measles was the first virus clearly identified to cause increased susceptibility to other microbial secondary infections. Most often, measles-associated deaths are caused by severe, overwhelming pneumonia and diarrhea.[16] Suppression of delayed hypersensitivity has been identified in tuberculin-sensitized individuals many weeks after complete resolution of MV infection (Fig. 49.3C).[19] Furthermore, several weeks after successful MV recovery, increased susceptibility to other infections has been reported, and T cell function and *in vitro* proliferation of T cells in response to mitogens has been shown to be markedly decreased (Fig. 49.4A and B).[1,20,21] Immunosuppression occurs during a period of intense immune activation that occurs during the onset of the MV rash and anti-MV immune responses (Fig. 49.3C and D). Lymphopenia, skewing of Th2-like chemokine polarized responses, and suppression of lymphocyte proliferation have also been documented (Fig. 49.3D). MV infection causes decreases in T and B cells in the blood during the MV rash period.[22-25] Altered trafficking and increased apoptosis of MV-infected and uninfected lymphocytes contribute to the development of lymphopenia.[22,26-30] While lymphocyte numbers rapidly return to normal in the blood after the rash resolves, immunologic abnormalities persist.[21,22,31,32] Immune suppression, Th2 cytokine polarization of CD4$^+$ T cells, and Treg induction have been associated with indirect immunosuppression caused by MV infection.[33,34] MV infection is also associated with suppression of IL-12 expression, lymphocyte CD30 expression, and IL-4, IL-10, and IL-13 expression after rash resolution.[35-37] Reduction of IL-12 production reduces T cell expression of type I cytokines, particularly IFN-γ[10,32] (Fig. 49.3D). It is possible that MV interacts with the complement regulatory molecule CD46 in polarizing Th2-like cytokine production, causing activation of signaling cascades that modify cell function, although this interaction is not firmly established.[38,39] The MV-CD46 interaction may alter innate immunity by selectively down-regulating receptor expression.[40-46] This would increase susceptibility to complement-mediated lysis of MV-infected cells, and decrease antigen presenting cell production of IL-12[47,48] and crosslinking of CD46 on T cells, leading to the induction of regulatory CD4$^+$ T cells and enhanced IL-10 levels.[49] These interactions would induce Th2-like polarization that would favor B cell maturation, provide lifelong MV antibody memory, and protect against MV re-infection. This polarization, however, would also depress APC activation and Th1-like responses to new pathogens.

MV suppresses PBMC proliferation to mitogens after MV resolution, and this continues for several weeks (Fig. 49.4B).[20,31] IL-2 supplementation can improve, but not fully restore, this responsiveness. This suggests that defective IL-2 expression is in part responsible for this proliferative defect.[50] Cell cycle arrest in G1 after *in vitro* infection with MV is a recognized cause of hyporesponsiveness to mitogens.[42,51-53] MV RNA can persist in PBMCs for months after MV resolution[54,55] and may reduce mitogen proliferation, although this has not been established. The receptor used by wild-type MV to infect cells, CD150, is a dual function co-receptor for lymphocyte activation, and enhances IFN-γ expression.[56-58] However, MV binding to CD150 can also downregulate receptor expression.[59,60] T cell signaling through the MV glycoprotein complex of H and F1-F2 in the membranes of virions or MV-infected cells[61-65] may also contribute to immunosuppression. This inhibitory signal prevents T cell S-phase entry for several days, and is independent of cell death, membrane fusion, soluble inhibitor production, or T cell infection.[52,61,62,65-67] Thus, there is a delay in cell cycle progression and an accumulation of T cells in the G0/G1 phase.[52,66,67] The mechanism by which H/F1-F2 suppresses mitogen-induced proliferation is unknown, but it is associated with MV-induced interference of T cell activation of phosphoinositide 3-kinase (PI3K) in T cells, or IL-2 receptor ligation.[68] IL-2 added to MV-treated cells activates signal transducer and activator of transcription 3 (STAT3) but fails to activate Akt kinase, which is required for cell cycle progression.[69] The modulatory effects of MV with glycoprotein complexes, and the downstream consequences of this
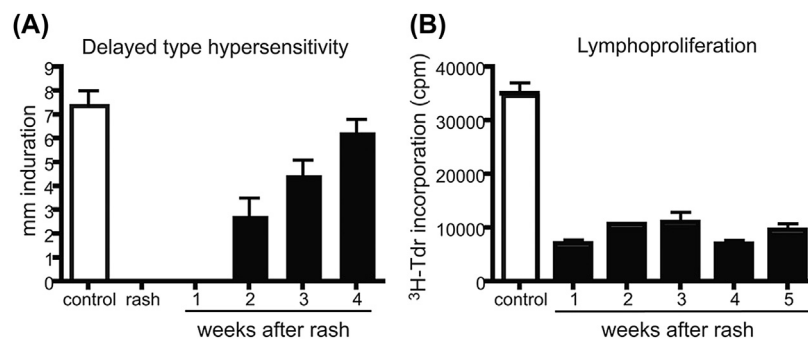
FIG. 49.4 Immune suppression during measles. (A) Delayed-type hypersensitivity skin test responses to tuberculin in Peruvian children before (control) and after the onset of measles. (B) Peripheral blood mononuclear cell proliferation in response to phytohemagglutinin from rhesus macaques during a primate center outbreak of MV. *Figure reproduced from Griffin DE. Measles virus-induced suppression of immune responses. Immunol Rev 2010;236:176−89 ©2010 John Wiley & Sons A/S.*

interaction, have recently been summarized.[10,68−70] While the relevance of these processes to the *in vivo* suppression of T cell lymphoproliferation remains to be identified. The combination of the established mechanisms leading to post-MV infection immunosuppression, and those that remain to be elucidated, cause, in select individuals, severe and on occasion, fatal secondary infection with other microbes.

A key epidemiologic factor in measles-related deaths is vitamin A deficiency. In the developing world, the World Health Organization recommends vitamin A supplementation. Studies have demonstrated improved outcomes and suggest an effect on the mucosal barrier and also on improved T cell function though by an undefined mechanism.

Influenza virus: temporary immunosuppression

Three world-wide (pandemic) outbreaks of influenza virus (IV) occurred in the 20th century, in 1918, 1957, and 1968. They are now known to represent three different antigenic subtypes of influenza A virus: H1N1, H2N2, and H3N2, respectively.[71] The 1918 "Spanish Flu" epidemic claimed an estimated 50 million lives and 20%−40% of the worldwide population became ill; approximately 675,000 Americans died during this epidemic.[72] Since then, IV infections have caused more than 20,000 deaths yearly in each of the 20 epidemics from 1957 to 1991,[73] and greater than 40,000 deaths occurred in each of the more recent epidemics, Thus, IV is a formidable pathogen.[74] While influenza-related mortality can in part be attributed to direct effects on the respiratory system, many of the deaths associated with IV infection are caused by increases in susceptibility to secondary bacterial pneumonia.[75] In fact, it has been suggested that the major mortality and morbidity resulting from IV infection may be caused by secondary bacterial infection that is associated with the inhibition of neutrophil function.[73] The bacteria commonly causing pneumonia in the most severely ill influenza patients are *Streptococcus(S.) pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*. Together, IV infection itself, and secondary bacterial pneumonia, were the most common causes of infectious death in the United States in 2002.[76] Research, clinical, and epidemiological studies show that there is a positive correlation between the increase in morbidity and mortality during influenza epidemics and pandemics, and an increase in secondary *S. pneumoniae* infection.[75,77,78] It has been hypothesized that influenza infection alters neutrophil function, thereby reducing the effectiveness of phagocyte-mediated killing of bacteria. An alternative hypothesis is that the tissue damage caused by IV alters the epithelial surface of the respiratory tract, thereby exposing different surface receptors to which *S. pneumoniae* adhere, and/or increasing the affinity of *S. pneumoniae* for its receptors, which may result in increased growth and decreased neutrophil killing of *S. pneumoniae* in the respiratory tract. Support for the former hypothesis comes from reports using both *in vitro* and *in vivo* models of influenza infection.[79−90] Neutrophils are important in resistance to *S. pneumoniae* infection independent of an influenza infection.[91] Influenza A virus alters the three major properties of the neutrophil that are crucial for bacterial clearance, namely chemotactic responsiveness, phagocytosis, and intracellular killing. This alteration of neutrophil function likely increases the susceptibility of an influenza-infected patient to *S. pneumoniae* infection because of decreased phagocytosis and killing of these bacteria by neutrophils.[80,84,89,92]

In humans, IV was reported to alter cell function by interacting with G proteins.[81,90,93] Human neutrophils express monomeric and trimeric G proteins that have critical roles in activation and regulation of various signal pathways, leading to chemotaxis and metabolic function.[94,95] Susceptibility to *S. pneumoniae* in mice is greatest at six days after influenza infection, consistent with the clinical findings.[96−99] Influenza-induced tissue damage is also greatest six days after influenza infection, as is adherence of *S. pneumoniae* to murine influenza-infected tracheas.[100] Influenza-induced neutrophil dysfunction is also greatest six days after influenza infection,[101] and murine mortality secondary to *S. pneumoniae* infection is greatest seven days after infection. Although neutrophils accumulate in the lungs of mice infected with influenza by day six, they do not function in resistance to *S. pneumoniae*. Thus, it is likely that bactericidal function of lung neutrophils is suppressed, making these influenza-infected mice susceptible to *S. pneumoniae*. Effective neutrophil phagocytosis and killing of *S. pneumoniae* is necessary to eliminate *S. pneumoniae* from the lungs.[102] Neutrophils are affected within 30 min of *in vitro* influenza infection,[83,84,87,89,103] with some effects seen as rapidly as 5 min after incubation with IV. Changes in infected neutrophils include decreased protein phosphorylation, accelerated apoptosis, decreased respiratory burst activity, an altered cytoskeleton, depressed bactericidal capacity identified by release of reactive oxygen species, decreased chemotactic ability, decreased adherence, decreased release of lactoferrin into phagosomes, and inhibition of lysosome−phagosome fusion.[81,82,84,87,89,92,103] In addition, the effects of influenza virus infection on neutrophil function are not limited to the lungs, indicating that these effects are systemic in nature.[89,90] Influenza infection also increases susceptibility to *S. pneumoniae* by increasing cytokine production (TNF, IFN-γ, MCP-1, IL-10, IL-6) in the lung.[75]

IL-10 is also elevated in post-influenza pneumococcal pneumonia, leading to increased susceptibility to *S. pneumoniae* long after an influenza infection has been resolved.[104] Susceptibility remains at least 14 days after a primary influenza

infection, and is thought to be mediated by IL-10 inhibition of neutrophil function, resulting in increased bacterial growth in the lungs leading to mortality.[104] Of note, viral influenza neuraminidase increases *S. pneumoniae* adherence in the lungs by cleaving sialic acid residues, and exposing receptors to which *S. pneumoniae* can adhere.[78] Thus, both neutrophil-dependent and -independent mechanisms cause increased susceptibility to secondary *S. pneumoniae* infection after a primary influenza infection. Novel therapies that can restore neutrophil function caused by IV infection may be helpful.[73,75]

Human immune deficiency virus: long-term immunosuppression

HIV is a double-stranded, enveloped RNA retrovirus from the genus Lentivirus within the subfamily Retroviridae, with a tropism for human $CD4^+$ cells, including T cells and macrophages.[105] Two HIV types have been identified, HIV-1 and HIV-2, and both cause similar but not identical human disease. The HIV genome contains three structural genes (*gag*, *pol*, and *env*) and six regulatory genes (*tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu*). These proteins, their function, and their role in forming the viral particle have recently been summarized.[105] The Env protein is cleaved to produce two envelope proteins, gp120 and gp41, which are involved in HIV binding to CD4 and the chemokine receptors CXCR4 and CCR5 on cell surfaces.[105] Tat, Nef, and Rev proteins play a role in downregulating classical MHC class I molecules on the surface of HIV-infected T cells.[106−108] In the case of Tat, HLA-C and HLA-E are spared.[109] The classical HLA presenting molecule HLA-C on antigen presenting cells is not as potent in presenting viral peptides to T cells similar to the non-classical MHC class I molecule HLA-E. However, the non-classical MHC class I molecule HLA-E, similar to HLA-A, HLA-B, and HLA-C, suppress NK function. This viral strategy to evade immune surveillance serves two functions: (1) prevent $CD8^+$ T cells from recognizing HIV peptides presented by class I MHC molecules, and (2) prevent NK cell recognition and activation because HLA-C and HLA-E remain on HIV-infected cells leading to inhibition of NK killing of class I MHC expressing target cells. The Nef protein also downregulates CD4 expression on the surface of HIV-infected cells, which is a co-receptor of the T cell receptor participating in T cell activation.[110] This facilitates HIV-infected cell escape from immune surveillance.

Following HIV gp120 protein binding to CD4 and CCR5 molecules on target cells, HIV-infected cells migrate to the lymph nodes, where initial replication and infection of nearby $CD4^+$ T cells occurs.[111] During acute HIV infection, gut-associated lymphoid tissues, predominantly memory $CD4^+$ T cells, are severely depleted. There is high HIV viremia and immune activation.[112,113] HIV induces T cell lymphopenia through several mechanisms: HIV-induced apoptosis; a viral cytopathic effect; non-specific immune activation-induced apoptosis; and cytotoxicity of HIV-infected cells.[105] Autophagy is also induced by HIV Env protein in uninfected T cells.[114] In addition, shedding of gp120 molecules by HIV triggers a series of events that cause the adaptive immune system to become less effective by altering the normal balance of immunoregulatory Th1 and Th2 T cells. Impaired function of HIV-infected macrophages and dendritic cells contributes to the failure of effective innate and adaptive immune responses to secondary infection.

The acute and latency phase of HIV infection is shown in Fig. 49.5.[115,116] Without combined antiretroviral therapy (cARV), $CD4^+$ T cell counts progressively decrease, and the host usually succumbs to infections with opportunistic organisms that occur because of HIV-induced secondary immune deficiency. Specific anti-HIV, $CD4^+$, and $CD8^+$ T cells, and neutralizing anti-HIV antibodies develop, however, these responses are eventually overcome by viral escape strategies.[105] Patients can present with constitutional symptoms, such as fever, weight loss, diarrhea, lymphadenopathy, secondary opportunistic infections, and viral skin infections, heralding the presence of an immunocompromised immune system. Peripheral $CD4^+$ T cell counts of <200 cells/mL herald the development of AIDS. This T cell depletion predisposes patients to develop opportunistic infections including, but not limited to, cytomegalovirus, *Herpes simplex*, varicella zoster virus, *Pneumocystis jirovecii* pneumonia, histoplasmosis, toxoplasmosis, coccidioidomycosis, *Cryptosporidium*, *Nocardia*, *Mycobacterium avium* complex, salmonella, and *Toxoplasma gondii*. If HIV-infected patients do not receive antiretroviral treatment, repeated infections with these opportunistic secondary infections ultimately lead to death. Thus, HIV infection exhausts the adaptive immune system, leading to chronic depletion of $CD4^+$ T cells and immune dysfunction of the multiple effector immune responses that are required to prevent secondary bacterial, viral, fungal, and protozoan infections.

Human T-lymphotropic virus: long-term immunosuppression

Human T-Lymphotropic viruses (HTLV) are complex type C retroviruses with a capsid that contains two simple RNA strands with associated reverse transcriptase and integrase enzymes which are essential for insertion of the virus into the host genome.[117] Several types of HTLV have been identified (HTLV-1, HTLV-2, HTLV-3, HTLV-4). While HIV-1 was
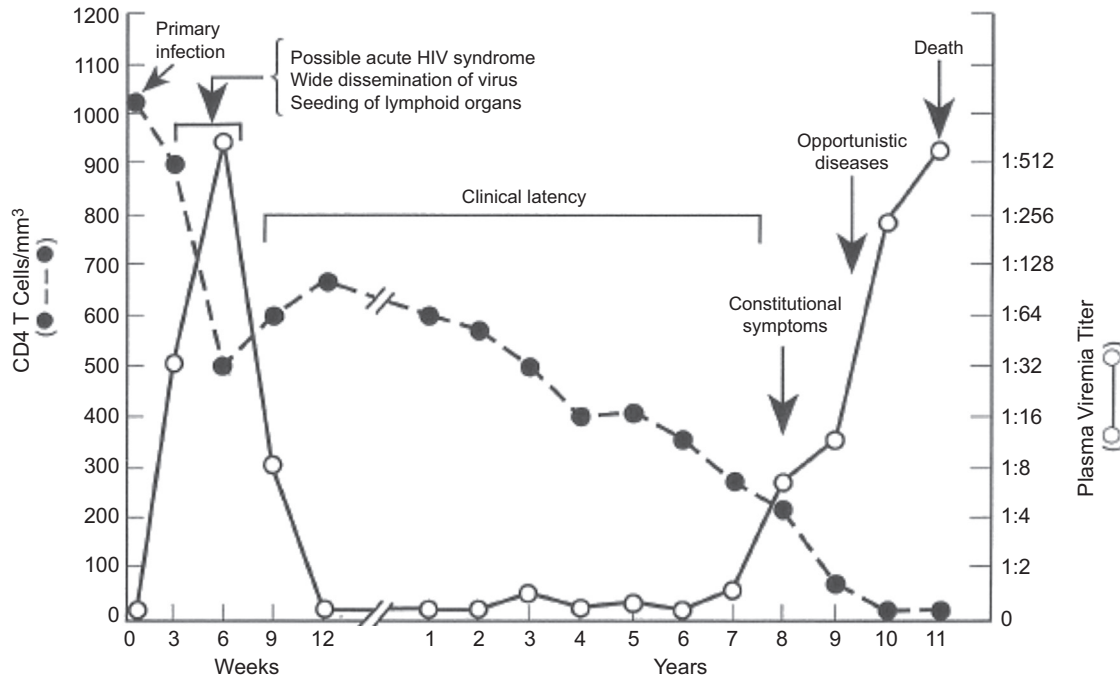
FIG. 49.5 **Typical course of HIV Infection**. During the early period after primary infection, there is widespread dissemination of virus and a sharp decrease in the number of CD4$^+$ T cells in peripheral blood. An immune response to HIV ensues, with a decrease in detectable viremia followed by a prolonged period of clinical latency. The CD4$^+$ T cell count continues to decrease during subsequent years, until it reaches a critical level below which there is a substantial risk of opportunistic diseases. *Figure reproduced from Reid S, McGrath L. HIV/AIDS. Sleep Medicine Clinics 2019;2(1):51−8 with permission from Elsevier.*

previously called HTLV-3, HTLV-3 is a different virus.[117] Similar to other retroviruses, HTLV-1 contains *gag*, *pro/pol* and *env* genes that have structural and functional roles. In addition, the pX region codes for regulatory proteins (such as transactivator protein, Tax, and the helix basic zipper protein, HBZ) essential for viral transcription, and inhibition of signal transduction pathways, such as NFκB (leading to decreased SOCS1), and AP-1. This leads to HTLV-1 inducing cytotoxic T cells that can kill virus-infected cells.[118]

The HTLV-1 *Tax* gene can decrease Th1-like antiviral signaling pathways both by modulating the suppressor of cytokine signaling 1 (SOCS1)[119] and also through the aryl hydrocarbon receptor protein (AIP) that binds to interferon regulatory factor 7 (IRF7), thus decreasing Type I interferon (IFN-α/β) expression.[120] HTLV-1 modifies the behavior of CD4$^+$ T cells and alters their cytokine production. HTLV-1 is clinically associated with adult T cell leukemia/lymphoma (ATL), and tropical spastic paraparesis/HTLV-1-associated myelopathy (PET/HAM)[121] and can cause autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosis, and Sjögren's syndrome.[117−120]

The development of the HTLV-1 induced autoimmunity is thought to rely on molecular mimicry, and HTLV-1 induced T cell immunosuppression is caused by direct infection of CD4$^+$ T cells. CD4$^+$ T cells that have altered function and cytokine production. Tax is the primary inducer of clonal infected T cell expansion, and genetic instability.[117] Tax expression promotes T cell activation, proliferation, and resistance to apoptosis.[122] Clinically, patients infected with HTLV1 have increased infections and increased autoimmunity, particularly rheumatoid arthritis and Sjogren syndrome. The autoimmunity correlates somewhat with viral load, however, there are immunologic mechanisms that probably facilitate breaks in tolerance leading to autoimmunity.

In addition, natural killer (NK) cells from individuals with PET/HAM have decreased expression of the activating receptor NKp30.[123] This likely results in decreased NK cell activation, leading to decreased ability of NK cells to kill virus-infected cells. HTLV infection is clinically associated with an increased risk of disseminated strongyloidiasis,[124] schistosomiasis,[125] likely due to high levels of IFN-γ, decreasing the production of Th2-like cytokines (IL-4, IL-5, IL-13) and IgE essential to contain these parasitic infections. Taken together, HTLV induces cytotoxic T cells to kill virus-infected cells, alters CD4$^+$ T cell function and cytokine production and it decreases NK cell activation leading to susceptibility to subsequent disseminated parasitic infections.

TABLE 49.2 Bone marrow pathologies associated with human viral infections.

Pathology	Virus	Comments
Pancytopenia	EBV	Self-resolving
	HCV	Affected by medication
Aplastic anemia	Parvovirus B19	Driven by infection of erythroid progenitors
	EBV, CMV, VZV, HHV, HIV, HAV, and HCV	Driven by a strong antiviral T cell response and ensuing cytokine production
	Dengue	Mechanism unknown
HLH	CMV	Driven by the ensuing antiviral immune response rather than the virus itself
	Parvovirus B19	
	Dengue	
	HAV	
	HIV (acute)	
Lymphoproliferative disorders and malignancies	EBV	Infectious mononucleosis and chronic active EBV disease
	HCV	Acute myeloid leukemia, primary myelodysplastic syndrome

Table reproduced from Pascutti MF, Erkelens MN, Nolte MA. Impact of viral infections on hematopoiesis: from beneficial to detrimental effects on Bone marrow output. Front Immunol 2016;7:364. Reprinted under https://creativecommons.org/licenses/by/4.0/.

Bone marrow (BM) suppression related to viral infection

Many viral infections have been associated with BM failure or hyperproliferative syndromes. Table 49.2 summarizes some of the human viral infections that cause self-resolving or persistent BM suppression.[126] However, the specific pathogenic mechanisms that underlie the reported virally induced BM manifestations have not been fully characterized. Nonetheless, many different viruses generate the same pathological condition. This suggests that a common underlying mechanism(s), specifically virologic or immunologic are responsible for the clinical pathologic outcome. Certain virus can also lead to different pathological manifestations in different patients heralding a genetic basis for aberrant immune activation in BM failure.

There are 4 different mechanisms by which viruses can affect hematopoietic stem and progenitor cells (HSPC). These mechanisms include: (1) direct viral infection, (2) viral recognition by HSPCs and indirect effects, (3) inflammatory mediators, and (4) changes in the BM microenvironment. Taken together, many types of viruses can affect hematopoiesis acutely (Parvovirus B19, dengue), transiently, permanently, chronically (CMV, HIV), systemically (HIV), locally (Influenza), directly, or indirectly, causing disruption of the hematopoietic process.[126]

Parasites that hijack immune responses to other microbes

Leishmaniasis: temporary immune suppression

Leishmaniasis is caused by protozoan parasites of the genus *Leishmania* of the family Trypanosomatidae, and is transmitted by a sand fly vector. It infects over 12 million individuals globally in tropical and subtropical regions, with approximately 2 million new clinical cases (0.5 million visceral leishmaniasis [VL] and 1.5 million cutaneous leishmaniasis [CL]) each year. The estimated death toll caused by these infections is approximately 50,000 persons per year.[127,128] Three major clinical forms of leishmaniasis are known (VL, CL, and mucocutaneous leishmaniasis [MCL]); all are the result of infection by different species of this parasite and the various host immune responses made to these microbes (Box 49.3). Leishmaniasis is transmitted by sand flies with dogs, rodents (East Africa, Ethiopia, the Sudan and Kenya) and foxes (Mediterranean and Asia) as reservoirs.

VL is fatal if not treated, and is caused by *Leishmania donovani*, *Leishmania infantum*, and *Leishmania chagasi*.[129,130] Immunity to leishmaniasis is mediated by the cellular and humoral arms of the mammalian immune system: the innate

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BOX 49.3 Leishmaniasis (L)

Visceral Leishmania.
    Fever, weakness, weight loss, splenomegaly.
    L. donovani.
Cutaneous Leishmania (simple or diffuse).
    Single or multiple ulcers.
    L. tropica.
    L. major.
    L. aethiopica.
    L. Mexicana.
    L. braziliensis.
Mucocutaneous Leishmania.
    Mucous membrane ulceration.
    L. braziliensis.

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system (by neutrophils, macrophages, and dendritic cells) and by adaptive (T cells) responses.[131] Sand-fly bites cause minimal tissue damage, but the bite promotes neutrophil recruitment.[132,133] Parasites can survive for a time within neutrophils, and eventually they parasitize neutrophils. Viable parasites are engulfed by macrophages or dendritic cells. Inside the macrophages, promastigotes change into amastigotes and they reproduce by binary fission, ultimately rupturing the macrophage and releasing amastigotes into the blood. Leishmania modulates the normal antimicrobial mechanisms of the macrophages. They increase membrane fluidity and thereby disrupt lipid rafts and APC antigen presentation as well as lysosomal fusion.[134] Leishmania-infected APCs interact with T cells, and together they express cytokines and chemokines that begin to "hijack" the immune system, which enables these parasites to survive.[135] Cell-mediated immunity is the principle host defense against *leishmania* species. T_h1-like cells primed mainly by APCs and IL-12 expression are major effector responses to this microbe.[136–139] The dichotomy between T_h1-like protection (IFN-γ, IL-2, and TNF) and Th2-like disease progression (IL-10, IL-4) in mice has been shown to be essential in CL infection,[140] although this paradigm is less clear in humans infected with VL.[141,142] The immunopathology of VL is complex, and involves cellular and genetic factors that confer disease susceptibility, versus resistance to *Leishmania* species.[143]

    Persistent VL correlates with a chronic Th2-like (IL-10, IL-4, IL-5, and IL-13) response to *L. donovani*[142] and increased serum IL-10 expression.[144–147] IL-10 is crucial in establishing and maintaining T_h2-dependent chronic suppression of Th1-like mediated immunity in CL.[148–150] and inhibits amastigote killing.[150,151] IL-10 also inhibits the production of IFN-γ.[152] Cellular immunity impairment correlates with active disease progression secondary to IL-10 expression, independent of IFN-γ levels.[153] In murine CL, $CD4^+CD25^+FoxP3^+$ natural Tregs are a major IL-10 source and are crucial for parasite survival.[154] However, IL-10 is also derived from non-Tregs.[146,155] This suggests that any therapeutic approach to treat leishmania infection will require species-specific manipulation of the immune responses made to these parasites. For example, the potent T_h2-like cytokine IL-4 is critical in CL, but not in VL.[141] Thus, modulating IL-4 expression may be helpful in VC, but not in the treatment of CL.[156]

    Resolution of human and murine VL depends on the production of Th1-like cytokines.[139,140,147,157–160] IL-12 and IFN-γ are crucial in controlling parasite growth and development.[157,161] While IL-10 suppresses host immunity and helps parasite survival, it is the antidote to inflammation that reduces tissue damage caused by exaggerated inflammation.[162] Since IFN-γ -producing cells can also produce small amounts of IL-10, this may act as a negative feedback in controlling tissue damage[142,146,163,164] and supporting immune memory. TNF stimulates IFN-γ -induced expression of nitric oxide by APCs that can kill VL parasites.[165–170] Th17-like cells that produce IL-17 are pro-inflammatory, and stimulate IL-6, TNF-α, and chemokine expression. However, *L. donovani* strongly induces IL-17 and IL-22, and enhances the secretion of these cytokines that protect this parasite.[171] $CD8^+$ cytotoxic T cells are also important in controlling CL and VL.[172] $CD4^+$ and $CD8^+$ T cells, and their pro-inflammatory cytokines, are required to control VL parasite proliferation and leishmaniacidal activity.[138,161,173–176] However, in canine VL, antibodies are insufficient in providing protection in the absence of -pro-inflammatory T cell responses.[132] Thus, in addition to protective T cell responses, other T cell subsets, including Tregs and Th17 cells, confer either susceptibility or resistance to animal verses human VC. Other cells may also be important in

the resolution of these infections, thus further investigation is required in designing vaccines or treatments for these diseases.

Greater than 20% of CL patients have reported secondary bacterial infections.[177] *S. aureus*, coagulase-negative *Staphylococcus*, *Escherichia coli*, *Proteus*, and *Klebsiella* have been cultured from lesions (listed in decreasing frequency). However, the incidence of these infections is higher in ulcerated compared to non-ulcerated lesions. Thus, both disruption of the skin, and possibly immunosuppression caused by CL, likely play roles in the development of secondary bacterial infection in CL, leading to severe or lethal bacterial infection.[177] Increased Treg numbers in CL have been linked to activation/reactivation of latent microbial infections (*Mycobacterium tuberculosis*, *Toxoplasma*, herpes viruses) that cause significant morbidity and mortality, possibly as a result of immunosuppression and other factors, although how activation/reactivation of dormant infections occurs remains unknown.[178] Thus, leishmania infection causes secondary infections, and activation/reactivation of dormant infections that can lead to severe or lethal outcomes through multiple mechanisms.[178] *L. donovani* infection can also clinically resemble and cause hemaphagocytic lymphohistiocytosis (HLH) and successful treatment of leishmaniasis can lead to the complete resolution of HLH symptoms.[179,180] These reports open the question as to whether HLH patients should be prescreened and aggressively treated for visceral leishmania infection prior to instituting stem cell transplantation for HLH when from endemic areas.[179] VL has been associated with significant secondary infections. These may be confounded by HLH where neutropenia is common. Infections ranging from sepsis to urinary tract infections occur in a significant subset of patients with VL. The most common pathogens causing sepsis are *S. aureus, Klebsialla pneumonia*, and *Pseudomonas aeruginosa*. Common laboratory features include neutropenia, eosinopenia and leukopenia. Co-infection with HIV alters the clinical presentation with more lung and gastrointestinal involvement.

Taken together, the innate response (professional APCs) is altered by leishmaniasis infection, leading to polarized adaptive immune responses that support or block persistent infection by *leishmania* organisms. This subverts or supports effective immunity to these parasites, and in patients with persistent infection, the Th2-like/Treg bias may predispose patients infected with *leishmania* species to develop or reactivate lethal secondary superinfections, and the development of HLH-like clinical symptoms.

Malaria: temporary immunosuppression

Malarial organisms are parasites with a major public health impact world-wide. There were an estimated 219 million cases of malaria (range 154−289 million) and 660,000 deaths (range 610,000−971,000) in 2010.[181] *Plasmodium* species cause malaria and can induce immunosuppression in infected individuals[182] resulting in increased susceptibility to secondary infections, such as non-typhoidal salmonella,[183] herpes zoster virus,[184] hepatitis B virus,[185] Moloney leukemia virus,[186] and Epstein-Barr virus reactivation.[187] Efficacy of heterologous vaccines can also be suppressed in malaria-infected patients,[188] further documenting the immunosuppressive effects of malaria infection.

Malaria parasites inhibit DC maturation[189] via uptake of malaria pigment hemozoin (HZ) from parasitized RBCs.[190] DC inhibition reduces T cell expansion, cytokine production, and migration into B cell follicles.[191] The effect on DC changes occurs during the different phases of this infection. Although DC function is impaired immediately following the initial burst of parasitemia, T and B cell responses to heterologous antigens change dynamically during the course of infection.[191] T cell proliferation, and effector function and migration are suppressed, and B cells do not expand or produce antibodies. HZ, prevents the formation of stable, long-lasting cell−cell contacts between T cells and DCs impairing co-stimulatory activity.[192] Nonetheless, there is also a T cells functional defect.[188] Taken together, impairment of both innate and adaptive signaling induced by malarial infection/HZ pigment skews the immune response toward tolerance instead of immunity, and this subversion of effective immunity leads to secondary infection with other organisms as a consequence of this parasitic infection.

Invasive infections in patients with malaria are due to *S. pneumoniae*, *H. influenzae* type b, *S. aureus, E. coli* and other gram-negative bacteria. Risk factors include younger age, recent malaria infection, severe anemia, splenomegaly, HIV-co-infection and severe malnutrition. Some of this susceptibility seems to reflect functional asplenia and impaired barrier function.

Bacteria that hijack immune responses to other microbes

Bordetella pertussis: temporary immunosuppression

B. pertussis, the causative agent of whooping cough, is an infection that can be fatal in infants, but in older children, adolescents, and adults usually causes a chronic cough of varying severity that generally persists long after clearance of the

infection. This bacterial infection of the airways is an important cause of infant death world-wide, and continues to be a public health concern even in countries with high vaccination coverage. While estimates of the incidence of new cases of pertussis vary,[193,194] pertussis infection world-wide varies between 16 million and 50 million cases yearly, 95% of which are in developing countries.[193,194] In addition, between 195,000 and 300,000 deaths, mostly of young infants who were either unvaccinated or incompletely vaccinated, occur yearly.[193,194] For several decades, infant immunization programs using pertussis vaccines of high efficiency have been highly successful in preventing severe pertussis in infants. However, pertussis continues to be a significant health issue world-wide.

Following an incubation period of 9–10 days (range 6–20 days) patients develop catarrhal symptoms including cough, and over 1–2 weeks develop coughing paroxysms that end in the characteristic "whoop" associated with this infection. Although the cause of the characteristic "whoop" associated with *B. pertussis* infection remains unresolved, a significant body of knowledge has accumulated to explain how *B. pertussis* induces immune suppression, evasion, and modulation, thereby leading to a poor clinical outcome. Fig. 49.6[195] gives an overview of several *B. pertussis* virulence factors that have immunomodulatory properties, the cells that they target, and the mechanisms thought to be involved in the induction of immune dysregulation caused by this infection. It has been shown that *B. pertussis*-derived filamentous hemagglutinin (FHA) is the major surface structure that mediates adherence of *B. pertussis* to host cells, primarily to cilia of airway ciliated epithelium. However, multiple factors likely contribute to this binding process,[196] including secreted adenylate cyclase toxin (ACT), which enhances FHA adherence to lung epithelial cells.[197] FHA also has immunosuppressive and modulatory activities by its ability to induce FHA-specific Tregs that secrete IL-10 and suppress T_h1-like responses to *B. pertussis*.[198] Anti-FHA antibodies can also reduce phagocytosis of these bacteria by human neutrophils.[199] ACT, a secreted toxin, targets host phagocytic cells by binding complement receptor 3 (CR3; CD11b/CD18).[200,201] ACT-deficient mutants of *B. pertussis* are more efficiently phagocytosed by human neutrophils,[202] and in mice, lower bacterial loads are found in the respiratory tract.[203] Secreted ACT upregulates major histocompatibility complex class II MHC and

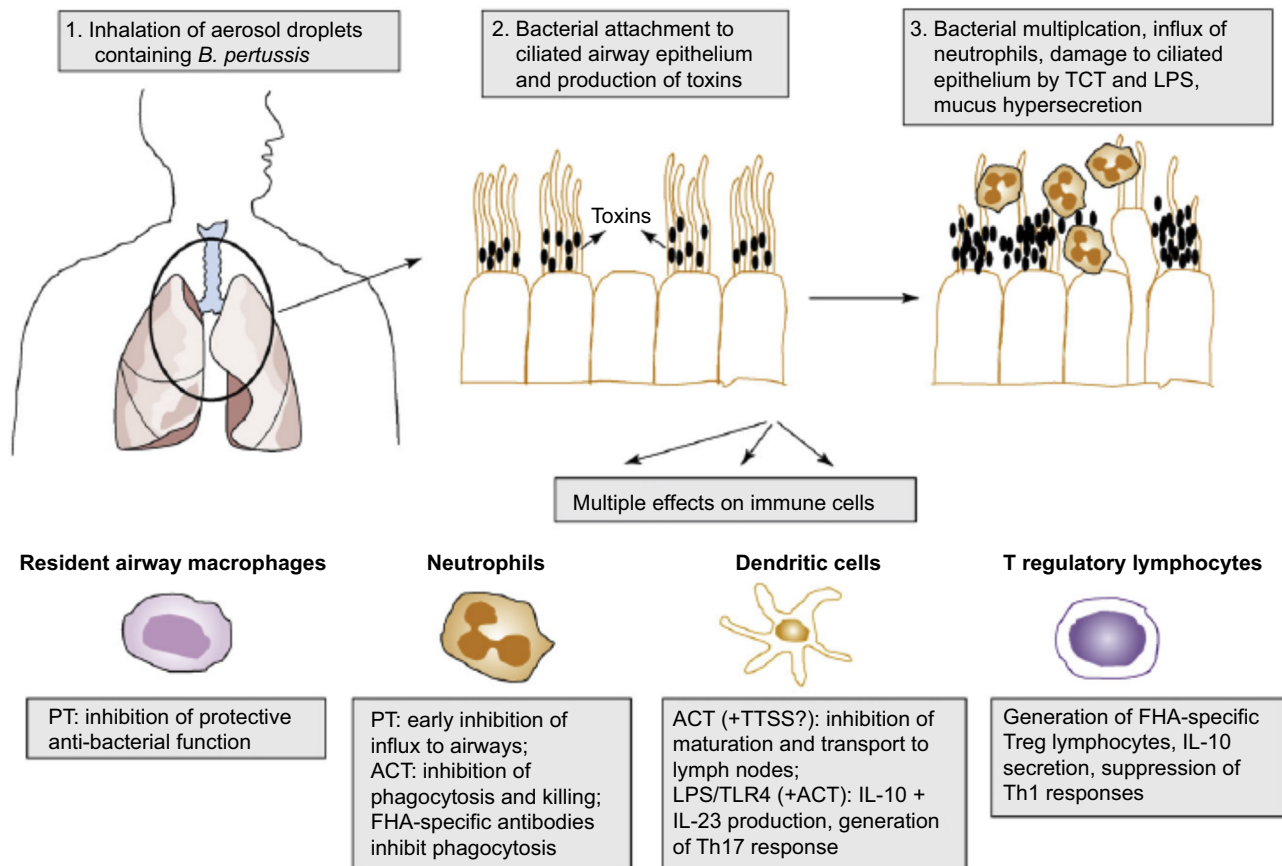**FIG. 49.6** **Bordetella infection.** *Bordetella pertussis* infection begins with infection of the respiratory tract. The toxins elaborated during the infection have multiple effects which modulate the immune response. *Figure reprinted from Carbonetti NH. Immunomodulation in the pathogenesis of Bordetella pertussis infection and. Curr Opin Pharmacol 2007;7(3):272–8 with permission from Elsevier.*

co-stimulatory molecule expression on dendritic cells (DCs). ACT also prevents maturity, and thereby decreases their pro-inflammatory cytokine production.[204−206] Tracheal cytotoxin (TCT) is also expressed at relatively high levels by *B. pertussis*, and is a disaccharide-tetrapeptide fragment of peptidoglycan. Purified TCT, in synergy with lipopolysaccharide (LPS), damages ciliated airway epithelial cells through production of IL-1a and nitric oxide,[207] causing deleterious effects on neutrophils.[208]

Pertussis toxin (PT), uniquely produced by *B. pertussis*, is another secreted toxin expressed by this bacterium. PT ADP ribosylates several heterotrimeric G proteins in mammalian cells, has long been known to disrupt signaling pathways with a wide range of downstream effects,[209] and can cause immunosuppression. PT causes lymphocytosis.[210] PT-deficient mutant strains show reduce levels of airway infection 24 h after inoculation because PT delays neutrophil recruitment and influx to the airways,[203,211,212] reduces anti-*B. pertussis* antibody-induced bacterial clearance,[211] depletes airway macrophages[213] enhancing infection.[214] Since ADP ribosylation of airway macrophage G proteins by PT has been shown to be long-lasting, and correlates with active infection-promoting longevity of this microbe.[212] This evidence supports the concept that the effects of PT on host cells in the airway may be particularly long-lived. PT also exerts multiple suppressive effects on the immune system beyond innate immune cells, including suppression of serum antibody responses to *B. pertussis* antigens following infection,[214−216] reduction of major histocompatibility complex class II expression on human monocytes,[217] and modulation of dendritic cell expression of surface markers.[218]

B. pertussis infection causes immunomodulation of Toll-like receptor (TLR4),[219] which recognizes the lipopolysaccharide found on *B. pertussis* and Gram-negative bacteria.[220,221] TLR4 signaling triggered by *B. pertussis* induces IL-10, which can inhibit inflammatory responses, and limit airway inflammation,[220] and can synergize with ACT to induce IL-10.[206] In addition, TLR4-dependent responses induced by *B. pertussis* drive lower levels of inflammatory cytokines.[222]

Thus, PT promotes *B. pertussis* infection by multiple mechanisms through its effects on innate immunity in the initial stages of disease in naïve individuals. This reduces adaptive immune responses during the initial infection, and promotes re-infection in partially immune individuals. The consequences of these suppressive effects on both the innate and adaptive immune responses induced by *B. pertussis* infection can cause secondary infection, typically pneumonia, which is the major cause of fatal outcome from this infection.[223] Infants are at highest risk of all complications related to *B. pertussis* infection but all ages have relatively high rates of secondary complications. Approximately 50% of infants exhibit apnea of greater or lesser duration and a quarter develop pneumonia. Roughly 5% have otitis media and 1% develop seizures. In adults, the most common secondary effect is pneumonia occurring in about 5%.

Conclusions

Distinguishing patients with secondary immune deficiency disease caused by a primary infection in an individual with an "intact" immune system from patients with an underlying PIDD is often a challenge. Recognizing primary infections that can cause secondary immunodeficiencies is an important factor in discrimination between these two groups of patients. Clinical immunologists need to always consider whether an acute, serious infection is causing a secondary primary infection in an "immunologically intact" individual, or is the herald of an underlying defect in a genetically defined immunocompromised patient with PIDD. The long term treatment and clinical outcomes of these two different patient populations is linked to understanding how severe primary infections cause disease in these two different settings.

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