evidence of viral infection, either by serology or NAAT, was found in controls, including in over 5% of healthy blood donors. XMRV later was proved to be a laboratory contaminant and is not thought to be associated with pathogenic human infection.[40]

Hepatitis B and D Viruses

HBV remains the virus with the highest residual risk of transfusion transmission despite screening; HBV is transmitted in approximately 1 in every 200,000 to 300,000 transfusions.[41,42] Risk persists both because the screening test is incompletely sensitive and because of the prolonged window period of about 2 months. In countries that screen for hepatitis B core antibody (HBcAb), most transmissions derive from the window period, whereas in those that do not check HBcAb status, half derive from the window period and the others are due to the insensitivity of the hepatitis B surface antigen (HBsAg) test as a screening test.[43]

NAAT for HBV recently has been implemented for blood screening using minipool testing. With current sensitivity of minipool testing, NAAT shortens the window period by about 7 days, leaving a residual risk for HBV of about 1 per 250,000 to 350,000 transfusions.[24,42] Sensitive screening tests are particularly needed in HBV-endemic areas, such as Taiwan, where HBcAb testing is not routinely performed and transfusion-acquired HBV is a relatively frequent event.[44] Testing for HBcAb, in addition to HBsAg, remains important; in some cases, it is more sensitive than NAAT, so implementation of new testing does not obviate the use of these other tests for donor HBV infection.[45] Increasing use of hepatitis B vaccination may further reduce the risk for transmission.

Screening of donors for HBsAg excludes most, but not all, carriers of hepatitis D, also known as delta virus.[46] Identification of donors with antibody to the delta agent is not done routinely, so there is a residual risk for transmission of delta virus to HBsAg-positive recipients.

Hepatitis C Virus

Hepatitis C, previously known as non-A, non-B hepatitis, was associated with a lifetime risk of 7% to 10% in transfusion recipients in the late 1970s and early 1980s.[47] The transmission rate of HCV has decreased with improved screening tests to identify the virus, providing an excellent example of how implementation of each new generation of screening technology has improved blood safety. More than 90% of recipients of HCV-contaminated blood products develop HCV infection.[48] An older survey using the second-generation test found that 3.6 per 1000 US donors were positive for HCV,[49] a prevalence lower than that in the US population. HCV infection in blood donors usually is the result of intravenous drug use, although other health care–associated risks have been identified, including questionable injection practices.

Before any testing, 0.45% of all transfusions transmitted HCV. With the introduction in 1986 of surrogate marker testing (alanine aminotransferase and HBcAb), the rate decreased to 0.19%, and with the introduction of the first-generation antibody test for HCV in 1990, the rate fell to 0.03%. The second-generation test lowered the rate even further, mostly by identifying chronic infections more accurately (i.e., increasing sensitivity) rather than by shortening the window period. Despite the continuing relatively high prevalence of HCV infection in the US population, the introduction of NAAT has reduced the transmission risk to about 1 in 1.5 million transfusions.[20,21,27]

Hepatitis A Virus

Transmission of hepatitis A virus (HAV) via transfusion has been described with RBCs, particularly in infants,[50,51] and with factor VIII concentrate.[52] Donors with early, asymptomatic infection may transmit HAV infection.[53] Factor VIII–associated transmission has occurred despite appropriate use of organic solvent and detergent to inactivate the virus. The lack of a lipid envelope around HAV may have contributed to incomplete virus killing during preparation of the concentrate. Because of this small but persistent risk, vaccination for HAV has been recommended for chronic recipients of products made from pooled plasma.[54] Review of all cases of hepatitis from 1998 to 2002 in the United States among persons with bleeding disorders revealed no acquisition of HAV via factor concentrates, although as the incidence of HAV infection increases in the US population, some plasma manufacturers voluntarily screen donation pools using NAAT.[55,55a]

Hepatitis E Virus

Hepatitis E virus (HEV) is endemic in many developing countries and is believed to have similar epidemiology to HAV with transmission via the fecal-oral route. HEV has been implicated in transfusion transmission worldwide but has not yet been reported in the United States.[56–58] However, some studies have documented high seroprevalence rates nationally among blood donors.[59,60] One US study included NAAT testing of blood donations and noted a frequency of 1 in 9500 donations with evidence of HEV RNA.[60] These findings have raised the concern about an underappreciated blood safety risk. Furthermore, because it is nonenveloped, HEV is not effectively inactivated by current approved PRT methods, with documented transfusion-transmission among psoralen-treated blood products.[61]

West Nile Virus and Other Arboviruses

WNV has been transmitted by blood transfusion to at least 32 persons since this route of transmission was first recognized during the summer of 2002.[4] In addition, it has been transmitted by organ transplantation.[62,63] In response to this emerging threat, NAAT for WNV was quickly developed and implemented by 2003 and is now in routine use for blood donor screening; thousands of WNV-infected donations have been interdicted.[22,23] Because of the logistic and financial burden of individual testing, WNV screening assays test pools of 6 or 16 donations (i.e., minipools), with follow-up screening of positive minipools by individual sample NAAT. However, "breakthrough" cases of WNV transfusion transmission still occur, because minipool testing is not as sensitive as individual sample NAAT. In response, blood banks are using strategies to "trigger" a switch from minipool to individual NAAT in areas with high epidemic activity during seasonal peaks.[64] Twelve transfusion transmissions have occurred despite use of minipool NAAT.[65] Five cases occurred after blood collection agencies voluntarily put in place processes to trigger more sensitive individual donation testing based on local WNV activity. There have been no recognized cases of transfusion transmission when individual donation testing has been used, although one transmission involved a positive minipool with a negative confirmatory individual test.[66] WNV has also been transmitted through granulocyte transfusion.[67] Clinicians should suspect WNV in individuals who develop unexplained encephalitis or flaccid paralysis and who have recently undergone transfusion or transplant procedures. Immunosuppressed patients, including solid-organ and stem cell recipients, are at greatest risk for developing complications.

ZIKV, a flavivirus transmitted primarily by *Aedes aegypti* mosquitoes, rapidly spread in the Americas in 2015 and 2016.[68] Although most infections are asymptomatic, ZIKV has been identified as a cause of adverse pregnancy outcomes, including microcephaly and other congenital brain defects,[69] and has been linked to Guillain-Barré syndrome[70] and severe thrombocytopenia.[71–73] Retrospective nucleic acid testing (NAAT) of blood donations after a large ZIKV outbreak in French Polynesia in 2013 and 2014 found detectable ZIKV RNA in 2.8% of blood donations,[74] and ZIKV infections that were likely transmitted by transfusion (via whole blood–derived platelets) have been documented in Brazil.[5,75]

To reduce the risk for transfusion-transmitted ZIKV infection in the United States, in February 2016 the FDA recommended that all US areas with active ZIKV transmission cease blood collections unless donations are screened with NAAT or treated with approved PRT.[76] Blood safety interventions in Puerto Rico, which experienced a significant ZIKV epidemic in 2016, included importation of blood units from unaffected US areas and treatment of plasma and apheresis platelets with PRT until early April 2016, when the FDA authorized the use of an individual donation NAAT test under an investigational new drug (IND) protocol.[76] Currently, the US blood supply is subjected to universal ZIKV individual donation NAAT under investigational protocols, and no transfusion-transmitted cases have been identified in the US states or Puerto Rico.[77,78]

Other arboviruses, including chikungunya virus, have been associated with widespread epidemics and theoretically can be transmitted through transfusion, although no cases have been recognized and documented to date. Transfusion-transmitted dengue has been reported, but published cases are far less frequent than would be expected, given the worldwide

burden of disease, perhaps because symptoms are mild in recipients who are immune or who receive donor antibodies with infected units.[79,80]

Herpesviruses

Human herpesvirus 8 (HHV-8), the cause of Kaposi sarcoma, is believed to be primarily white cell associated, suggesting a low risk for transmission via leukoreduced blood transfusion, and few cases of transmission have been documented. The low rate of recognized transmission may reflect, in part, the difficulty in test performance and the high positive background rate, but studies have suggested a link.[81,82] One epidemiologic study completed in Uganda estimated the rate of transmission to be 2.8% for nonleukoreduced RBC units, with excess risk associated with storage times shorter than 4 days.[83] Further studies are needed to determine whether leukoreduction can completely mitigate this risk, but it is more likely partially effective, because viral loads in free plasma have been found in infected individuals with Kaposi sarcoma.[84] Transmission of HHV-8 resulting in Kaposi sarcoma has been described more frequently in recipients of solid-organ transplants.[85]

The transmission risk for cytomegalovirus (CMV) has been well summarized.[86] CMV, similar to HHV-8, is highly cell associated and can be transmitted with white blood cells that persist in RBC or platelet transfusions. Transmission of CMV from fresh-frozen plasma or cryoprecipitate has not been reported. The insensitivity of the serologic test has resulted in a residual risk for transmission of 0% to 6%, even when CMV-seronegative donors are used.[86] Because the demand for CMV-seronegative blood outstrips the supply, approaches such as leukocyte filtration of CMV-seropositive blood are often used, although the two approaches may not be equivalent in reducing CMV transmission risk.[18]

Screening for Epstein-Barr virus and other herpesviruses is not performed routinely, despite sporadic reports of transfusion-associated transmission.

Parvovirus B19

Parvovirus B19 has been transmitted in coagulation factor concentrates, resulting in NAAT screening by some plasma manufacturers. The risk for transmission to cryoprecipitate recipients may persist despite treating with solvent and detergent and heating to 100°C after lyophilization.[87] An epidemiologic study showed a significant correlation between receipt of treatment products, B19 seropositivity, and joint range-of-motion limitations.[88]

Non–A-E Hepatitis

The search for the cause of hepatitis not caused by hepatitis A, B, C, D, or E virus has yielded many contenders but no indisputable etiology to date. Hepatitis G virus (HGV) has been found in 1% to 7% of donors and can be transmitted by transfusion.[89] The risk for transmission is in the range of 5.3 per 10,000 units.[90] However, HGV has been shown not to be a cause of non–A-E hepatitis, and the clinical implications of HGV infection remain undetermined.[89]

Two somewhat related, single-stranded, unencapsulated DNA viruses, called transfusion-transmitted virus (TTV) and SEN virus (designated by the initials of the first patient investigated) have been considered as causes of non–A-E hepatitis.[91,92] Both viruses are present worldwide and are often found in the blood of persons with post-transfusion non–A-E hepatitis. However, after initial interest, no causal association was established.

BACTERIAL PATHOGENS

Infusion of blood products contaminated by bacteria is a relatively frequent and potentially lethal risk of blood transfusion.[6,93–94a] As the risk for transfusion-transmitted viral infection has decreased dramatically, the frequency of transfusion-transmitted bacterial infection has remained unchanged. A possible exception to this persistent risk is transfusion transmission of *Treponema pallidum,* the etiologic agent of syphilis, which has not been reported to have occurred for decades, presumably because of poor spirochete survival under current storage conditions.[95–97]

Bacterial contamination may arise from donation, processing, storage, or transfusion and can result in transfusion-transmitted sepsis and death. Because platelets are stored at room temperature, they are at higher risk for bacterial growth than RBCs, which are stored at refrigerated temperatures. Bacterial contamination of blood components was the cause of approximately 10% of transfusion-related fatalities reported to the FDA between 2011 and 2015.[98] Although visual inspection can sometimes reveal a significantly contaminated unit, this is not always the case (Fig. 304.2).

FIG. 304.2 Pooled platelet unit containing *Klebsiella pneumoniae* (quantitative culture, 6.5 colony-forming units per milliliter), showing fibrinous coagulation 4 days after laboratory inoculation. *(From Hay S, Brecher M. Egg drop soup platelets: gross bacterial contamination of a platelet product. Transfusion. 2007;47:1335–1336.)*

Based on culturing, estimates have placed the rate of bacterial contamination at 1 per 2000 to 3000 units for platelets and at 1 per 30,000 units for RBCs.[94,99–101] Estimates of the rate of clinically evident reactions after transfusion of bacterially contaminated blood products vary more widely, from 1 in 5000 to 1 in 100,000, although it is generally agreed that pooled platelets confer a greater risk per therapeutic dose than do platelets collected by apheresis.[102] A national study, Assessment of the Frequency of Blood Component Bacterial Contamination Associated With Transfusion (BaCon), was designed to identify severe reactions that resulted in confirmed transfusion-transmitted sepsis through passive reporting. Over a 3-year period, there were 56 reports and 34 confirmed cases, principally from contaminated platelets. Although *Staphylococcus* and other gram-positive organisms were most frequently associated with transfusion-transmitted sepsis, gram-negative organisms, such as *Escherichia coli* and *Serratia* species, were statistically associated with fatal outcome. Nine persons (26.5%) died of the transmitted infection. The BaCon study estimates of transfusion-transmitted sepsis were 1 in 100,000 units for platelets and 1 in 5 million units for RBCs, reflecting the difficulty of recognition and confirmation of these poorly appreciated clinical events.[7,103]

For both RBCs and platelets, longer storage time is well established as a risk factor for bacterial contamination. However, gram-negative organisms can be fast growing and can result in lethal endotoxin levels in 3-day-old platelets. Further shortening of the current 5-day platelet storage times is not feasible, because it would probably result in discarding too many uninfected units, exacerbating the nation's intermittent blood supply shortage of platelets. In addition, contamination may occur during production and packaging of blood bags.[104] The AABB (formerly known as the American Association of Blood Banks) requires members to use a method to detect bacterial contamination in platelets;

in apheresis platelets, liquid culture media methods are typically used by the blood collection centers, whereas for pooled platelets the methods are varied. This has resulted in a risk that is significantly reduced but still present. The American Red Cross has described a decrease in risk for septic reactions due to apheresis platelets from 1 in 33,000 to 1 in 75,000.[105] Other approaches to risk reduction are being actively pursued in the United States and have already been implemented in other countries. These include avoidance through improved skin preparation and diversion of the initial 15 to 30 mL of the blood draw; optimization of volume and storage time before culture; development of point-of-use tests at the time of transfusion; and pathogen reduction methods, including inactivation by means of photochemical treatment of units.[6] Routine culture of apheresis platelets has led to the discovery of unusual pathogens in asymptomatic donors, including *Listeria* species.[106]

In December 2014, the FDA published a draft guidance on bacterial detection testing. This document provides recommendations for testing for bacterial contamination of platelets by blood collection centers and transfusion services, but it is not yet a regulatory requirement. Although the AABB standard results in most apheresis platelets being tested, most pooled platelets remain untested, with presumably higher risk compared with units collected by means of apheresis.

Red Blood Cells

Gram-negative bacteria, including *Yersinia enterocolitica, Pseudomonas fluorescens, Serratia marcescens,* and *Serratia liquefaciens,* accounted for most of the reported cases of transfusion-transmitted infection caused by contaminated RBCs historically (Table 304.3).[99,107] Transmission of bacterial infection through RBCs is less common than through platelets, because RBCs are stored at refrigerated temperatures, allowing a longer shelf life. Storage of RBCs may extend 35 to 42 days depending on the type of additive used. Almost all instances of infection are associated with erythrocytes stored longer than 9 days and appear to derive from enhanced growth of certain organisms at cold storage (4°C) temperatures.[108,109] This storage growth is best exemplified by multiple cases of transfusion-associated *Y. enterocolitica* in autologous blood donors, who became bacteremic after receiving their own stored blood.[110–113]

Donors with *Y. enterocolitica* infection are typically symptom free at the time of blood donation, although many recall having had a diarrheal illness about 1 month before donation. Although diarrhea may indicate exposure to contaminated food, a donor question regarding diarrheal illness has not been adopted into the standard questionnaire because of lack of specificity of the complaint. If it were used as a screening question, up to 10% of donors would be excluded.[99] Despite its suggestion of an association with *Y. enterocolitica*–contaminated products, the BaCon study detected only one case of transfusion-transmitted sepsis caused by *Y. enterocolitica* and heralded replacement of this organism in RBC contamination with other gram-negative organisms, such as *E. coli* and unusual *Pseudomonas* and *Serratia* species.[107] Patient bacteremia with *P. fluorescens* or *S. liquefaciens* should prompt a thorough search for a potential health care–associated source, such as contaminated transfusion or infusion products. Unlike platelets, there are no current laboratory-based screening measures in place to reduce the risk for bacterial contamination in RBCs, although development of a rapid endotoxin test is underway.

Platelets

A different spectrum of bacteria is associated with transfusion of platelets.[114,115] The most commonly recovered organisms are staphylococcal and streptococcal species. Gram-negative bacteria, including the Enterobacteriaceae (*E. coli, S. marcescens, Enterobacter* spp.) are less common but may be associated with rapid growth, production of endotoxin, and death (see Table 304.3).[7]

As with RBCs, contaminated platelets tend to be older (e.g., 4 or 5 days of storage).[116] Because of this, the FDA in 1985 shortened the acceptable storage time for platelets from 7 days to the current 5 days. Recently, the FDA has recommended strategies to extend platelet storage time to 7 days. These strategies can include primary and secondary culture (no earlier than day 4), primary culture and secondary rapid testing, or large volume delayed sampling.[117]

TABLE 304.3 Organisms Implicated in Fatal Blood Transfusion–Transmitted Bacteremia, Including Association With Endotoxin (Results From BaCon Study)

Platelets
Group B streptococci
Escherichia coli
Providencia rettgeri[a]
Serratia marcescens[a]
Red Blood Cell Units
Staphylococcus epidermidis
Serratia liquefaciens[a]

[a]Associated with 9090 to 273,500 endotoxin-forming units per milliliter.
From Kuehnert MJ, Roth VR, Haley NR, et al. Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. Transfusion. *2001;41:1493–1499.*

OTHER AGENTS TRANSMITTED THROUGH BLOOD COMPONENTS

Tick-borne Bacteria

Anaplasmosis and other tick-borne diseases, including human ehrlichiosis and Rocky Mountain spotted fever, represent a potential risk for transmission via blood transfusion in the United States.[118] Screening for a recent history of tick bite is unlikely to identify high-risk donors, because this exposure is unlikely to be recalled and may result in needless loss of uninfected blood donors.[118] As the incidence of tick-borne diseases increases, physician vigilance for possible transmission of these agents via transfusion also should increase. *Anaplasma phagocytophilum,* the causative agent of human granulocytic anaplasmosis, has been reported to have been transmitted by transfusion of RBCs.[119] Rickettsiae also may rarely be transmitted by blood transfusion.[118] Because *Rickettsia, Ehrlichia,* and *Anaplasma* infect white blood cells, leukoreduction techniques would be expected to reduce the risk for transmission through cellular components, although transfusion-transmitted *Ehrlichia ewingii* through a leukoreduced platelet unit has been reported.[120] Lyme disease has long been postulated to be transmitted by transfusion, but no single case of transmission through blood components has yet been recognized. Possible infection with tick-borne agents should be suspected if transfusion recipients develop unexplained thrombocytopenia or hemolytic anemia after transfusion, especially if accompanied by fever. Simultaneous infection with multiple tick-borne agents (e.g., *Babesia* and *Anaplasma* spp.) also should be considered.[119]

Parasites

T. cruzi, which causes Chagas disease, is endemic in certain areas of Mexico, South America, and Central America. Rare cases of *T. cruzi* transmitted by blood transfusion have been reported by US investigators.[121] More than 300,000 persons with *T. cruzi* infection reside in the United States. In Los Angeles and Miami, where immigration from endemic areas is high, a study found that 7.3% and 14.3% of all blood donors, respectively, had a risk for *T. cruzi* by history. Of these, 1 in 7500 to 9000 had detectable antibody. In a lookback study, no seropositivity or disease was found in 18 recipients of the units from seropositive donors, but the data were limited.[122] Although prevalence of the disease among donors is low overall, the availability of a blood antibody test resulted in voluntary adoption of screening by multiple blood centers in 2007, followed by an FDA recommendation for one-time screening for all donors.[123] An estimated 1 in 30,000 donors had evidence of *T. cruzi* infection at initial screening and confirmatory testing; the most frequent positive results were reported from California and Florida, although there was a nationwide distribution, reflecting immigration broadly from endemic countries.[123] Lookback studies in progress indicate that the transmission rate may be very low, and treatment of the hundreds of infected donors recognized at screening is a difficult issue.[124,125] The number of donors with evidence of infection who have no clear risk factors has also raised the possibility that there may be more autochthonous cases of Chagas disease than currently appreciated, with an estimate of 1 in 354,000 donors.[126]

Babesiosis is the most common cause of RBC transfusion–associated infections reported in the United States and accounted for 3.7% of transfusion-associated deaths between 2005 and 2010.[127,128] Most investigated cases have been found to be due to *Babesia microti,* found mostly in the Northeast and upper Midwest states. However, other species, such as *Babesia duncani* (previously known as WA-1), have also been implicated. In one series in which data from 84 patients with transfusion-associated *B. microti* infection between 1979 and 2009 were available, the interval from transfusion to clinical manifestations ranged from 11 to 176 days, with a median onset of 37 days.[129]

Because of donor travel and because blood products are transported outside endemic areas, transfusion-transmitted babesiosis can occur anywhere in the United States.[130] Patients who are asplenic or otherwise immunocompromised are at particular risk for increased disease severity. Patients with more than 4% parasitemia are at increased risk for clinically manifest infection, including severe, potentially life-threatening *Babesia* infections. Since 2011, laboratory screening of blood donations is conducted by blood collection centers in some endemic areas of the United States under investigational protocols.[131,132] Elsewhere in the United States, blood donor screening for babesiosis is required by questionnaire only, a method shown to be ineffective.[133] Boundaries such as geography and seasonality would not exclude asymptomatic donors, who can remain parasitemic for more than a year.[134] Because the number of recognized cases of transfusion transmission of babesiosis appears to be increasing, the need for more widespread screening through laboratory testing of donors is more urgent.

In May 2015, the FDA's Blood Products Advisory Committee recommended that available scientific data support the concept of nationwide, year-round testing of blood donors for *Babesia* risk with an antibody-based test, and that nucleic acid amplification–based testing should be performed in blood donations in certain high-risk states, including Connecticut, Massachusetts, Rhode Island, New York, New Jersey, New Hampshire, Maine, Minnesota, and Wisconsin.[76]

Transfusion-related transmission of malaria has long been recognized. In the United States between 1963 and 1999, 93 cases of transfusion-associated malaria were diagnosed and 10 patients died.[135] The majority of the infected donors would have been excluded had current deferral criteria been in place, or fully implemented, at the time of donation. Transfusion transmission of malaria has continued to decline, with the few cases recognized being associated with a history of malaria or with residence in a malarious area, rather than an isolated history of brief travel.[136]

Prions

The risk for transmission of sporadic Creutzfeldt-Jakob disease via transfusion is unknown, although no cases have been recognized.[137] In contrast, vCJD, which is acquired from eating beef and beef products contaminated with the agent that causes bovine spongiform encephalopathy, has been documented to be transmitted by transfusion. Between 2003 and 2007, there were four reports, all in the United Kingdom, of individuals who acquired the vCJD agent through RBC transfusions. Two of the RBC recipients developed vCJD and died of the disease; the third died of an unrelated illness but had evidence of infection, and the fourth affected individual developed symptoms of vCJD 8½ years after having received a transfusion of RBCs.[138,139] These cases were unlikely to have been detected without a robust system operating in the United Kingdom for follow-up of health care outcomes in transfusion recipients. Before cases were reported, considerable concern in the United States led to exclusion of blood donors from Great Britain and of those with prolonged stays in western Europe. Although significant donor deferrals resulted, the precautionary measures appeared to be justified.[140]

INFECTIOUS DISEASES TRANSMITTED THROUGH TRANSPLANTATION OF SOLID ORGANS AND OTHER TISSUES

Advances in health care technology have led to a proliferation in biologic products collected to sustain and improve the quality of life; over 35,000 solid organs and 2 million tissue allografts are distributed each year for transplantation. However, these advances also have increased the opportunities for transmission of infectious pathogens, including viruses, bacteria, and parasites, particularly for solid-organ transplant recipients.[141] One organ and tissue donor potentially can transmit disease, including infections and malignancies, to as many as 100 recipients. Data from mandated reporting have led to estimates that unexpected infectious diseases or malignancies may be suspected to be transmitted to as many as 1% of all solid-organ transplant recipients, and to many more in whom transmission goes unrecognized.[142,143] Transmission of disease through solid-organ and tissue transplantation is both a public health and patient safety issue, because events can result in serious illness and death in transplant recipients over a wide geographic area, making recognition difficult. For organs, there is a delicate balance between safety and availability, given the number of patients on the transplant wait list. There is no behavioral risk factor or test result that uniformly disqualifies an organ donor, unlike extensive deferral criteria for donors of blood and tissue. For instance, organs from donors who test positive for active hepatitis B or C virus are often accepted for transplantation and are most often matched to individuals already infected with these diseases, particularly with the increasing prospect for successful therapies.[144,145]

Progress has been made in increasing the availability of organs through the passage of a new law to also allow the use of organs donated from HIV-positive individuals. Given progress in treatment of HIV, increasing numbers of infected patients are on the transplant wait list. Entitled the HIV Organ Policy Equity (HOPE) Act, the law removes the prohibition against use of organs from HIV-positive donors for HIV-positive patients contingent on research showing beneficial outcomes. The US Health Resources and Services Administration has published rules allowing transplantation of organs from HIV-infected donors under research protocols, and results will be reviewed to determine whether these transplants can be done in the future without required participation in clinical research trials.[146]

Organ Transplant–Transmitted Bloodborne Pathogens

Examples of organisms transmitted through organs or other tissues include HIV, HAV, HBV, and HCV. HAV transmission has been reported in the United States in a multi–visceral organ transplant recipient.[147] In this case, the donor was unvaccinated and transmission occurred to the organ recipient and multiple health care workers, underscoring the increase in incidence of this infection and importance of achieving higher hepatitis A vaccination coverage in the US population.[147] Previously, HIV and HCV were transmitted to four organ recipients, and HIV was transmitted from a living donor to a kidney transplant patient. In both cases, only serology was performed for screening, and NAAT performed at the time of donation could have prevented transmission.[148,149] In 2013, a Public Health Service guideline for the reduction of HIV, HBV, and HCV transmission through organ transplantation was published and provides recommendations for donor screening, recipient testing, informed consent, and disease tracking and reporting; it recommends the use of NAAT in donors at increased risk for HIV and among all donors for HCV.[150] Despite NAAT, HCV transmission through organ transplantation has still occurred owing to window period infection in donors with nonmedical intravenous drug use.[151] The risk of undetected window period HIV or HCV infection among increased-risk donors in the setting of negative NAAT results is highest at 1 day after exposure, but is negligible at 1 month.[152] Through modeling, it has been estimated that the risk for transplant-transmitted HIV is approximately 1 in 50,000 and the risk of transplant-transmitted HCV is about 1 in 5000. The risk is higher for those donors with risk factors for bloodborne pathogens; the rate is highest for HCV associated with increased-risk donors and is estimated at 1 in 1000.[153]

Pathogens Causing Encephalitis

In addition to major bloodborne pathogens, other pathogens also can be transmitted through organ transplantation and are of concern (Table 304.4). Over the past decade, several emerging pathogens causing encephalitis among organ transplant recipients have been described and include WNV, rabies, lymphocytic choriomeningitis virus (LCMV), and *Balamuthia mandrillaris.* Each of these pathogens have been

TABLE 304.4 List of Notable Infections Transmitted by Solid-Organ Transplantation

Viruses
Cytomegalovirus
Eastern equine encephalitis virus
Epstein-Barr virus
Human immunodeficiency virus
Hepatitis A virus
Hepatitis B virus
Hepatitis C virus
Human herpesvirus 8
Herpes simplex virus
Lymphocytic choriomeningitis virus
Rabies virus
West Nile virus
Bacteria
Multiple species[a]
Mycobacteria
Mycobacterium tuberculosis
Fungi
Apophysomyces elegans
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Encephalitozoon cuniculi
Parasites
Balamuthia mandrillaris
Leishmania spp.
Strongyloides stercoralis
Toxoplasma gondii
Trypanosoma cruzi

[a]Morbidity associated with antimicrobial-resistant strains (e.g., methicillin-resistant *Staphylococcus aureus*) and gram-negative organisms (e.g., *Francisella tularensis,*[177] *Pseudomonas* spp.).

Modified from Machado CM, Levi JE. Transplant-associated and blood transfusion–associated tropical and parasitic infections. Infect Dis Clin North Am. *2012;26:225–231; and unpublished data from the Centers for Disease Control and Prevention.*

described to have been transmitted from donor to recipient on multiple occasions. More recently, eastern equine encephalitis virus has also been reported to have been transmitted from donor to recipients.[153a] It is critical for health care providers to recognize unusual outcomes in these patients and to communicate information about suspected transmission in such cases as quickly as possible, so that public health authorities can investigate and help initiate prevention measures in other recipients of organs from the same donor.

The natural mode of transmission of WNV is through infected mosquitoes, primarily of the *Culex* species, with birds serving as amplifying hosts.[154] In 2002, several cases of serologically confirmed WNV infection occurred in persons with little or no known mosquito exposure, and epidemiologic evidence suggested transmission of the virus through blood transfusion. Later in 2002, the first recognized cases of organ transplant–transmitted WNV infection were described in the United States. In fact, the two mechanisms of transmission (transfusion and solid-organ transplant) were linked early in the epidemic, when an organ donor who had been transfused with WNV-contaminated blood was infected. The occurrence of WNV encephalitis in two recipients of kidneys and the recipient of a heart and of febrile illness in a fourth recipient of a liver, all from the common donor, raised the concern of transmission through transplantation. Laboratory and epidemiologic data substantiated this mode of transmission and documented that the organ donor had likely acquired WNV infection through blood transfusion.

The 2002 WNV cluster resulted in heightened awareness about the potential increased severity of WNV infection in transplant recipients, and subsequent studies have substantiated a higher risk for severe manifestations, particularly neuroinvasive disease, which includes meningitis, encephalitis, and myelitis, among immunocompromised populations.[155] In contrast to transfusion transmission, which has become uncommon since initiation of blood donor screening with NAAT, this may not be the case in transplant recipients because no organ donor screening has been mandated. There have been seven organ-transmission WNV clusters reported in the United States, in which 16 of 20 organ recipients were infected; 12 of 16 infected organ recipients developed encephalitis, and 6 of these patients died.[63,156] In these clusters, onset of neuroinvasive disease among recipients likely led to recognition.[63,156] In the setting of blood transfusion, experience has suggested that transmission is unusual from an immunoglobulin M (IgM)–positive donor, presumably because a WNV-specific neutralizing antibody response results in clearing of viremia, rendering the blood as no longer infectious and possibly safe for transfusion.[157] However, in two of the reported transplant transmission clusters, there were detectable WNV IgM antibodies but no detectable RNA in donor serum specimens collected shortly before organ recovery. In one cluster, donor serum contained neither detectable RNA or WNV IgM antibodies.[63,156]

In July 2004, three solid-organ recipients and one additional recipient of an iliac artery segment from a common donor all developed encephalitis, eventually found to be due to rabies virus infection.[158] All four recipients died. Although several cases of rabies transmission through corneal transplants had been previously described,[159–162] solid-organ transplant transmission of rabies was not previously recognized. The common-source outbreak of transplant-associated rabies infection highlighted the difficulties inherent in the evaluation of encephalopathy in a potential organ donor. Prior to death, the organ donor had been twice evaluated in an emergency department after complaining of nausea, vomiting, and dysphagia. He eventually presented again with a subarachnoid hemorrhage and died. In retrospect, after determination of transmission of rabies infection through organ transplantation in multiple recipients, it was noted that the donor had additional symptoms consistent with encephalitis and had been bitten by a bat. Although this transmission was initially thought to be a unique event, another transplant cluster of rabies infection was reported from Germany soon after, demonstrating the potential importance of increased awareness from known transmission events.[163]

In the two previously recognized clusters of rabies virus transmission through solid-organ transplantation, infection was attributed to bat or canine virus variants, respectively. All recipients, except one in the German cluster who was previously vaccinated, experienced rabies symptoms within 6 weeks of transplantation and died.[164] These observations suggested a high infectivity rate and incubation periods of approximately 6 weeks in unvaccinated recipients of solid organs from donors with rabies. In 2013, another case of transplant-transmitted rabies virus infection was identified in the United States.[165] A raccoon rabies virus variant was identified in both the organ donor and infected recipient. In contrast to previous transplant rabies transmissions, the infected recipient developed symptoms approximately 17 months after transplant and three unvaccinated recipients remained asymptomatic. Postexposure prophylaxis was initiated in the three asymptomatic recipients, and all developed an appropriate protective neutralizing antibody response, suggesting that rabies infection can be prevented in organ transplant recipients if timely preventive measures are implemented.

In 2003 and 2005, two clusters of meningoencephalitis caused by LCMV occurred among solid-organ transplant recipients in the United States.[166] The first was reported among organ recipients from a common donor from Wisconsin. In this cluster, however, there was no serologic evidence of LCMV infection or rodent exposure in the donor. Eventual identification of LCMV through cell culture and electron microscopy of specimens from all four organ recipients led to pathogen identification and attribution of the source infection to the organ donor.[166] A second cluster occurred in 2005 among four organ recipients from a common donor who had died from an ischemic stroke.[167] Pathologic study and immunohistochemical staining of specimens led to LCMV diagnosis in this cluster. Investigation of this cluster revealed that the donor had had exposure to a pet hamster.[167] Although the donor had no evidence of active LCMV infection, the pet hamster was infected with a strain of LMCV that was genetically similar to those infecting the recipients. In 2008, hepatic insufficiency, multiorgan system failure, and death were reported in two kidney recipients with a common organ donor.[168] Although neither recipient exhibited signs of encephalitis, the donor had

had aseptic meningitis at death and retrospectively was found to have serum antibodies to LCMV. The donor was homeless and likely had had multiple opportunities for rodent exposure in his living environment.[168] Another cluster in which three organ transplant recipients died of encephalitis within 6 weeks of transplant was reported from Australia and was found to be caused by a novel arenavirus classified as LCMV.[169] This virus was identified through unbiased high-throughput sequencing.[169] The donor had died of a hemorrhagic stroke but had serologic evidence of recent infection and travel history to rural southern Europe, where he may have had rodent exposure.[169] It appears that transplant-associated LCMV infection may be an uncommon, but quantifiable, infectious risk in organ transplantation. Immunosuppression among these patients predisposes them to development of severe disease, including encephalitis, even though infected donors do not have central nervous system abnormalities, apart from the observation that the majority of those recognized die of cerebrovascular accident. Recognition of the potential for donor-derived LCMV, however, can result in reduced risk of mortality among recipients through prompt reduction of immunosuppression and perhaps implementation of antiviral therapy.[170]

Transplant-transmitted infection caused by *B. mandrillaris,* a free-living ameba described as causing a granulomatous amebic encephalitis, was first identified in 2009 after reports from clinicians in Mississippi noting a cluster of encephalitis in two kidney recipients from a common donor.[171] The organ donor, aged 2 years, reportedly had copious soil and water exposure before dying of a subarachnoid hemorrhage that was deemed secondary to seizures in the setting of what was initially diagnosed as an immune-mediated encephalitis but was later shown to be *Balamuthia* infection.[171] A second cluster was reported in 2010 when two organ transplant recipients in Arizona developed encephalitis with multiple ring-enhancing lesions revealed by cerebral magnetic resonance imaging.[171] The organ donor was presumed to have died of a stroke. Both patients ultimately died, and diagnosis was confirmed by immunohistochemical staining and reverse-transcriptase polymerase chain reaction detection of *Balamuthia* DNA in brain biopsy specimens.[171]

Transplant-transmitted infections resulting in encephalitis highlight several important diagnostic and clinical challenges related to recognition and treatment of certain emerging infections. Encephalitis resulting from WNV, rabies, LCMV, and *Balamuthia* among transplant recipients is quite rare and may not be immediately recognized by clinicians. Diagnosis is further complicated by limitations with laboratory screening for several of these diseases. Clinically, few effective treatment options are available once patients exhibit symptoms. However, there is some limited evidence that prophylaxis or treatment, even among asymptomatic transplant recipients, may be effective after exposure to these diseases. As a result, identification of possible infectious encephalitis among organ donors and establishment of proactive notification systems for transplant centers is crucial. It is critical for health care providers to recognize unusual outcomes in these patients and to communicate information about suspected transmission in such cases as quickly as possible, so that public health authorities can investigate and help initiate prevention measures.[172]

Strongyloidiasis

In a review of 21 symptomatic cases of *Strongyloides stercoralis* transmitted through solid-organ transplantation, symptom onset averaged 82 days after transplantation (range, 33–270 days), reflecting time for the worm burden to increase in the recipient by means of autoinfection.[173] Symptoms included gastroenteritis and, with larval migration through the lung, diffuse pneumonia. Most organ donors were from Central America, South America, or South Asia.[173,174] Diagnosis has been made by finding larvae in bronchoalveolar lavage fluid, cerebrospinal fluid, stool, or urine.[173] Screening of high-risk donors for antibody to *Strongyloides* and empirical use of ivermectin in at-risk recipients can be considered.

Microsporidiosis

Three organ recipients acquired *Encephalitozoon cuniculi* infection after transplantation of organs from a woman who had emigrated from Mexico a year earlier.[175] Infection manifested as unexplained fever beginning 7 to 10 weeks after transplantation.

Ehrlichiosis

Life-threatening transplant-associated ehrlichiosis occurred in both recipients of kidneys from the same deceased donor.[176]

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B Infections in Special Hosts

305 Infections in the Immunocompromised Host: General Principles

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COMPONENTS OF HOST DEFENSE

Appreciation of the predisposing risk factors is an essential but perplexing exercise because it suggests that each individual component plays an independent role. Certain organisms infect patients with specific defects, and these associations should be taken into account when selecting therapy. However, this is by no means always predictable. Theoretically, a specific deficiency increases the patient's susceptibility to the very pathogens that are eradicated by that particular host defense mechanism (Table 305.1; see Chapters 4 through 9). Although a basic pattern is recognizable, the types and severity of infectious complications are often unpredictable. Single, isolated deficiencies are infrequently encountered, and malfunction of one part of the system often influences several other components. Moreover, therapeutic interventions and the underlying disease will disturb a range of defense mechanisms. Although the risks associated with neutropenia are well known, other toxicities, especially those affecting the mucosal barrier, are considered to be of greater importance than was previously the case. The earlier advent of aggressive treatments and, recently, targeted therapy has altered the concept of specific defects of host defense mechanisms in the various types of diseases because the effects of these drugs and irradiation are now seen as the primary factors determining the nature and extent of the defect. Also, transplantation (especially of hematopoietic stem cells) can cause defects in host immunity as a result of graft-versus-host disease (GVHD), as well as of immunosuppressive therapy. Patients with impaired humoral immunity as manifested by defective opsonization and phagocytosis of bacteria will also be exposed to therapy-induced neutropenia or deficient cellular immunity as a result of treatment with purine analogues, monoclonal antibodies, or targeted therapies (e.g., tyrosine kinase inhibitors [TKIs] and inhibitors of phosphatidylinositol 3 kinase [PI3K]) for treating malignancies.

The genetic makeup of the host also has an impact on the risk for infection because functional changes due to polymorphisms in immune genes influence individual susceptibility for infection.[1,2] The specific context of an immune deficiency determines which of the remaining components of the immune system will be most important. Therefore, variation in the genes that correspond to these components may become clinically important. Components of the innate immune system are believed to survive chemotherapy and contribute to immune defenses. Consequently, in the setting of cancer therapy and hematopoietic stem cell transplantation (HSCT), most gene polymorphisms associated with the risk for infection involve innate immune genes, especially those coding for pattern recognition receptors and cytokines.[3,4]

Cellular and Humoral Immunity

The host defense against pathogenic microorganisms encompasses innate and acquired immunity. The innate immune system comprises both cellular components, including monocytes, neutrophils, natural killer (NK) cells, and innate lymphoid cells, and humoral components, including complement, some antibodies ("natural" antibodies, perhaps directed against normal microbiota), antimicrobial peptides, and lysozyme. This mechanism is very effective in dealing with the vast majority of infectious agents. It has become clear that the innate immune system not only specifically recognizes various classes of microorganisms via pattern recognition receptors (microbe-associated molecular patterns) that sense conserved structures of the invading microorganisms, but also initiates and modulates the subsequent adaptive responses delivered by T cells and B cells through their interaction with antigen-presenting cells (especially dendritic cells).

Innate Immunity

Granulocytes

In normal circumstances, neutrophils, sometimes accompanied by eosinophils, congregate at the site of inflammation and are followed by macrophages. Formation of this inflammatory exudate is the result of activation of humoral factors and normal function of the vascular endothelium (see Chapter 8). Meanwhile, in the peripheral blood, granulocytosis evolves as a consequence of release of the marrow reserve and increased granulocytopoiesis, which is regulated by hematopoietic growth factors such as interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor, and granulocyte colony-stimulating factor.[5]

Virtually all cytotoxic drugs used in the treatment of malignant diseases have a deleterious effect on the proliferation of normal hematopoietic progenitor cells. Therefore, after obliteration of the mitotic pool and depletion of the marrow pool reserve, neutropenia ensues. Likewise, therapeutic radiation can induce clinically important neutropenia, depending on the dose rate, total dose given, and irradiated area of the body. Total-body irradiation, as used to prepare for HSCT, is the most obvious illustration of the possible negative impact of irradiation. Thus, profound neutropenia is an unavoidable consequence of the treatment of malignancy and may persist for 3 or 4 weeks or even longer. Neutropenia or a treatment-related decrease in the granulocyte count is probably the most important primary risk factor for infection. Fever develops in nearly all cases of profound neutropenia (i.e., a granulocyte count $<100/mm^3$ for more than 2–3 weeks), whereas only one-fifth of the febrile episodes in cancer patients occur when granulocyte counts are normal.[6] Moreover, during iatrogenic neutropenia, the risk for infection and infection-related mortality increases proportionally with time.

Granulocytes that accumulate at the site of infection are of little use if they are unable to function normally. Antineoplastic drugs and irradiation interfere with these nonproliferating cells and their function, resulting in decreased chemotaxis, diminished phagocytic capacity, and defective intracellular killing by granulocytes. Glucocorticosteroids seem to enhance granulocytopoiesis and mobilize the marginal and the marrow pool reserve, but these putative positive effects on neutrophilic granulocytes are offset by numerous disadvantages. These drugs curb the accumulation of neutrophils at the site of inflammation by reducing their adherent capacity and diminishing their chemotactic activity. Furthermore, they decrease phagocytosis and intracellular killing of microorganisms. The lack of functioning neutrophils deprives the host

TABLE 305.1 Immunodeficiencies and Associated Prevalent Pathogens

DEFECT	PATHOGEN
Neutropenia	Gram-positive cocci *Staphylococcus aureus* Coagulase-negative staphylococci *(S. epidermidis, S. haemolyticus, S. hominis)* Viridans-group streptococci *(S. mitis, S. oralis)* *Granulicatella* and *Abiotrophia* spp. (formerly nutritionally variant streptococci) Enterococci *(E. faecalis, E. faecium)* Gram-negative bacilli *Escherichia coli* *Pseudomonas aeruginosa* *Klebsiella pneumoniae* *Enterobacter* and *Citrobacter* spp.
Damaged integument	
Skin and central venous catheter related	Coagulase-negative staphylococci *(S. epidermidis, S. haemolyticus, S. hominis)* *Staphylococcus aureus* *Stenotrophomonas maltophilia* *Pseudomonas aeruginosa* *Acinetobacter* spp. Corynebacteria *Candida* spp. *(C. albicans, C. parapsilosis)* *Rhizopus* spp.
Oral mucositis	Viridans-group streptococci *(S. mitis, S. oralis)* *Abiotrophia* and *Granulicatella* spp. (nutritionally variant streptococci) *Capnocytophaga* spp. *Fusobacterium* spp. *Rothia mucilaginosa* *Candida* spp. *(C. albicans, C. tropicalis, C. glabrata)* Herpes simplex virus
Gut mucosal barrier injury	*Escherichia coli* *Pseudomonas aeruginosa* Coagulase-negative staphylococci Enterococci *(E. faecalis, E. faecium)* *Candida* spp. Viridans-group streptococci *(S. oralis, mitis)*
Neutropenic enterocolitis	*Clostridium* spp. *(C. septicum, C. tertium)* *Staphylococcus aureus* *Pseudomonas aeruginosa*
Impaired cellular immunity	Herpesviruses Cytomegalovirus Respiratory viruses *Listeria monocytogenes* *Nocardia* spp. *Mycobacterium tuberculosis* Nontuberculous mycobacteria *Pneumocystis jirovecii* *Aspergillus* spp. *Cryptococcus* spp. *Histoplasma capsulatum* *Coccidioides* spp. *Talaromyces marneffei* *Toxoplasma gondii* Human papillomavirus Polyomavirus (BK, JC, and others)
Impaired humoral immunity	*Streptococcus pneumoniae* *Haemophilus influenzae* Norovirus Hepatitis B virus Polyoma virus (JC) Hepatitis B virus *Campylobacter/Helicobacter*
Compromised organ function	
Splenectomy	*Streptococcus pneumoniae* *Haemophilus influenzae* *Neisseria meningitidis*
Deferoxamine for iron overload	*Rhizopus* spp.
New targeted drugs	
Bruton tyrosine kinase inhibitor (ibrutinib); a specific inhibitor of B-lymphocyte signaling	*Aspergillus* spp. *Pneumocystis jirovecii*
JAK-STAT inhibitor (ruxolitinib); downregulates proinflammatory cytokines, impairs dendritic cell, NK cell, and $CD4^+$ T-cell function	*Mycobacterium tuberculosis* *Hepatitis B reactivation*
PI3K inhibitor (idelalisib); specific inhibitor of phosphatidylinositol-3-kinase delta-Akt pathway B-lymphocyte signaling	*Pneumocystis jirovecii*

of a primary defense mechanism against invading microorganisms, which are consequently able to readily establish themselves, initiate local infection, disseminate unhindered, and eventually lead to fulminant sepsis and death unless managed promptly and effectively.

Monocytes and Macrophages

Monocytes reside in the bloodstream and contribute to rapid responses against bacteria and fungi that gain access to the bloodstream. Monocytopenia occurs in parallel with neutropenia after cytotoxic therapy and contributes to the susceptibility to bacteremia and fungemia in cancer patients.

The descendants of monocytes, the tissue-residing type l macrophages, have a limited capacity for killing. Various intracellular microorganisms are able to survive and replicate inside the cell, unless the macrophage becomes activated. Activation of macrophages is a complex process, primarily under the control of cytokines (e.g., interferon-γ) provided by T lymphocytes. This explains the prominent susceptibility of patients with hairy cell leukemia to opportunistic infections, including those with filamentous fungi, because there exist synergistic intrinsic (monocytopenia and decreased interferon-γ release) and extrinsic (therapy-related, including purine analogues) immune defects.

With the use of the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, there has been an increase in pulmonary and cerebral aspergillosis in patients with lymphoid malignancies, in the context of corticosteroids use. Because ibrutinib was considered to be a specific inhibitor of B-lymphocyte signaling, this was unanticipated. Further analysis, however, revealed a role for BTK in monocytes and granulocytes and additional inhibition of inducible tyrosine kinase by ibrutinib in lymphocytes that explain at least partially this unexpected event. This highlights the complexity of approaching patients with cancer and choosing therapies and illustrates the challenges with presumably specific and less toxic targeted therapies.

Natural Killer Cells

NK cells are cytotoxic lymphocytes belonging to the pool of innate lymphoid cells. Although thought to mainly contribute to responses against viral infections and antitumor immunity, NK cells have been identified as important effectors in bacterial and fungal infections. Depletion of NK cells by monoclonal antibodies and during HSCT contributes to the overall susceptibility to viral and probably fungal infections. It turns out that the surface receptor CD56 of NK cells is a pattern recognition receptor of *Aspergillus fumigatus* and plays a role in fungus-mediated NK cell activation.

Impact of Treatment on Cellular Immunity

Both antigen-specific and antigen-nonspecific cells contribute to the development of cellular immunity. The antigen-specific branch of cell-mediated immunity can be divided into two major categories. One category involves cytotoxic effector cells, which are able to lyse virus-infected or foreign cells, including malignant cells. The second category involves subpopulations of helper T cells that mediate differentiated cytokine reactions (e.g., Th1, Th2, Th17) after antigen recognition.

This fine-tuned system can easily be deregulated by congenital defects or defects acquired as a result of a disease or its treatment. Long-term cytotoxic therapy, extensive irradiation, and immunosuppressive drugs such as corticosteroids, azathioprine, cyclosporine, tacrolimus, and mTOR inhibitors (sirolimus, and everolimus) suppress cellular immunity. Some monoclonal antibodies, such as alemtuzumab, are being used as

antitumor and immunosuppressive agents and can exert profound and prolonged effects on cellular immunity. Purine analogues, including fludarabine and cladribine, are particularly detrimental to cellular immunity and create a situation similar to acquired immunodeficiency syndrome. Likewise, lymphatic malignancies, particularly Hodgkin lymphoma and chronic lymphocytic leukemia (CLL), are associated with impaired cellular immunity. Emerging targeted therapies—including the TKIs imatinib, dasatinib, and bosutinib; small molecules such as BCL2 inhibitors (venetoclax); JAK-STAT inhibitors; and PI3K inhibitors, often used in heavily pretreated patients—have an impact on specific cellular immunity (see Chapter 6). This is exemplified by the occurrence of opportunistic infections with the use of ruxolitinib (*Mycobacterium tuberculosis* and hepatitis B reactivation), ibrutinib (aspergillosis), and idelalisib (*Pneumocystis jirovecii*). On the contrary, the use of immunomodulatory drugs (lenalidomide) or proteasome inhibitor drugs (bortezomib) increases the risk of severe nonspecific infections, especially in the relapsed/refractory phase of multiple myeloma, and mostly as a result of therapy-related neutropenia.

Allogeneic stem cell transplantation brings about a long-lasting dysfunction of T and B cells, especially in association with GVHD and its treatment (Table 305.2). The coordination of cellular immunity is often lost, and when aided and abetted by suppressed humoral immunity, the paracrine mediators that are released go on to induce the sepsis cascade, which may culminate in multiorgan failure instead of arresting infection.[7]

TABLE 305.2 Sequence of Infective Events in Relation to the Phases of Allogeneic Stem Cell Transplantation

	EARLY PHASE	MID-RECOVERY PHASE	LATE PHASE
Host Defense Mechanisms Without Graft-Versus-Host Disease			
Phagocytes	Absent	Deficient	Normal
Integument Skin Mucous membranes	 Damaged Severely damaged	 Damaged Damaged	 Intact Intact
Cellular immunity	Slightly impaired	Impaired	Impaired
Humoral immunity	Normal	Impaired	Severely impaired
Host Defense Mechanisms With Graft-Versus-Host Disease			
Phagocytes	Absent	Deficient	Normal
Integument Skin Mucous membranes	 Damaged Damaged	 Damaged Severely damaged	 Damaged Damaged
Cellular immunity	Slightly impaired	Severely impaired	Severely impaired
Humoral immunity	Normal	Impaired	Severely impaired
Prevalent Infections			
Mucosa	Herpes simplex virus Viridans streptococci Coagulase-negative staphylococci	Herpes simplex virus *Candida* spp.	Herpes simplex virus *Candida* spp.
Lung	Gram-negative bacilli *Aspergillus* spp.	Cytomegalovirus *Aspergillus* spp.	*Streptococcus pneumoniae* Viruses, including cytomegalovirus *Pneumocystis jirovecii*
Blood	Viridans streptococci Staphylococci Gram-negative bacilli *Candida* spp.	Staphylococci *Streptococcus pneumoniae* *Candida* spp.	*Neisseria meningitidis*

Impact of Treatment on Humoral Immunity

The humoral branch of the immune system, which is primarily responsible for clearing extracellular bacteria, involves the interaction of B cells with antigen and their subsequent proliferation and differentiation into antibody-secreting plasma cells (see Chapter 5). An important difference in antigen recognition by T cells and B cells is that the latter can recognize some antigens without the help of an antigen-presenting cell. The humoral system can identify a plethora of bacterial or viral microorganisms, in addition to the soluble proteins that they release. When challenged by an antigen, immunoglobulins are produced that bind to the antigen. The specific functions of immunoglobulin G (IgG) and immunoglobulin M (IgM) include neutralization of the antigen, and complement activation and opsonization—that is, enhancement of phagocytosis of the antigen by neutrophils and macrophages. Secretory immunoglobulin A (IgA), which is found on mucosal surfaces, is not an opsonin but nonetheless inhibits the motility of bacteria and prevents them from adhering to epithelial cells. The production of immunoglobulins is decreased in lymphoproliferative disorders such as CLL and multiple myeloma, whereas humoral immunity is generally well preserved in patients with acute leukemia. However, intensive irradiation and chemotherapy will lead not only to neutropenia but also, ultimately, to hypogammaglobulinemia. In particular, monoclonal antibodies such as rituximab and blinatumomab and CD19- and CD22-targeted chimeric antigen receptor (CAR) T cells deplete B lymphocytes, inducing profound and long-lasting hypogammaglobulinemia and, consequently, infections.[8] The impact of new therapies such as BTK and PI3K inhibitors is currently less clear, but considering the fact that they target molecules with vital roles in B-cell maturation and function, disrupted antibody responses can be anticipated. At the least, reduced serologic responses to vaccination indicate impaired humoral immunity.

Cytokines and chemokines are indispensable for communication between innate and acquired immune and nonimmune cells in shaping effective antimicrobial immune reactions. Hence, interference by anticytokine antibodies and cytokine scavengers (e.g., infliximab, anakinra, tocilizumab) results in increased risk for infection in autoimmune diseases, transplantation, and cancer therapy.[9]

Humoral Immunity and the Spleen

The primary immunoglobulin response of spleen-produced specific opsonizing antibodies is necessary for efficient phagocytosis of encapsulated bacteria. Macrophages that occupy strategic positions within the organ are subsequently able to remove them. Splenectomy may result in a reduced level of the complement factor properdin and thereby lead to suboptimal opsonization, a decrease in functional tuftsin, and low levels of circulating IgM.[10] The lack of opsonizing antibodies in serum against common encapsulated bacteria impairs the activity of all phagocytic cells, including granulocytes, monocytes, and macrophages. As a consequence, infections with *Streptococcus pneumoniae* and *Haemophilus influenzae* are often more severe in splenectomized patients and in those who have undergone HSCT and are functionally asplenic. Opsonizing antibodies are also important for effective antibody-dependent cell-mediated cytotoxicity of NK cells.

Platelets

The protective role of platelets in healthy individuals is often underestimated but becomes obvious during treatment of patients with malignant disease. Thrombocytopenia is an almost inevitable repercussion of intensive chemotherapy and irradiation, but decreased thrombocyte function is also a matter of concern. Thrombocytopathy is either disease related or caused by concurrent medication. The consequences of both increased susceptibility to infection and a decreased capacity to repair damaged tissues can be considerable and may have an impact on the eventual outcome of a treatment episode. Thrombocytopenia also appears to be an independent risk factor for bacteremia,[11] and the incidence of major hemorrhage at autopsy of patients who die with or of an infection is striking.[12]

The Integument as Host Defense

The skin, the respiratory tract (including the nasal cavity), the ears and conjunctiva, the alimentary tract, and the genitourinary tract are in contact with the environment and provide a first line of defense against microbial invasion. The skin and the mucosal surfaces of the alimentary and respiratory tracts form principal barriers against microbial invasion. These surfaces are normally colonized with a variety of microorganisms, including many different genera of bacteria, viruses, and yeast that have an intimate association with a particular ecologic niche and help to maintain the function and integrity of this first line of defense. When intact and healthy, both the mucosa and the skin are capable of resisting colonization with the allochthonous organisms found in the immediate environment, as long as an ecologic balance is maintained within the indigenous microbial microbiota. Acidity plays a crucial role both in disinfecting the stomach and in regulating the microbial milieu of the vagina. The integrity of the mucosa, production of saliva and mucus, peristalsis, bile acids, digestive enzymes, and levels of defensins, trefoil factors, and secretory IgA also play an important role in maintaining a favorable microecology. Elimination of an inoculum is achieved by sneezing and coughing of microbes trapped in mucus, whereas flushing of the mouth and esophagus with saliva, micturition, and peristalsis inhibit continuous intimate contact between a given surface area and unattached invasive microorganisms.

Skin

Healthy skin provides an effective barrier against invasion by microorganisms, mainly by remaining intact. Desquamation helps limit the opportunities for transient organisms to establish residence. Normally, very little water is present on the skin surface. Colonization with organisms sensitive to desiccation, such as gram-negative bacilli, is not favored. The skin also forms an acid mantle with a pH of 5.0 to 6.0, and its surface temperature is on average approximately 5°C lower than the core body temperature.[13] Besides containing secretory IgA, sweat also possesses sufficient salt to create a high osmotic pressure. Organisms that can withstand these conditions and compete successfully for binding sites and nutrients include staphylococci, corynebacteria, and the lipophilic yeast *Malassezia furfur.* These organisms further modulate the microecology of the skin by releasing fatty acids from sebaceous secretions to produce a hydrophobic milieu, and lactic and propionic acids, which help maintain a low pH. Many of the bacteria also elaborate bacteriocins that inhibit other microorganisms, and induce antimicrobial peptides and heterologous immune responses that protect the skin barrier.

The composition of the skin microflora is influenced by general factors including climate, body location, age, sex, race, occupation, and the use of soaps, detergents, and disinfectants. Antibiotics secreted in sweat disturb the balance within the commensal microbiota and leave the surface vulnerable to colonization by exogenous gram-negative bacilli. Antibiotics also exert selective pressure on the skin microbiota and cause resistance to emerge, as has been observed during treatment with ciprofloxacin. Moreover, ciprofloxacin is excreted in sweat and induces resistance among skin staphylococci within a few days of exposure.[14] β-Lactam antibiotics, including ceftazidime, ceftriaxone, cefuroxime, benzyl penicillin, and phenoxymethylpenicillin (penicillin V), can also be found in sweat, which might explain the ready selection of resistant staphylococci. Chemotherapy and irradiation can cause radical changes in healthy skin that cause hair loss, dryness, and loss of sweat production.

Needle punctures and catheters provide a ready means of access for microorganisms through the stratum corneum and into the bloodstream. When the skin is broken, the release of fibronectin is thought to assist colonization with *Staphylococcus aureus,* whereas other changes facilitate colonization with gram-negative bacilli such as *Acinetobacter baumannii* and enteric bacteria. Abraded skin can lead to local infection, which can be a reservoir that promotes further spread to entry sites of intravenous catheters. When the balance is lost between host defenses and commensal microbiota around hair follicles, the follicles can become inflamed and necrotic and form a potential nidus of infection. Clinical infection therefore results from breaks in the skin, loss of local immunity, and disturbances within the resident microbiota. Some common environmental organisms, mycobacteria among them, are prominent skin pathogens because of their preferential growth at lower temperatures.

Vascular devices have gained widespread acceptance as a relatively safe form of long-term venous access, but regular use is associated with a marked increase in the incidence of bacteremia with coagulase-negative staphylococci, which frequently colonize the catheter lumen (see Chapter 300). These staphylococci are commonly resistant to aminoglycosides, trimethoprim-sulfamethoxazole, and penicillinase-resistant penicillins and may also be resistant to fluoroquinolones. Unless the catheter ends in an implanted port, skin commensal microbiota have potential access into the bloodstream. The hub is the most likely source of contamination, leading to catheter colonization,[15] and the risk increases with use.[16] Infections related to the external surface of the catheter (exit site infections and tunnel infections) can result in serious soft tissue infection, most notably with *S. aureus.* Exit site infections occur much less frequently than does intraluminal contamination. The latter may be caused by a variety of bacteria, many of which have relatively low virulence. Once established, these infections can be very difficult to treat without removing the device, particularly those caused by *Bacillus* spp., *Candida* spp., and *Pseudomonas aeruginosa.*[17,18]

Respiratory Tract

The lung appears to be very vulnerable to damage by cytostatic chemotherapy and irradiation and is exquisitely susceptible to infection. Immunopathologic reactions mediated by pulmonary macrophages that survive chemotherapy can lead to various other syndromes, including respiratory distress. Lung hemorrhage as a result of profound thrombocytopenia further imperils the lung and thereby increases the risk for infection. Inhalation of spores of *Aspergillus* spp. and other molds may lead to infection of the sinuses, bronchi, and lungs.

Alimentary Tract and Normal Microbiota as Host Defense

Anaerobic bacteria predominate among the resident microbiota of the oral cavity and large intestine population and play a crucial role in maintaining a healthy commensal microbiota by providing the facility to withstand the establishment of exogenous organisms, which is known as *colonization resistance.*[19] However, the microbiota is not the only participant in the establishment and maintenance of colonization resistance. There has been renewed interest in the human commensal microbiota, which can be divided into the microbiome, mycobiome, and virome, all of which are associated with health and disease. The various species also participate in training and shaping the immune response, maintaining it, and keeping it healthy. In fact, the host-microbial interaction is far more complex than hitherto imagined, involving host pattern recognition receptors, bacteriocins, and lactic acid, to name but a few, in addition to competitors for available nutrients and the release of host antimicrobial peptides.[20,21,22]

Dysbiosis

Many antibiotics also exert a negative influence on the commensal microbiota. Very susceptible bacteria such as the oral *Neisseria* spp. are suppressed by a wide range of antimicrobial agents, whereas oral viridans-group streptococci, such as *Streptococcus mitis* and *Streptococcus oralis,* and other unusual oral commensal microbiota, such as *Rothia mucilaginosa* and *Capnocytophaga* spp., are likely to be selected by antimicrobial agents, to which the bacteria are only marginally susceptible, if at all. In particular, penicillins, rifampin, clindamycin, macrolides, bacitracin, and vancomycin significantly impair colonization resistance, probably because they inhibit the gram-positive nonsporulating, lactic acid–producing bacilli such as bifidobacteria. Certain cephalosporins are also detrimental, whereas trimethoprim-sulfamethoxazole and the quinolones have been declared "friendly," hence their frequent use as prophylaxis.[23] Unexpectedly, imipenem used at higher doses has led to an increase in cases of diarrhea caused by *Clostridioides difficile* (formerly *Clostridium difficile*).[24] Newer antibiotics such as tigecycline, with activity against anaerobic gram-positive bacteria, may lead to increases in the numbers of patients with *Candida.* This change usually reflects marked perturbations of the gut ecology.[25] However, this effect does not increase

the risk for infection due to *C. difficile*.[26] Chlorhexidine mouthwashes used to minimize plaque and gingivitis also influence the microflora.[27]

Because the normal commensal microbiota attach to the surfaces of the epithelium, their loss creates an ecologic vacuum that allows other organisms to establish colonization by occupying the vacant cell surfaces or by taking advantage of the surfeit of nutrients. Collapse of the ecology invariably manifests with yeast overgrowth and colonization with nosocomial bacteria such as *Klebsiella pneumoniae* and *P. aeruginosa* and failure to detect viable anaerobes directly or indirectly.[28–30] Examples of infectious complications associated with disturbance of the normal microbial equilibrium include the selection of previously uncommon species such as *Enterococcus faecium* and *Clostridium septicum*.

Dyspepsia is sufficiently commonplace for antacids such as histamine-2 (H2) blockers and proton pump inhibitors to be regularly prescribed. Reduced gastric acidity inadvertently destroys the natural barrier that prevents gastric and intestinal colonization by oral commensal microbiota, many of which are resistant to most of the antimicrobial agents used for prophylaxis in impaired hosts. When patients swallow large amounts of mucus as a result of severe mucositis, any oral commensal microbiota may survive passage to the bowel. Loss of the gastric barrier therefore effectively extends the area of potential sites for colonization to the full length of the alimentary tract, which may explain the pathogenesis of viridans-group streptococcal bacteremia.[31]

Finally, the ecology of the gut microbiota is markedly altered by damage induced by treatment with certain cytostatic agents such as cytarabine,[32] by GVHD,[33] and by total-body irradiation.[34] The direct impact of enterocyte and Paneth cell damage on the microbiota seems mostly related to changes in production and release of antimicrobial peptides, normally involved in controlling microbial abundance and composition. Nevertheless, the strongest impact remains the detrimental effect of antimicrobial agents used in immunocompromised hosts.

Mucosal Barrier Injury

Injury to the mucosal barrier induced by chemotherapy and radiation therapy is probably the most substantial and earliest breach in the host defenses against infecting microorganisms. The process is more complex than just the direct effect of cytotoxic therapy on cells with a high mitotic index, such as epithelial cells of the mouth and gastrointestinal tract, and the indirect effect of local infections associated with evolving neutropenia. Sonis[35] postulated that the pathobiology of mucositis involves five sequential but overlapping phases (Fig. 305.1), culminating in tissue damage that manifests clinically as mucositis. The initiation phase involves free-radical generation and induction of apoptotic cell death induced by both DNA and non-DNA damage. The primary damage response phase occurs next, during which the master transcription factor, nuclear factor kappa B (NF-κB), leads to the upregulation of several genes, resulting in the production of the proinflammatory cytokines (tumor necrosis factor-α [TNF-α], IL-1β, and IL-6) and then signal amplification. The net result is the ulceration phase, in which microorganisms and microbe-associated molecular patterns such as peptidoglycan and lipopolysaccharide can translocate the damaged physical barrier more easily and are able to activate tissue macrophages to produce more proinflammatory cytokines, thereby exacerbating the damage.[36,37] In addition, damage-associated molecular patterns, including endogenous ligands, the alarmin, high-mobility box group-1, ATP, and heat shock proteins released as a result of tissue damage, all contribute to inflammation and tissue damage.[35] Last, the healing phase occurs and is to a certain extent dependent on the rate of recovery of stem cells that are capable of repopulating the epithelium. Cytostatic chemotherapy regimens and irradiation injury induce varying degrees of mucosal barrier injury with differing dynamics, although the progression and decline of signs may be similar.[38] Individual patients are also likely to vary in their susceptibility to mucosal damage, suggesting that there are genetic differences in the expression of proinflammatory cytokines or proteins that control stem cell apoptosis (e.g., TP53 and BCL2 along the gastrointestinal tract).

There is extensive gastrointestinal-associated lymphoid tissue in which lymphocytes and macrophages are located and that responds to irradiation and chemotherapy with inflammation.[39,40] Moreover, gut epithelial cells actively participate in the innate and adaptive immune

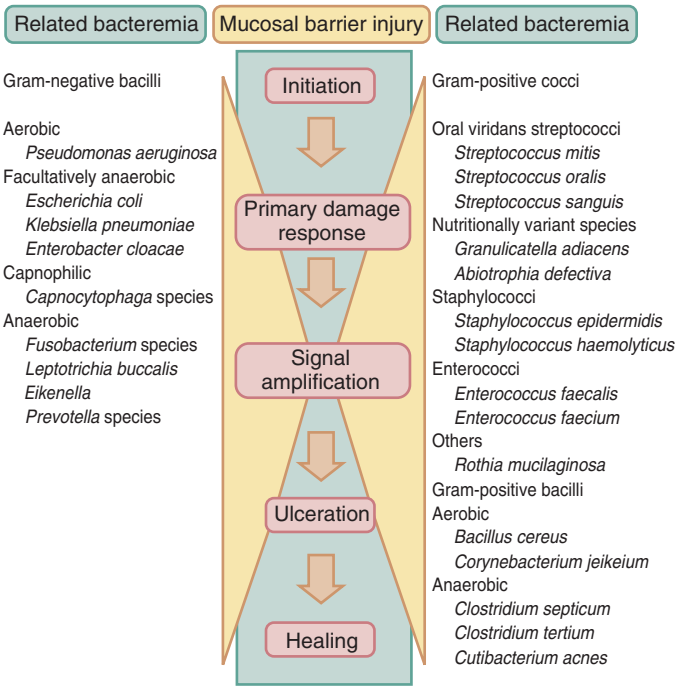

FIG. 305.1 Mucosal barrier injury induced by cytostatic chemotherapy and irradiation is believed to occur in five more or less sequential phases. The process elicits a local and systemic inflammatory response, which may be accompanied by signs and symptoms of oral mucositis and gut dysfunction and even sepsis. Infection may be local but often involves dissemination via the bloodstream to distant sites. Bacteremia can be caused by a variety of normally commensal resident flora found on the skin and mucous membranes of the alimentary tract and by potential pathogens acquired exogenously.

response. They are capable of producing and secreting proinflammatory cytokines and upregulating the production of major histocompatibility complex class II molecules and other adhesion molecules after sensing specific microbe-associated molecular patterns, such as lipopolysaccharide (endotoxin), muramyl dipeptide, and other bacterial antigens.[39] In mucosal barrier injury, the innate immune response is dysfunctional and host microbe interactions that are normally beneficial now result in detrimental inflammation and perpetuation of mucosal damage. Uncontrolled activation of pattern recognition receptors appears to play a key role. Muramyl dipeptide is sensed by NOD2, an intracytosolic pattern-recognition receptor expressed in Paneth cells, dendritic cells, neutrophils, and monocytes. *NOD2/CARD15* polymorphisms result in uncontrolled inflammation of gut mucosa in Crohn disease and gut GVHD after allogeneic stem cell transplantation.[41]

Oral and gastrointestinal mucositides are the clinical manifestations of mucosal barrier injury, and the duration of mucositis may define the period of risk for infection more strongly than even neutropenia in some contexts (HSCT).[42] Oral mucositis is characterized by functional complaints, such as pain and difficulty in swallowing (dysphagia), and by anatomic changes, such as edema, erythema, ulceration, pseudomembrane formation, and alterations in mucus consistency with changes in saliva production (xerostomia). Gastrointestinal mucositis is accompanied by nausea and vomiting, diarrhea, intolerance for enteral nutrition, and abdominal pain. Mucositis results in significant morbidity and markedly lowers the quality of life for several weeks after cytotoxic chemotherapy and irradiation. Modern remission induction cytostatic chemotherapy and conditioning regimens for HSCT and GVHD regimens containing methotrexate often induce substantial injury to the mucosa, and reduced intensity conditioning may not lessen this risk.[43] Combinations containing melphalan, etoposide, methotrexate, cytarabine, and idarubicin have all been shown to induce mucositis, which can be very severe when anthracyclines are combined with total-body irradiation and cyclophosphamide to condition patients for HSCT or reinfusion.[44] Systemic drug exposure is the key determinant driving severe mucositis risk in

high-dose chemotherapy-treated recipients of autologous transplants.[45] Patients receiving a melphalan dose of 70 mg/m^2 or greater had a 23-fold increased risk for developing mucositis compared with those receiving lower doses.[46] The duration and incidence of fever, parenteral narcotic use, total parenteral nutrition, antibiotic therapy, and the length of stay in a hospital are all correlated with the severity of mucositis, as is the risk for significant infections and mortality.[45,47,48] It is likely that severe mucositis leads to a commensurate increase in the number of unusual bacteria causing infection by providing them with a portal of entry, which may explain the increase in bacteremia caused by oral commensal gram-positive cocci such as the oral viridans streptococci, *R. mucilaginosa,* and *Capnocytophaga* spp.[31,49,50] The consequences of probable dietary exposure in neuroinvasive *Bacillus cereus* infections in leukemic patients are supported by a case-control analysis that identified food contamination in all cases.[51] Besides damage to the oropharyngeal, esophageal, and gastric mucosa, chemotherapy and irradiation impair gut function and lead to rapid alterations in permeability. The increased absorption of sugars such as rhamnose, mannose, and lactulose and the decreased uptake of xylose after chemotherapy, irradiation, or a combination of both indicate a loss of integrity and damage to tight junctions.[52] Perturbed gut function has been shown to be one of the factors that, together with antibiotic use and colonization with *Candida* spp., predispose patients with leukemia to invasive candidiasis, and it also appears to be a risk factor for neutropenic enterocolitis. Impaired gut function and integrity may also facilitate translocation, particularly translocation of gram-negative bacilli such as *P. aeruginosa,* into the bloodstream of patients colonized with the organism.

Gut toxicity has also been shown to be responsible for the reduced absorption of quinolones[53] and has been implicated in the erratic bioavailability of the antifungal agents itraconazole and older formulations of posaconazole.[54] Finally, a dysfunctional gut will have a marked effect on the nutritional status of the patient, not least because of the lower release of citrulline, the nitrogen transporter of the human body, as a result of the reduced number of functioning enterocytes.[55]

Nutritional Status

Patients who weigh less than 75% of their ideal body weight or who have experienced rapid weight loss and have hypoalbuminemia are severely nutritionally deficient, which correlates inversely with survival. Poor nutritional status endangers the integrity of host defenses because of the catabolic state induced by cachexia and the malnutrition that results from anorexia, therapy-induced nausea and vomiting, gastrointestinal obstruction, altered permeability, mucositis, and metabolic derangements. A state of iron deficiency reduces the microbicidal capacity of neutrophils and T-lymphocyte function in vitro. Nutrition may be given parenterally or via a nasogastric tube to redress the balance, but neither is entirely without risk because each introduces yet another breach in the normal barriers and increases the risk for aspiration, particularly when consciousness is impaired.

Comorbidity and Host Defense

Psychological stress is thought perhaps to suppress host defense mechanisms. This possibility has been corroborated by observations that psychological stress has a negative influence on the function of T cells and NK cells. Indeed, stress appears to be connected with an increased risk for acute viral respiratory illness, a risk that was related to the amount of stress, most likely mediated by endogenous opioids, hormones from the hypothalamic-pituitary-adrenal axis, catecholamines, and cytokines. The gut microbiota also influence the brain and vice versa.[56]

Concomitant chronic illnesses enhance the risk for infection. Patients with a preexistent immune disturbance, such as a congenital immunodeficiency syndrome, are doubly jeopardized. The negative impact of smoking on patients with primary lung tumors is obvious and due to colonization of their airways with virulent encapsulated microorganisms and impaired clearance of secretions. Patients with diabetes mellitus are prone to genitourinary tract and wound infections, and they frequently have concurrent vascular disease and neuropathy. The proclivity to infection in patients with poorly controlled diabetes mellitus is not difficult to explain in view of aberrations such as impaired opsonization and decreased chemotactic activity of granulocytes and monocytes. Opportunistic bacteria and fungi depend on free iron for a growth advantage, and iron overload has been associated with infections with *P. aeruginosa,* staphylococci, *Vibrio vulnificus, Listeria monocytogenes, Yersinia enterocolitica,* and members of the order Mucorales.[57] In HSCT the risk for invasive mold disease has been related to iron overload.[58] Treatment of iron overload with deferoxamine predisposes to rhinocerebral and pulmonary mucormycosis by providing the fungus with an available source of iron.[59,60] The mechanisms of increased susceptibility to infection with iron overload are related to impairment of phagocytosis, chemotaxis, and cellular immunity.

Tumors themselves may predispose to infection through local organ dysfunction. In patients with solid tumors, obstruction of natural passages can lead to inadequate drainage of secretory or excretory fluids from nasal sinuses, bronchi, bile ducts, and so forth. Furthermore, tissue invasion may create connections between normally sterile spaces and the outside world through disruption of epithelial surfaces. Examples include perforation of the esophagus by mediastinal tumors, invasive gynecologic malignancies with local pelvic abscesses caused by gram-negative bacilli and anaerobes, skin ulceration with cellulitis and even deep soft tissue infections, and invasion of the bowel wall by tumors of the lower gastrointestinal tract with seeding of bacteria into the bloodstream. Central nervous system (CNS) tumors, spinal cord compression, and paraneoplastic neuropathy are associated with an increased risk for infection because of a diminished ability to cough and swallow or vomit and incomplete emptying of the bladder.

Treatment of malignancy inevitably damages healthy tissue. Even when the tumor is localized in a single area, relatively superficial, and readily removed, any surgery and local irradiation will nonetheless extend impairment of the normal defenses.

FEVER AND THE INFLAMMATORY RESPONSE

An infectious origin of a fever can be confirmed microbiologically or clinically in only 30% to 50% of all febrile neutropenic patients (Fig. 305.2). Infectious complications usually arise insidiously in these patients because of a muted inflammatory response and the lack of pus, which can be attributed to the absence of granulocytes; even the presence of chills or rigors does not always correspond with bacteremia.[61] However, foci of infections can also remain undetected because the physical examination

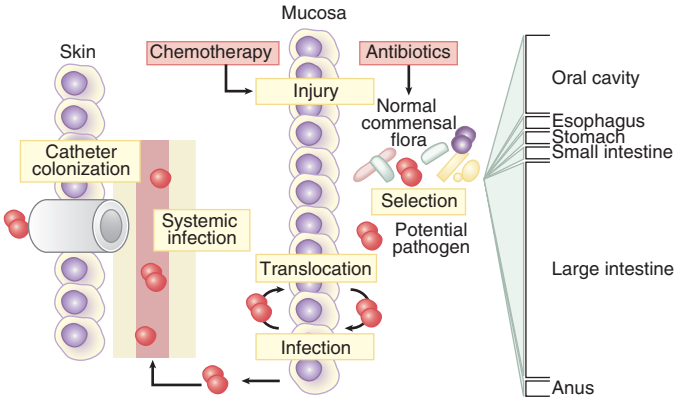

FIG. 305.2 Model to explain the origins of infection in neutropenic patients. Chemotherapy induces injury to the mucosal barrier. At the same time, antimicrobial agents used for prophylaxis (e.g., fluoroquinolones) exert selective pressure on the ecology, whereby more resistant members of the resident flora (e.g., viridans streptococci, staphylococci, gram-negative bacilli, and yeasts) increase in number. The gastric acid barrier of the stomach is usually breached by the use of drugs such as the histamine type 2 antagonists (e.g., ranitidine) and proton pump inhibitors (e.g., omeprazole) so that microorganisms that are ingested pass onward to the small intestine and beyond. Any colonization occurring on damaged mucosa would allow translocation from the alimentary tract or local infection, either of which can lead to bloodstream invasion and ultimately to systemic infection. In the case of the coagulase-negative staphylococci (e.g., *Staphylococcus epidermidis*), the alimentary tract might be the original source of bacteremia leading to colonization of the lumen of a vascular catheter.

was too cursory, specimens were either inappropriate or not collected at all, or the microbiologic investigations were incomplete or too insensitive. Obtaining a careful recent medical history and examining the patient thoroughly for any evidence of inflammation or infection should be considered obligatory, but getting a proper specimen is much more difficult because aspiration or biopsy is usually required, which is ill advised for thrombocytopenic patients. Besides, even when a specimen is obtained from a normally sterile site, the yield is generally low. Consequently, failure to undertake an adequate physical examination and to obtain appropriate samples will result in fever being unexplained. Yet the fact that most patients without any proven infection improve clinically after treatment with broad-spectrum antibacterial agents suggests the presence of an occult bacterial infection in many cases. However, noninfectious inflammatory complications of cancer therapy and transplantation contribute to episodes of unexplained fever because mucositis and GVHD are known to be inflammatory complications.[62,63]

Systemic Inflammatory Response Syndrome, Immune Reconstitution Inflammatory Syndrome, and Host-Directed Therapy (See Chapters 49 and 73)

Although neutropenic patients cannot mount a normal host response to tissue injury, the systemic inflammatory response syndrome and sepsis can and do develop when inflammation is uncontrolled and proinflammatory substances spread to other distant sites, ultimately leading to multiple organ dysfunction. Oral viridans streptococci elicit a proinflammatory response that may play a role in the pathogenesis of shock[64] but is associated with life-threatening complications, including septic shock and acute respiratory distress syndrome (ARDS). High-dose cytarabine in particular appears to predispose to these conditions.[65,66] Systemic inflammatory response syndromes are not always the result of endotoxemia or even infection and can be brought about by noninfective tissue injury, such as severe burns, acute pancreatitis, elective surgery, and trauma. They also result from extensive mucositis because the levels of some proinflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α, are elevated and parallel the course of mucosal damage after chemotherapy and conditioning therapy for HSCT. The degree of gastrointestinal mucositis after conditioning therapy as measured by low citrulline levels strongly correlates with the inflammatory response seen after HSCT and the occurrence of ARDS induced by viridans streptococci.[63] Determination of C-reactive protein and cytokines such as IL-6 is recommended by some for diagnosing bacterial infection,[67,68] whereas others remain unconvinced.[69,70] Fever as a symptom of a systemic inflammatory response can be measured, as can C-reactive protein, lipopolysaccharide-binding protein, and IL-8. The inflammatory response might precede bacteremia by several days.[71] Earlier observations indicated that ARDS associated with *S. mitis* bacteremia could be prevented through preemptive use of corticosteroids, pointing toward an imbalance in host-related inflammatory response.[72] Among Spanish patients admitted with severe community-acquired pneumonia and a high initial inflammatory response, the acute use of methylprednisolone compared with placebo decreased treatment failure.[73] Treatment failure was defined as development of shock, need for invasive mechanical ventilation, or early death. The proper and timely use of corticosteroids is still debated, as blocking the production of potent inflammatory cytokines activating local and systemic inflammatory processes that are involved in protective immune responses against infections could be detrimental instead. However, their dysregulated production and signaling can aggravate tissue damage during infection, inflammatory diseases, and chemotherapy-induced mucositis.

Corticosteroids are also used in the advent of an immune reconstitution inflammatory syndrome (IRIS). Increasing evidence suggests that chronic disseminated candidiasis is a form of IRIS.[74] A retrospective multicenter study of patients with symptomatic chronic disseminated candidiasis with fever unresponsive to antifungal therapy suggested that systemic corticosteroids for at least 3 weeks can result in rapid clinical improvement. The duration of antifungal therapy and corticosteroids in symptomatic chronic disseminated candidiasis patients has been reported to be as long as several months. The hallmark of IRIS is an increasing number of cytokine-activated neutrophils and monocytes producing myeloperoxidase and oxygen radicals that might promote clinical deterioration. But normalization of $CD4^+$ helper T cells (Th1 and Th17) and $CD8^+$ cytotoxic T cells after successful cancer therapy in general, and more specifically after HSCT, can occur. It is worth noting that new therapeutic modalities, such as bidirectional T-cell contacts and CAR T cells, may induce noninfectious inflammatory states—that is, the cytokine release syndrome.[75] In some cases, the pathophysiology will include defined roles of cytokines, such as IL-6, which limits their usefulness in the diagnosis of an infectious episode, and excessive cytokine release syndrome sometimes requires anti-IL-6 directed therapy (tocilizumab).[76] Nowadays the use of immune checkpoint inhibitor therapy of cancer (PD-1/PD-L1 antibodies) can induce severe immune-related organ toxicities that are difficult to distinguish from real infections and necessitate immediate immunosuppressive therapy. Of course, this latter use will increase the likelihood of opportunistic infections.[77]

On the other hand, host-directed therapeutic strategies are now becoming viable adjuncts to standard antimicrobial treatment. Host-directed therapies include commonly used drugs for noncommunicable diseases with good safety profiles, immunomodulatory agents, biologics (e.g., monoclonal antibodies), nutritional products, and cellular therapy using the patient's own immune or bone marrow mesenchymal stromal cells.[78]

INFECTIONS BY SITE

Bacteremia

Blood cultures are usually the most productive microbiologic investigation and help explain 10% to 40% of fevers, but the sensitivity of blood cultures is crucially dependent on the volume of blood cultured, with 30 to 40 mL per session being recommended for optimal results.,[79–83] It has become common practice to draw at least 10 mL of blood for culture by venipuncture when investigating fever immediately before starting empirical therapy, together with at least 10 mL through each lumen of a central vascular catheter when fever is present. During the past decade a change from gram-negative to gram-positive bacteria has occurred,[84] but virtually any microorganism can cause infection in severely immunosuppressed patients, depending on a variety of factors, including the type of cancer therapy, the use of antimicrobial agents, and whether the patient is at home or in the hospital. Infusion of the appropriate antibiotic through catheter ports that are culture positive may be helpful in clearing colonized catheters. Once therapy is started, the value of further blood cultures is small if the patient is responding clinically. Patients with catheter-acquired sepsis who remain febrile with positive blood cultures usually need their catheters removed. In the past, at least in clinical trials, blood cultures have been repeated 3 or 4 days after the start of empirical therapy, as a means of detecting persistent bacteremia.

Bacteremia Related to Intravascular Catheters

Coagulase-negative staphylococci are still the most common cause of catheter-acquired sepsis,[85] but they are also recovered from catheter-drawn blood under circumstances that suggest they are not causing the fever that prompted the blood culture. It is always easier to interpret the results of culturing of blood drawn from a peripheral vein. Simultaneous quantitative blood cultures from the catheter and a peripheral vein have been advocated but have not convincingly enabled discrimination between catheter-acquired sepsis, sepsis from another source, asymptomatic intraluminal colonization of the catheter, and accidental contamination that occurred while blood was being drawn from the catheter hub. The usefulness of differential time to positivity of blood cultures drawn through a catheter lumen in relation to those drawn simultaneously by venipuncture to distinguish "true bacteremia" from catheter-related bacteremia is debated.[86,87] In all cases, the decision to treat is based not just on the blood culture but also on the clinical findings. Infections associated with intravenous catheters are assumed to mostly originate from contamination of the catheter hub. The contaminated catheter may have already been removed since the culture was obtained, or the culture may have been contaminated at the time that blood was drawn. In afebrile patients, repeating blood cultures may be all that is indicated. In other cases, the organism can be cultured repeatedly from blood drawn through the same catheter port but not from blood drawn

peripherally, thus suggesting that the organism has not yet been able to cause sepsis but has colonized the catheter. Removing the device or administering antibiotics through the same port may be indicated to circumvent future sepsis[88] (see Chapter 300).

Bacteremia From the Gastrointestinal Tract

Oral viridans streptococcal bacteremia is related to mucosal barrier injury of the upper part of the digestive tract, particularly the oral cavity, whereas enteric gram-negative bacillary bacteremia and neutropenic enterocolitis are related to the lower part of the digestive tract. The digestive tract has long been implicated as the principal origin of infections caused by the enteric gram-negative bacilli, including *Escherichia coli, K. pneumoniae,* and *Enterobacter* spp., providing the motivation for adopting prophylaxis with fluoroquinolones.[89]. Especially in patients who prophylactically receive oral quinolones, oral viridans streptococci, usually *S. mitis,* will survive on damaged mucous membranes.[31,72] The signs and symptoms of viridans streptococcal infection might be inconspicuous to completely absent. In view of the direct correlation between the rate of positive blood cultures and the severity of damage to the mucosal surface, the normal habitat for these organisms, it is questionable whether viridans streptococci are true pathogens in all cases or whether they represent only an epiphenomenon.[63] In fact, during the course of a normal day, the acts of chewing and tooth brushing lead to transient bacteremia caused mainly by viridans streptococci. However, significant gastrointestinal mucositis has also been shown to predispose to bacteremia with coagulase-negative staphylococci and viridans streptococci.[90] Various coagulase-negative staphylococci, including *Staphylococcus epidermidis,* are also present in the endogenous microbiota of the digestive tract of neutropenic patients.[91] Plasmid pattern analysis of coagulase-negative staphylococcal bloodstream isolates showed that the mucosa was the origin of bacteremia in 70% of patients managed in a hematology ward of one center.[92] However, there is clear evidence that the coagulase-negative staphylococci responsible for bacteremia can originate from both the mucosa of the oral cavity and the gut, as well as from the catheter.[93] The use of new definitions of bloodstream infections (BSIs) such as CLA-BSI (central line–associated BSI, stratified as mucosal barrier injury–related, laboratory-confirmed BSI [MBI-LCBI] versus non–MBI-LCBI) and secondary BSI, using National Healthcare Safety Network (NHSN) definitions, could help in a patient-centered, clinically relevant approach to better assess across-center and within-center differences in infection rates, including CLA-BSI.

Oral Cavity Infections

The oral cavity is a complex region providing other likely portals of entry besides mucositis, which essentially affects the nonkeratinous areas of the inner lips, buccal mucosa, underside of the tongue, and roof of the mouth. Moreover, mucosal changes normally progress to a peak severity, coinciding independently with the nadir of bone marrow aplasia, and then begin to recover as hematopoiesis returns.[62] Extensive mucosal damage is often accompanied by a decline in saliva production, leading to dry mouth. Any mucus produced may be extremely viscous and difficult to either swallow or cough up. Periodontal disease may be exacerbated, and minor oral cuts and abrasions may become inflamed and ulcerated. The health of the periodontium probably also plays a role. For instance, organisms found in periodontal pockets, including viridans streptococci, appeared in the bloodstream of 13 (65%) of 20 patients soon after probing.[94] Tooth brushing[95,96] and more invasive procedures, including tooth extraction and periodontal and endodontic treatment, can also lead to transient bacteremia. Important to note, a recent prospective study supports the hypothesis that chronic oral foci of infection can be left untreated because this does not increase infectious complications during intensive chemotherapy.[97,98] Not surprisingly, the origin of several different species of bacteria-causing bacteremia has been traced to the oral cavity. These include, in addition to the oral viridans-group streptococci, *Fusobacterium* spp. and the related *Leptotrichia* spp.,[99] and even *S. epidermidis*.[92,100] Oral infections are difficult to diagnose by appearance in patients with mucositis. Polymerase chain reaction (PCR) assay (culture if drug resistance is suspected) of oral lesions for herpes simplex virus (HSV), even in the presence of prophylaxis, and smears of scrapings for *Candida* pseudohyphae can be helpful.

Respiratory Tract Infections

The proliferation of diagnostic assays, usually molecular, often available as multiplex panels, has increased the ability to detect organisms. The ability to clearly associate the findings from such assays with clinical disease remains a challenge. Nevertheless, previously innocuous pathogens such as rhinoviruses or even viruses (human herpesvirus 6 [HHV-6]) not considered respiratory pathogens are now detected in the lower respiratory tract of severely compromised patients and are associated with disease, although causality, as so often is the case in complex settings, has not been established.[101,102]

Apparently trivial complaints such as a persistent dry cough may prove to be early signs of impending pneumonia from *Aspergillus* spp., respiratory syncytial virus, or influenza virus. Thoracic computed tomographic scans are more sensitive in detecting pulmonary infiltrates compatible with aspergillosis than are plain chest radiographs.[103,104] Bronchoalveolar lavage specimens from patients with pulmonary infiltrates should undergo a battery of tests that usually includes smears for *P. jirovecii,* acid-fast bacilli, and *Nocardia* spp., bacteria, and molds, and culture for fungi and bacteria, including *Legionella* spp., *Mycobacterium* spp., *Nocardia* spp., and respiratory viruses (influenza and parainfluenza viruses, adenovirus, respiratory syncytial virus, and cytomegalovirus [CMV]). *Aspergillus* galactomannan antigen can also be detected in bronchoalveolar specimens, although the sensitivity and specificity of the test on respiratory specimens are unclear.[105,106,107] Changing patterns in prophylaxis in transplantation may explain the need to prolong the period of suspicion for CMV disease after lung transplantation.[108] Rapid assays by enzyme-linked immunosorbent assay, direct fluorescent antibody, or dot blot are also available for influenza virus, respiratory syncytial virus, and adenovirus but are often replaced by PCR now. Nasopharyngeal swabs in children and nasopharyngeal washes in adults, formerly used in culturing respiratory viruses in patients with upper respiratory symptoms, are now being tested with molecular panels, with results available within hours. These panels are also used on lower respiratory tract specimens. Molecular assays for *Pneumocystis* pneumonia await an international standard and further work to establish the appropriate thresholds for organism burden sufficient to diagnose disease, as reported in a multiinstitutional study from France.[109] Testing for *Legionella* antigen in the urine of patients with pneumonia is also useful when local epidemiology suggests that *Legionella pneumophila* type 1 is the predominant clinical isolate. *Toxoplasma gondii,* most commonly associated with CNS (including the eye) disease, may be an agent of aggressive pulmonary or disseminated disease, and PCR as a diagnostic tool with both cerebrospinal fluid (CSF; for CNS disease) and blood may allow early detection and treatment.[110]

Skin Infections

Identifying the cause of skin and underlying soft tissue infections is equally difficult because culturing swabs of lesions rarely discriminates between pathogens and commensal microbiota. As an exception, Gram stain and culture from pus expressed from a catheter exit site can be useful. Culture and histologic examination of skin punch biopsy specimens is very helpful in the diagnosis of isolated maculopapular or ulcerated lesions. Disseminated infections by *Candida* spp., *Trichosporon* spp., and *Fusarium* spp. in a neutropenic patient may manifest with skin lesions, while blood cultures remain negative. Skin lesions may be the source of *Fusarium* fungemia.[111] Ecthyma gangrenosum from *P. aeruginosa* may be accompanied by positive blood cultures, but *Aspergillus* spp. or the agents of mucormycosis can cause lesions with the same appearance in a neutropenic patient with negative blood cultures. These fungal lesions require biopsy for diagnosis. Aspiration of skin lesions is seldom successful unless pus is present. Cutaneous *L. pneumophila* and *Legionella longbeachae* (usually associated with potting compost), may occur in the context of transplant or chronic corticosteroid use. Biopsy is necessary to make the diagnosis.[112,113] New associations with specific immunosuppression may aid in the understanding of the physiology of some cutaneous infestations, as demonstrated by a nosocomial outbreak of Norwegian scabies in patients under TNF-α inhibitor treatment.[114] *Demodex* mites may proliferate in conditions that are associated with sebaceous gland dysfunction and cause a pruritic rash that resembles rosacea but may also be mistaken for GVHD.[115] Firm

diagnostic criteria to distinguish colonization of the skin from disease caused by the mites is lacking, although a heavy burden of infestation may suggest that a trial of ivermectin is appropriate.

The increasing breadth of defined immunocompromising conditions has also increased the understanding of the role of human papillomaviruses (HPVs) in skin disease, both warts and cancer. Careful screening for HPV and aggressive medical and surgical follow-up and vaccination are now commonly implemented.[116]

Gastrointestinal Tract Infections

It is difficult to diagnose enteric infection, especially when nausea, vomiting, diarrhea, bowel cramps, and melena can all be due to toxicity related to chemotherapy, irradiation, GVHD, or primary immunodeficiency. The role of norovirus continues to expand as a pathogen in patients with immunodeficiencies such as X-linked severe combined immunodeficiency who lack adequate humoral reconstitution after transplantation, in common variable immunodeficiency, and occasionally after solid-organ or hematologic malignancy transplantation.[117,118] Endoscopy can be critical in the diagnosis of herpes simplex, *Candida* spp., and CMV mucosal lesions. Molecular diagnostic panels that identify multiple targets retain the same caution as noted earlier; the virtue of high analytical sensitivity may be offset by the identification of infectious agents that are not the cause of disease, and there is insufficient guidance in current clinical experience to solve this problem. Detection of HSV and CMV in intestinal biopsy specimens can be enhanced if both culture and immunoperoxidase staining of the tissue are done. The gut microbiota can become the major reservoir of vancomycin-resistant enterococci, *Candida albicans, K. pneumoniae*, and *P. aeruginosa.* Organisms can be spread from the bowel onto the skin and, by the fecal-oral route, into the mouth. Skin organisms can be spread to other patients by the hands of health care workers and, through intravenous catheters, into a patient's bloodstream. Oral microbiota can be aspirated into the airway, particularly when the patient is intubated. Passage of bowel organisms into the bloodstream can occur through chemotherapy-induced ulcers. Fever in the presence of diarrhea or abdominal pain should prompt a PCR assay on stool for the *C. difficile* toxin gene. That test has largely replaced the more cumbersome cytotoxicity test. The enzyme immunoassay for toxin is less sensitive. Neutropenic patients with right lower quadrant pain may have developed neutropenic enterocolitis, which predominantly localizes in the cecum, the diagnosis of which can be supported by an edematous colonic wall on abdominal contrast-enhanced computed tomography. Recovery of *C. septicum* from the bloodstream usually portends neutropenic enterocolitis. In view of the extent of the damage in many cases, it is not surprising that *C. septicum* and *Clostridium perfringens* septicemia, classically with massive hemolysis and diffuse intravascular coagulation, can arise,[119] but also various toxin-producing bacteria, including *S. aureus, P. aeruginosa,* and even *B. cereus.*[120–123] Neutropenic enterocolitis is also an independent risk factor for invasive candidiasis. Colonization by *Candida* spp. of the mucosal surfaces appears to be a prerequisite for local mucosal infection and subsequent invasive disease.[124] Mucosal barrier injury and exposure to antimicrobial agents may explain the emergence of most infections arising in neutropenic patients (Fig. 305.3).

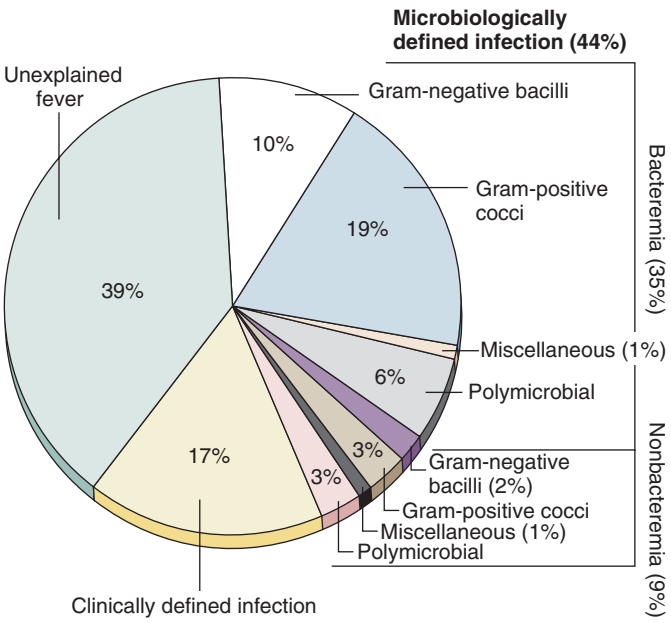

FIG. 305.3 Causes of infection in 968 episodes of fever and neutropenia. *(Unpublished data derived from the study of De Pauw BE, Deresinski SC, Feld R, et al. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer: a multicenter randomized trial.* Ann Intern Med. *1994;120:834–844.)*

Urinary Tract Infections

Urine should be obtained for standard culture when there are signs or symptoms of a urinary tract infection, but not otherwise. Urine from patients after HSCT who have hemorrhagic cystitis should be tested for adenovirus by culture, and BK virus quantity by PCR assay. Although classically a cause of nephritis in the transplanted kidney, native organ disease caused by BK virus after solid-organ and hematopoietic transplantation has been reported.[125,126] Urinary tract infections, although rare in the absence of a Foley catheter, can be initiated through hematogenous spread from the gut and by means of perianal or vaginal contamination.

Central Nervous System Infections

Infections of the neuraxis can be difficult to diagnose in patients whose thrombocytopenia is not sufficiently correctable by platelet transfusion to permit lumbar puncture. CSF is useful not only for microbial culture but also for testing of cryptococcal polysaccharide, *Aspergillus* galactomannan, flow cytometry or cytology for malignant cells, and PCR for JC virus, CMV, Epstein-Barr virus (EBV), and HHV-6. CNS infection is usually hematogenous, although direct infection can occur as a rare complication of neurosurgery, intrathecal cancer chemotherapy, or extension of invasive mold sinusitis. Magnetic resonance imaging is the imaging procedure of choice, particularly with fluid-attenuated inversion recovery (FLAIR) imaging. Positron-emission tomography (PET) scan with ^{18}F-fluorodeoxyglucose is of limited usefulness in distinguishing malignant from infectious brain lesions in cancer patients, in that both can be PET avid.

Diagnosis can be challenging in the absence of CSF or brain biopsy, but diagnosing a brain abscess in an immunosuppressed patient based on diagnosis of a lung lesion with a probable agent, such as *Nocardia*, *Aspergillus*, or *Mucorales,* may be sufficient. Clinical syndromes are rarely diagnostic, although the posterior reversible encephalopathy syndrome (PRES) is distinctive. Limbic encephalitis caused by HHV-6 should be considered in allogeneic stem cell transplant patients, particularly those receiving cord blood cells, who have memory loss, decreased consciousness, and seizures.[128] The use of OKT-3 or alemtuzumab for in vivo T-cell depletion is associated with an increased risk of viral encephalitis after allogeneic stem cell transplantation. Different viruses (HHV-6 [28%], EBV [19%], HSV [13%], JC virus [9%], varicella-zoster virus [VZV; 6%], CMV [6%], and adenovirus [3%] in 32 patients with a viral encephalitis out of 2628 HSCT patients) are frequently associated with distinct characteristics, such as onset time, response to treatment, and outcome. Patients with HSV encephalitis had the most favorable outcome, with no encephalitis-related deaths.

Liver Infections

The presence of markers of hepatic inflammation or biliary tract obstruction should initiate a search for infectious etiologies. Serologic screening for acute disease in this context is insufficient, and PCR for hepatotropic viruses should include hepatitis B, C, and E (if available), in addition to organ-specific or disseminated infections with adenovirus and CMV.

Two considerations related to hepatotropic viruses deserve emphasis. First, the course of infection with a virus in the immunocompromised patient can be aggressive (hepatitis A and E) or lead to chronicity (hepatitis E).[129,130] Although the incidence of development of acute

hepatitis E after allogeneic HSCT is relatively low, the probability of development of chronic hepatitis with genotype 3 in severely immunocompromised patients is high. Therefore, before transplantation, allogeneic HSCT recipients from countries where genotype 3 is prevalent should be screened with hepatitis E virus (HEV) serology and RNA. Furthermore, a differential diagnosis, including hepatitis E, is mandatory in all allogeneic HSCT patients with severe liver enzyme abnormalities. Second, immunodeficiencies and chemotherapy (especially B-cell–depleting agents) may allow the recrudescence or progression from asymptomatic chronicity or latency of hepatitis B virus. Thus, screening for hepatitis B antecedent to iatrogenic immunosuppression is recommended, and prophylactic strategies include anti–hepatitis B immunoglobulin (usually after orthotopic liver transplant) and antiviral agents such as entecavir, which may be preferred over older agents such as lamivudine.[131,132]

SEQUENCE OF INFECTIONS

The sequence of risk factors (Fig. 305.4) determines to a large extent the order of infectious events in granulocytopenic cancer patients, which means that the types of infection occurring early in the granulocytopenic period differ from late infectious complications. Profound neutropenia and mucosal damage usually ensue approximately 10 days after initiation of a course of chemotherapy and are followed by fever and bacteremia within a few days, when toxicity is at its most pronounced. Clinically defined infections usually lag behind by a few days. Invasive pulmonary aspergillosis develops in a few patients early in the course of neutropenia.[133] Infections related to central venous catheters have to be considered approximately 10 days after their insertion, with the risk increasing with the length of time that the catheter is left in place.[85]

The initial risk period resolves with recovery of the granulocyte count. Very intensively treated patients are still at risk because of granulocytopathy, deficient cell-mediated immunity, and hypogammaglobulinemia. The kind of infectious complications for such patients is determined by the pace of reconstitution of these other components of the immune system (Fig. 305.5).[134] The major factor that influences immunologic reconstitution after allogeneic stem cell transplantation is acute GVHD and its treatment. CMV, adenovirus, and fungi, including *P. jirovecii,* constitute the major pathogens during this episode. A third major risk period in these patients begins approximately 3 months after allogeneic stem cell transplantation, when chronic GVHD develops. Sinopulmonary infections and cutaneous infections are common and probably related to the IgA deficiency, with or without sicca syndrome and severely impaired cellular immunity. Varicella-zoster is probably the most frequent cutaneous infection, and pulmonary infections caused by CMV and *P. jirovecii* are regularly encountered. Months, if not years, after successful engraftment or recovery from other very aggressive treatment, encapsulated organisms can cause rapidly fatal bacteremia and severe respiratory tract infections because of the lack of opsonizing antibodies.

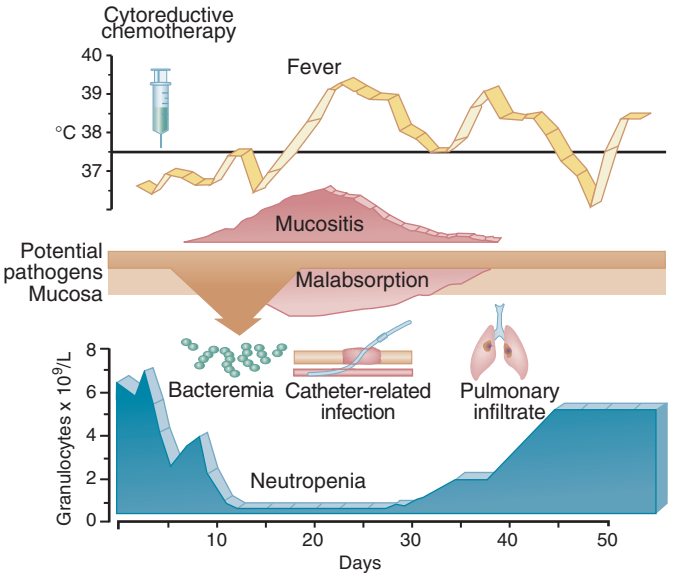

FIG. 305.4 Sequence of events during neutropenia. Profound neutropenia and mucosal damage usually develop approximately 1 week after the start of cytoreductive chemotherapy. Thereafter, infectious and other complications tend to coincide with one another, placing the patient at greatest risk. Fever develops approximately 1 week later, and if there is bacteremia, it mostly occurs at this time. The risk for infections related to the central venous catheter increases with the length of time that the catheter is left in place, but signs and symptoms usually manifest during the first few days of fever—that is, during the third week after the start of chemotherapy. Infectious complications related to the lung tend to occur a few days later and often are recognized only after 5 or 6 days of fever. The period of risk for bacterial and fungal infection diminishes with recovery of the granulocytes, when the clinical manifestations of tissue infections may be temporarily exacerbated before finally resolving.

ROLE OF MOLECULAR DIAGNOSTICS IN INFECTIONS IN THE IMMUNOCOMPROMISED HOST

Molecular diagnosis, most often PCR based, continues to increase in frequency and breadth. The labor and material burdens of traditional culture-based diagnostics limit their use, and the appearance of multiplex panels with little need for operator training explains the proliferation of this technology. Panels for the detection of viral, bacterial, and fungal pathogens are in use for respiratory, gastrointestinal, blood, and CSF specimens, with the determination of drug susceptibility targets not far behind. In considering molecular diagnostics in the immunocompromised host, several considerations should be taken. First, a broad literature that assesses potential differences in sensitivity and specificity by host predisposition is generally lacking. Second, the immunocompromised host may provide a substrate with competing diagnostic considerations (e.g., GVHD in hematologic transplant) that make the issue of specificity crucial. Third, drug susceptibility testing tends to still be culture derived, and so limiting diagnosis to molecular assays, until such assays include well-defined approaches to resistance determinants, has flaws. Finally, a lack of specificity may be an important flaw when assessing results as positive for rhinovirus or enterovirus, because specific viruses or strains may be important in different contexts (enterovirus D68 in recent outbreaks of severe respiratory tract disease in hematologic or transplant patients or coxsackievirus in CNS disease in patients with rituximab-induced loss of humoral immunity).[135,136]

Nevertheless, these sensitive assays improve our understanding of the range of pathogens whose role in disease processes must be understood. Furthermore, the sensitivity of molecular diagnostics for rapid detection of pathogens to prevent nosocomial spread is a major advance. This is demonstrated for pathogens newly discovered (a novel poxvirus associated with equine exposure) or not previously commonly diagnosed (human metapneumovirus). These sensitive tests may help to define possible transmission patterns *(P. jirovecii)*[137–139] and understand persistence of infection with agents such as influenza virus, norovirus, or varicella virus (vaccine strain), whose course may be atypical and prolonged in some patients.[140–142] Finally, new pathogens such as astrovirus VA1/HMO-C, reported as a cause of encephalitis, are now identified through use of deep sequencing, a technology whose general application is yet to be determined.[143]

CONCLUSION

Bacterial infections were once a major obstacle to the treatment of patients with acute leukemia. Improvement in management strategies, including the use of broad-spectrum antibacterial drugs targeting gram-negative bacteria, has reduced the mortality in neutropenic patients who develop bacteremia and other severe infections. In many countries these achievements are threatened by development of multidrug-resistant bacteria, such as *K. pneumoniae, P. aeruginosa,* and methicillin-resistant *S. aureus,* but also triazole-resistant *Aspergillus* spp. New approaches are required in order to overcome "old" infectious complications in immunocompromised hosts.[144]

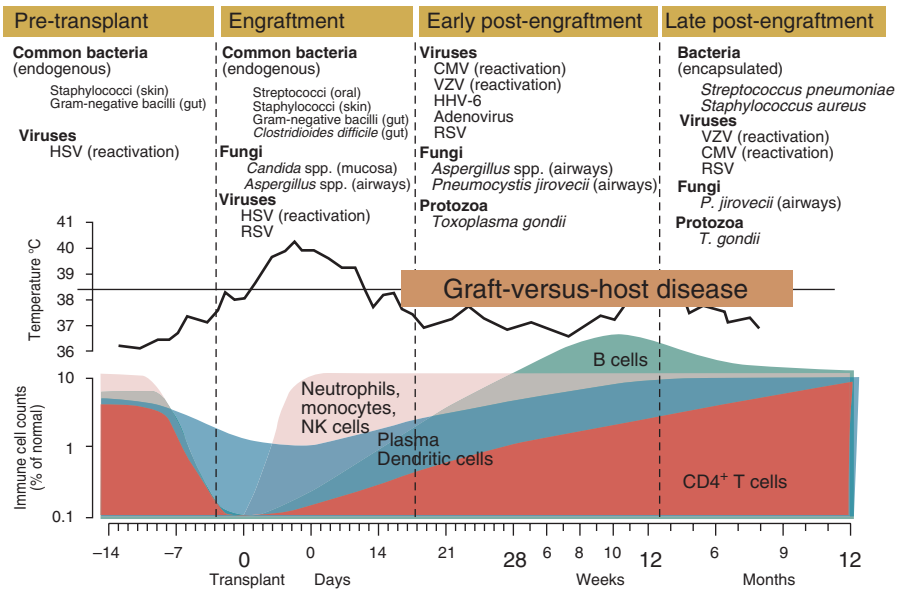

FIG. 305.5 Infectious phases after transplant. The infectious complications that occur most commonly are set against the phases before and after an allogeneic hematopoietic stem cell transplant. Note that the time scale progresses from days to weeks, then to months. The fluctuations in the different components of the immune system are represented at the bottom of the figure and show when severe deficiency coincides with the time of engraftment and begins to recover thereafter. The various classes of microorganism change during the different phases, but note that viruses and fungi can cause infections throughout the entire period. *CMV,* Cytomegalovirus; *HHV-6,* human herpesvirus 6; *HSV,* herpes simplex virus; *NK,* natural killer; *RSV,* respiratory syncytial virus; *VZV,* varicella-zoster virus.

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The complete reference list is available online at Expert Consult.

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