Amar Safdar
Editor

Principles and Practice of Transplant Infectious Diseases

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ISBN 978-1-4939-9032-0 ISBN 978-1-4939-9034-4 (eBook)
https://doi.org/10.1007/978-1-4939-9034-4

This Springer imprint is published by the registered company Springer Science+Business Media, LLC part of Springer Nature.
The registered company address is: 233 Spring Street, New York, NY 10013, U.S.A.

This book is dedicated to my parents, Taj & Safdar, for enduring inspiration and tenacity of purpose.

Preface

In pursuit of recognizing the risk of infection in patients undergoing transplantation, prescient cognizance requires sagacious understanding of hosts' home and healthcare environment, factors pertaining to the level of immune suppression that may have accumulated overtime, and, importantly, recent alterations in immune function resulting from additional immunosuppressive treatments such as donor lymphocyte transfusion, antineoplastic therapy, and immune modulatory biologic drugs and medical disorders like graft-versus-host disease, donor allograft rejection, posttransplant opportunistic malignancies, recrudescent or newly acquired cytomegalovirus infection, and relapsed hematologic neoplasms.

It is prudent to establish a targeted approach toward diagnosis, an approach which portends recognition of the true etiology with the help of assiduous investigation based on patient-specific vulnerability for infection. Special consideration needs to be placed upon the possibility of noninfectious processes that clinically are often difficult to distinguish from infection or sepsis-like syndrome. Toxicity due to commonly used drugs in the posttransplant period, thromboembolic events, acute engraftment syndrome, postsurgical deep tissue and body cavity hematoma, tissue ischemia and necrosis, opportunistic malignancies, and the potential for less common paraneoplastic disorders including tumor fever may initially present as a nonspecific acute febrile illness, with or without features suggestive of systemic inflammatory response syndrome. Similarly, a host of noninfectious maladies involving the skin and skin structures, brain, orointestinal tract, liver, kidneys, and lungs may clinically resemble infection. It is important to take into account that such processes may occur concurrently or sequentially in patients with a known infection diagnosis. Furthermore, in immunosuppressed patients after hematopoietic or solid organ allograft transplantation, plurality of simultaneously occurring infections makes selection of targeted, pathogen-specific empiric therapy a daunting task.

Individuals' genetic haecceity and its influence on susceptibility or inherent resistance to certain infections is evolving. Once validated and available for clinical use, this has the potential to reliably identify select subgroups of transplant recipients that are additionally vulnerable to specific infection(s). Infection prevention and empiric or preemptive treatment strategies in such patients may advance from the putative and arbitrary risk profiles presently in use.

This volume aims to provide a comprehensive and in-depth review of the issues pertaining to infectious diseases in patients undergoing transplantation.

El Paso, TX, USA — Amar Safdar, MD

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Part I

Principles of Transplantation and Overview of Infectious Diseases

Infections in Transplantation: Introduction and Overview

1

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Transplantation remains a pioneering scientific innovation that has a significant impact on restoring well-being for patients and benefit society as a whole. Blood and marrow hematopoietic stem cells have become accepted and, in some instances, established approach to treat incurable neoplastic diseases and congenital disorders of immune system [1]. Similarly, use of allografts in patients with end-stage organ disease involving the liver, kidneys, intestines, heart, and lungs has provided a possibility for continuation of life and a potential for patients to integrate and resume participation in their communities [2]. Recent advances in limb, integument, and face transplantation underscore the substantial leap forward in restoring normalcy for individuals with devastating and often catastrophic physical encumbrance [3, 4].

In patients undergoing solid organ transplantation, advancement in understanding the complex interplay within various facets of immune response against the transplanted allogeneic tissue that recipients' immune system fails to recognize as "self" has resulted in encouraging long-term outcomes [5]. These achievements in decoding higher mammalian immunity underscore the recent progress made in development and implementation of refined strategies to harness potentially devastating immune rejection of the implanted solid organ allograft [6]. The antirejection strategies, as expected, involve a delicate balance that favors preservation of a functioning allograft and aims at limit severity of drug-induced suppression of recipients' immune function, which is crucial for the surveillance against various neoplastic processes; conventional and opportunistic infections.

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A similar, albeit an opposing role of undesired immune response comes into play in patients undergoing hematopoietic blood and marrow stem cell transplantation from a foreign donor. The conflict arises from aforementioned disconnect between immune recognition of self versus nonself [7, 8]. These transplanted stem cells install foreign effector immune cells in the recipient, and if remain unabated, the resulting graft-versus-host disease is capable of unleashing potentially ruinous systemic inflammation resulting in irreversible tissue damage and death [7]. The stem cell graft restores immunity and functional marrow in patients in need for myeloablative antineoplastic therapy. Furthermore, it is the foreign, graft-mediated, adaptive cancer immune surveillance that has now been widely recognized as the pivotal feature that sustains cancer in remission following successful allogeneic hematopoietic stem cell transplantation. This feature of stem cell graft-assisted antitumor response is recognized as "graft-versus-leukemia or graft-versus-tumor effect." Donor-derived adaptive antitumor immunity is an important objective of allogeneic stem cell transplantation, especially in patients with hematologic malignancies, and forms the bases for donor lymphocyte infusions to treat cancer recurrences during posttransplant period [9]. As in patients following solid organ transplants, in recipients of allogeneic HSCT, anti-GVHD therapy is assessed and continuously refined to achieve the lowest possible cumulative iatrogenic immune suppression required to prevent or treat GVHD, whereas an earnest attempt is made for preservation of recipients' immune function such that the risk of conventional and opportunistic infections and malignancies do not overwhelm the projected efficacy and feasibility of these lifesaving procedures.

A number of agents have been successfully used for prevention and treatment of graft-versus-host disease and solid organ allograft rejection [8, 10]. Severity of immune dysfunction is in most instance a direct consequence of treatment with these agents that are commonly prescribed

A. Safdar (ed.), *Principles and Practice of Transplant Infectious Diseases*, https://doi.org/10.1007/978-1-4939-9034-4_1

as combination drug regimens. Cyclosporine was the first major breakthrough in this regard; subsequent generation calcineurin inhibitors (CNI) have improved therapeutic index although resultant severe immune suppression and the risk for opportunistic infection like CMV, BK virus, and certain posttransplant cancers question the therapeutic feasibility for agents such as tacrolimus, especially in patients with low risk for allograft-related complications. Serious infections due to cytomegalovirus including viremia and end-organ disease, BK virus viremia, viruria, and BK virus allograft nephropathy with risk for potential graft compromise, rare progressive multifocal leukoencephalopathy due to polyomavirus, higher potential for opportunist cancers such as Kaposi's sarcoma, EBV lymphoproliferative disorders among others, are well-recognized limitations in individuals given tacrolimus for extended duration with doses leading to prolong high serum drug concentration [11]. Experience with sirolimus, a macrolide xenobiotic that induces potent immune suppression via inhibition of mechanistic target of rapamycin (mTOR; a conserved threonine and serine protein kinase) was associated with lower incidence of CMV infection in solid organ transplant recipients. This protective antiviral effect of mTOR inhibitors against BK virus nephropathy after renal transplantation has not been noted consistently. Additionally, antitumor properties of mTOR inhibitors may favorably influence the lower incidence and risk for posttransplant malignancies in recipients of solid organ allografts, especially those with a profile that indicates low risk for graft rejection [12].

Monoclonal antibodies against T- and B-cell pathways have also gained prominence, as potential treatment options. Alemtuzumab (Campath) is a monoclonal antibody that targets C52 antigen expressed on all lymphocytes. Treatment with Campath results in profound lymphocyte depletion. The drug-induced immune suppression may last for up to 9 months, although maximum degree of lymphopenia is noted between 8 and 9 weeks after therapy. As part of HSCT preparatory condition regimen, treatment with alemtuzumab was associated with reduced risk for GVHD following allogeneic hematopoietic stem cell transplantation [13].

In kidney transplant recipients, the risk for organ rejection was low in patients given alemtuzumab; however, this benefit was mainly observed in patients that were at a low risk for allograft rejection [14]. Other trials are underway with the aim to explore regimen(s) that may spare CNI (tacrolimus) for the prevention of allograft rejection.

Humanized monoclonal antibody rituximab that targets CD20 antigen expressed prominently and selectively on B lymphocytes forms the cornerstone for treatment of solid organ antibody-mediated renal allograft rejection. It is also considered the standard of care for the treatment of posttransplant B-cell lymphoproliferative disorders [15].

Systemic glucocorticoids have maintained relevance in drug cocktails given to prevent and treat solid organ graft rejection and GVHD. Since the early observation enabled addition of corticosteroids to successfully reduce cyclosporine dose that was traditionally needed to prevent rejection of transplanted allograft, this observation was regarded as a major breakthrough and forged the path for preservation of transplanted organs without serious, life-threatening CNI toxicity. Detailed discussion regarding immunosuppressive agents for prevention and treatment of allograft rejection is provided in chapters throughout this book.

A keen understanding of patients' underlying immune defect(s) is the knowledge cornerstone, essential for optimizing infection risk stratification, assessing need for preventive, preemptive or empiric antimicrobial therapy. This information serves as an imperative in establishing meaningful patient-centered management and infection prevention paradigm [16, 17]. Table 1.1 provides an outline for such a relationship between underlying immune defects and susceptibility for particular group of pathogens. It is also important to note that a combination of unrelated immune defects may overlap. Furthermore, such patients may present with multiple infections concurrently, sequentially, or in close proximity to a primary infection episode, with a variety of conventional and opportunistic microorganisms.

An extensive exposure to hospital environment poses risk for transplant recipients to acquire infections that may not respond to conventional antimicrobial drugs. The recent interest in exploring the potential influence of perturbation and reorganization of hosts' microbial flora or microbiota resulting from extensive exposure to healthcare environment, broad-spectrum antimicrobial drugs among other factors, has yielded greater insight into a field that was largely underappreciated for decades. Altered orointestinal microbiota has been proposed in limited observational studies to influence the risk for acquiring infection, recurrence of previously resolved infection, suboptimum response to antimicrobial therapy, and importantly, long-term viability of the transplanted allograft [18–20]. The possibility of noninfectious complications and their potential relationship with altered hosts' microbiota are currently under investigation.

An important approach in the assessment of transplant patients lends from the understanding and knowledge of temporal relationship for the risk of infection that may occur during various clinical phases after transplantation procedure (Table 1.2, with Figs. 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6). For example, patients with long-standing chronic GVHD are

Table 1.1 Infections in transplant patients in relationship with the underlying immune defects

Immune defect	Bacteria	Yeasts and dimorphic fungi	Filamentous molds	Viruses	Parasites
Granulocytopenia	*Staphylococcus aureus*	*Candida* spp.	Hyalohyphomycetes (hyaline or clear wall)	Herpes simplex virus type I and II	
[ANC < 500 cell/ml]	*Streptococcus pneumoniae*	*Candida albicans*[a]	*Aspergillus fumigatus*	Varicella zoster virus	
	Streptococcus gp A, and gp B	Non-*albicans Candida* spp.	*Aspergillus flavus*		
	Enterococci including VRE[b]	*Candida glabrata*[c]	*Aspergillus niger*		
	Coagulase-negative *Staphylococcus*[d]	*Candida krusei*[e]	*Aspergillus terreus*[f]		
	Enterobacteriaceae	*Candida parapsilosis*[g]	*Aspergillus nidulans*		
	Escherichia coli	*Candida guilliermondii*[g]	Non-*Aspergillus* hyalohyphomycetes		
	Klebsiella species	Non-*Candida* yeasts[h]	*Fusarium* spp.[i]		
	Enterobacter spp.	*Trichosporon asahii*	*Paecilomyces*		
	Proteus spp.	*Saprochaete capitata*[j]	Mucormycoses		
	Citrobacter spp.	*Saccharomyces*	*Mucorales species*[k]		
	Serratia spp.	*Magnusiomyces capitatus*	Dematiaceous (black or melanin pigmented) molds		
	Nonfermentative gram-negative bacteria	*Rhodotorula mucilaginosa*	*Alternaria*, *Bipolaris*, *Curvularia*, *Exserohilum* spp.		
	Pseudomonas aeruginosa	*Wickerhamomyces anomalus*	*Pseudallescheria boydii*		
	Stenotrophomonas maltophilia	*Pichia kudriavzevii*	*Scedosporium apiospermum*		
	Acinetobacter species	*Cyberlindnera fabianii*	*Scedosporium prolificans*		
	Achromobacter spp.	*Kodamaea ohmeri*			
		Lodderomyces elongisporus			
		Pseudozyma			
Cellular immune defects	*Nocardia asteroides complex*	*Cryptococcus neoformans*	*Aspergillus* spp.	Human cytomegalovirus	*Toxoplasma gondii*
	Salmonella typhimurium	Endemic mycoses	Non-*Aspergillus* hyalohyphomycetes	Respiratory viruses	*Strongyloides stercoralis*[l]
	Salmonella enteritidis	*Histoplasma capsulatum*	*Pneumocystis jirovecii*	Influenza A and influenza B	*Microsporidium* spp.
	Rhodococcus equi	*Coccidioides immitis*	Dematiaceous (black pigmented wall) molds	Respiratory syncytial virus	*Cryptosporidium*
	Rhodococcus bronchialis	*Blastomyces dermatitidis*	Mucormycoses	Parainfluenza type-3	*Microspora* spp.
	Listeria monocytogenes	*Paracoccidioides brasiliensis*	*Cryptococcus neoformans*	Adenovirus	*Cyclospora* spp.
	Mycobacterium tuberculosis		Endemic mycoses	Human coronavirus HKU1, NL63, OC43 and C229E[m]	*Leishmania donovani*[n]
	Nontuberculous mycobacteria		*Histoplasma capsulatum*	Corona virus, SARS, MERS[o]	*Leishmania infantum*[p]
	Legionella spp.		*Coccidioides immitis*	Human metapneumovirus[q]	
	Yersinia spp.		*Blastomyces dermatitidis*	Varicella	
	Campylobacter jejuni[r]		*Paracoccidioides brasiliensis*	Varicella zoster virus	
				Human herpes virus 6	
				Parvovirus B19	
				Hantavirus	

(continued)

Table 1.1 (continued)

Immune defect	Bacteria	Yeasts and dimorphic fungi	Filamentous molds	Viruses	Parasites
Humoral immune defects	Encapsulated bacteria			Varicella zoster virus[s]	*Giardia lamblia*
	Streptococcus pneumoniae			Echovirus and other enteroviruses	*Babesia microti*
	Haemophilus influenzae				
	Neisseria meningitidis				
	Campylobacter jejuni				
Splenectomy and functional hyposplenism	Encapsulated bacteria				*Giardia lamblia*
	Streptococcus pneumoniae				*Babesia microti*
	Haemophilus influenzae				
	Neisseria meningitidis				
	Capnocytophaga canimorsus				
Mixed immune defects	*Streptococcus pneumoniae*		*Pneumocystis jirovecii*	Respiratory viruses	*Toxoplasma gondii*
	Staphylococcus aureus		*Aspergillus* spp.	Adenovirus	*Strongyloides stercoralis*
	Haemophilus influenzae		*Candida* spp.	Varicella zoster virus	
	Klebsiella pneumonia		*Cryptococcus neoformans*		
	Pseudomonas aeruginosa		Mucormycoses		
	Acinetobacter spp.		Endemic mycoses		
	Enterobacter spp.		Dematiaceous (black) molds		
	Stenotrophomonas maltophilia				
	Nocardia asteroides complex				
	Listeria monocytogenes				
	Legionella spp.				
	Campylobacter jejuni				

Patients with mixed immune defects include recipients of allogeneic hematopoietic stem cell transplant; patients receiving treatment for acute or chronic graft-versus-host disease; acute or chronic solid organ allograft rejection

Abbreviations: VRE vancomycin-resistant enterococci, *SARS* severe acute respiratory syndrome, *MERS* Middle East respiratory syndrome

[a]In the past two decades, the prevalence of non-albicans invasive candidiasis is seen in excess of *Candida albicans* infections; the emergence of invasive disease due to *Candida auris* with limited susceptibility to currently used antifungal drugs is a challenge

[b]Certain transplant units across the USA have seen a high level of VRE colonization and subsequent risk for invasive disease; these infections are often a surrogate and reflect hosts' high-risk status

[c]Increasing reports of echinocandin resistance among clinical isolates of *C. glabrata* is an alarming trend, where this to become more prominent in the future

[d]Among CoNS group of bacteria, an emerging and recently described highly virulent *Staphylococcus lugdunensis* causes tissue-destructive infections similar to *S. aureus* with an emphasis on necrotizing and difficult-to-treat endocarditis

[e]*Candida krusei* is intrinsically nonsusceptible to fluconazole and to some extent itraconazole; these yeasts are uniformly susceptible to the broad-spectrum triazoles such as voriconazole, posaconazole, and isavuconazonium sulfate

[f]*Aspergillus terreus* is the only clinically relevant *Aspergillus* species that exhibit variable degree of resistance to amphotericin B, thereby increasing the probability of failure to amphotericin-based therapy

[g]*Candida parapsilosis* and *C. guilliermondii* have demonstrated less inherent in vitro susceptibility to the echinocandins; alternative antifungal agents are suggested to treat such infections

[h]Non-*Candida* and non-Cryptococcal yeasts are rare cause of fungemia seen mainly in patients with severe immune dysfunction and those with chronic lung disease

[i]*Fusarium* spp. infections are now increasingly attributed to food-related intestinal tract colonization and invasive disease during periods of severe immune suppression, such as profound and prolonged neutropenia, especially in patients with extensive orointestinal mucosal disruption; other filamentous fungal pathogens from food are *Aspergillus* and *Mucor* spp. Rare organisms linked to food and food products include *Lichtheimia*, *Curvularia*, *Phoma*, *Trichoderma*, *Alternaria*, *Acremonium*, *Paecilomyces*, *Penicillium*, *Achaetomium*, *Amesia*, *Botryotrichum*, *Chaetomium*, *Dichotomopilus*; *Microascus*, *Scopulariopsis*, and *Wallemia*. *Mucor circinelloides* was isolated from yogurt samples and presumed to cause illness in >200 consumers

Table 1.1 (continued)

[j]*Geotrichum capitatum* is now named *Saprochaete capitata*
[k]Mucormycoses in transplant recipients remain an uncommon cause of invasive fungal disease, although patients with voriconazole breakthrough mold disease have significantly higher probability of mucormycosis
[l]*Strongyloides stercoralis* may lead to serious, life-threatening hyperinfection syndrome in patients with marked cellular immune defects following allogeneic allograft transplantation, albeit, this remains a rare complication in patients undergoing transplantation even in the endemic regions
[m]These strains of human coronavirus may cause potentially serious lower respiratory tract disease in the immunocompromised host
[n]*L. donovani* and *L. infantum* may lead to serious visceral leishmaniasis in patients with profound cellular immune defects; *L. donovani* is seen in Africa and Asia
[o]These novel outbreak stains of coronavirus have been observed to cause serious illness in immunosuppressed patients and those with diabetes mellitus, ischemic heart disease, or end-stage kidney disease
[p]*L. infantum* is seen in Africa, Europe, Mediterranean, Central and South America
[q]Systemic extrapulmonary infection including viral encephalitis along with viral pneumonitis in allogeneic stem cell transplant recipients has been noted to cause devastating and life-threatening illness
[r]The incidence of campylobacter disease in AIDS patients is 40-fold higher than in the general population; patients with humoral and cellular immune defects are considered susceptible; it is important to recognize the serious sequelae such as Guillain-Barre syndrome, and reactive arthritis may follow acute infection episode in a small group of patients
[s]VZV is rarely associated with systemic dissemination in patients with humoral immune defects or even those with mixed immune dysfunctions

Table 1.2 Infections in recipients of allogeneic hematopoietic stem cell transplantation

Pathogens	Pretransplant disease or high-risk exposure-related infections	Pre-engraftment during neutropenia (0–30 days)	Post-engraftment including acute GVHD (30–100 days)	Posttransplant including chronic GVHD (>100 days)	Posttransplant seasonal community-onset infections
Bacteria	*Streptococcus pneumoniae*[a]	*Staphylococcus aureus*[b]	GPB and GNB bacteremia[c]	Encapsulated bacteria[d]	Community acquired pneumonia
	Staphylococcus aureus[b]	Coagulase-negative staphylococcus[e]	*Listeria monocytogenes*[f]	GPB and GNB bacteremia[c]	Community onset sinusitis
	Coagulase-negative staphylococcus[e]	*Enterobacteriaceae*[g]	Nocardiosis[h]	*Listeria monocytogenes*	Community onset or travel-related enterocolits
	Enterobacteriaceae[g]	*Escherichia coli*		Nocardiosis	Community onset urinary tract infection including pyelonephritis
	Escherichia coli	*Klebsiella pneumoniae and Klebsiella oxytoca*			Community onset *Clostridium difficile*-associated diarrhea
	Klebsiella pneumoniae and Klebsiella oxytoca	Nonfermentative gram-negatives[i]			
	Nonfermentative gram-negatives[i]	*Pseudomonas aeruginosa*			
	Pseudomonas aeruginosa	*Stenotrophomonas maltophilia*			
	Stenotrophomonas maltophilia	*Clostridium difficile*-associated diarrhea[j]			
	Clostridium difficile-associated diarrhea[j]				
Mycobacteria	*M. tuberculosis*[k]			Reactivation of latent tuberculosis	
	M. kansasii[l]			Relapse of previously treated *M. kansasii* infection	
	Nontuberculous mycobacteria			New or relapse MAC infection[m]	
	Rapid-growing mycobacteria				
	Slow-growing mycobacteria				

(continued)

Table 1.2 (continued)

Pathogens	Pretransplant disease or high-risk exposure-related infections	Pre-engraftment during neutropenia (0–30 days)	Post-engraftment including acute GVHD (30–100 days)	Posttransplant including chronic GVHD (>100 days)	Posttransplant seasonal community-onset infections
Viruses	Herpes simplex type 1 and II	Herpes simplex type I and II	Cytomegalovirus[n]	Cytomegalovirus[o]	Influenza A and B[p]
	Human cytomegalovirus[q]	Varicella zoster virus[r]	Human herpesvirus[s]	Human herpesvirus 6[s]	Parainfluenza
	Varicella zoster virus	Cytomegalovirus[t]	Adenovirus[u]	Adenovirus[u]	RSV[v]
		Human herpesvirus 6[s]	BK virus cystitis[w]	Epstein-Barr virus PTLD[x]	hMPV[y]
		Adenovirus[u]	Epstein-Barr virus PTLD[x]	Parvovirus B 19[z]	hCoV[aa]
				BK virus cystitis[w]	
				JC virus PML[ab]	
Molds and yeasts	Invasive aspergillosis	*Candida fungemia*[ac]	Invasive aspergillosis[ad]	Invasive aspergillosis[ae]	
	Endemic mycosis	Invasive aspergillosis and rare molds[af]	Invasive candidiasis[ag]	Invasive candidiasis[ah]	
	Cryptococcal disease		*Pneumocystis jirovecii*[ai]	*Pneumocystis jirovecii*	
	Invasive candidiasis		Zygomycosis[aj]	Zygomycosis[aj]	
			Fusariosis[ak]	Fusariosis[ak]	
			Dematiaceous (melanin pigmented) molds[al]	Dematiaceous (melanin pigmented) molds[al]	
			Cryptococcal disease[am]	Cryptococcal disease[am]	
Parasites	*Toxoplasma gondii*		*Toxoplasma gondii*[an]	*Toxoplasma gondii*[an]	
	Strongyloidiasis[ao]		Strongyloidiasis[ap]	Strongyloidiasis[ap]	
	Chagas disease[aq]		Chagas disease	Chagas disease	
	Leishmaniasis[ar]		Leishmaniasis	Leishmaniasis	

[a]Pneumococcus is the leading cause of community-onset bacterial pneumonia, and patients with hematologic malignancies, especially those with cancer or antineoplastic therapy-related humoral immune dysfunction and various other medical comorbid conditions such as diabetes mellitus, chronic structural lung diseases like emphysema, end-stage kidney disease, and cirrhosis of liver to name a few, are at risk for potentially severe systemic disease

[b]The emergence and global spread of community-acquired methicillin-resistant *S. aureus* has made empiric use of anti-staphylococcal penicillin's obsolete

[c]Catheter-related bloodstream infection, extensive healthcare environment exposure and hospital-acquired pathogens, persistent mucositis, orointestinal or cutaneous hyper-acute and acute GVHD, and accelerated iatrogenic immune suppression including need for high-dose corticosteroids are salient factors that promote invasive bacterial infections during this period. Pretransplant colonization due to VRE, MRSA, or MDR GNB including MRD Pseudomonas, ESBL-producing *Enterobacteriaceae*, and some food-borne fungi such as Fusarium spp., especially in transplant unit located in certain geographic areas, are thought to promote infections due to these pathogens

[d]Hyposplenism after HSCT is a late complication and commonly attributed to late-onset acute GVHD, most frequently noted in patients with chronic GVHD. It is however important to recognize that a number of allogeneic HSCT recipients without clinical diagnosis of GVHD may have functional hyposplenism and are at risk for severe, systemic infection due to encapsulated bacteria

[e]Indwelling prosthetic devices including intravascular access catheters; surgical drains; implanted prosthesis such as heart valves, joints, biliary, bronchial, urinary tract stents; and other various implantable surgical devices promote infections due to CoNS and *Candida* spp. that commonly colonizes the skin and genitourinary and orointestinal tracts

[f]Listeria bacteremia and meningitis are rare complications in patients receiving TMP-SMX prophylaxis for PCP. The incidence of bacterial meningitis is 30-fold higher in HSCT recipients compared with persons without HSCT. As expected, patients undergoing allograft stem cell transplant are at a significant higher risk compared with those undergoing autologous HSCT (70 vs. 16 per 100 000 patients per year). In HSCT recipients *Streptococcus pneumoniae* is the most common pathogen associated with bacterial meningitis, *Neisseria meningitidis*, *Streptococcus mitis*; listeriosis may be rarely seen

[g]Increasing frequency of multidrug-resistant strains to fluorinated quinolones and regional high prevalence of extended-spectrum beta-lactamases producing GNB including carbapenem-resistant *Enterobacteriaceae* has seriously curtailed treatment options for such infections. *Enterobacteriaceae* include *Salmonella* spp., *Escherichia coli*, *Yersinia pestis*, *Klebsiella* spp., *Shigella*, *Proteu*s, *Enterobacter*, *Serratia*, and *Citrobacter*

[h]CNS nocardiosis is difficult to distinguish from brain toxoplasmosis, tuberculosis, aspergillosis and other neurotropic clear (hyaline) and black mold infections, and CNS lymphoma

[i]Nonfermentative gram-negatives include *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, other *Acinetobacter* spp., *Alcaligenes* and *Achromobacter* spp., and emerging cases of *Sphingomonas paucimobilis*. Inherent or acquired drug resistance is a major concern in selection of effective empiric therapy for pathogens in this group, which may either lack the drug target site or produce extended-spectrum hydrolyzing enzymes aginst a variety of commonly used antimicrobials; these bacteria may also exhibit phenotypes with reduced expression of outer membrane porins and/or heightened expression of efflux pumps among other mechanisms for antimicrobial drug resistance

[j]Orointestinal mucositis increases the risk of CDAD and so does exposure to broad-spectrum antimicrobials and possibly antineoplastic chemotherapy-induced alteration in hosts' intestinal protective anaerobic microbiota

Table 1.2 (continued)

[k]It now considered standard of care to perform interferon-gamma release assays for diagnosis of latent tuberculosis infection; treatment with isoniazid is considered gold standard and should be administered for a minimum of 6 months prior to the transplantation procedure, with the aim to prevent active tuberculosis infection during the post-transplant period. Such infections tend to be more serious and, due to potential drug toxicity and drug-drug interaction, often difficult to treat after allograft transplantation

[l]*M. kansasii* leads to clinical disease indistinguishable from *M. tuberculosis* infection; risk for infection relapse, drug resistance, and infection recalcitrance are reason for longer duration of therapy

[m]In a recent study from South Korea, in 7342 SOT and 1266 HSCT recipients, 22 patients developed NTM after a median 2 years following transplantation. *Mycobacterium avium-intracellulare* complex was the most common pathogen isolated; nodular bronchiectasis (~80%) was common presentation. A near 70% response to antimicrobial therapy in this group was encouraging. However, disseminated NTM including MAC disease in severely immunosuppressed patients following high-risk allogeneic HSCT may occasionally present as salvage therapy-refractroy recalcitrant bacteremia with high fatality

[n]Risk of CMV infection is highest in CMV-seronegative recipients in whom allograft is given from a CMV-seropositive donor. Ganciclovir prophylaxis effectively prevents CMV disease in high-risk patients during the first 100 days after allogeneic HSCT

[o]Late CMV disease is associated with high mortality rate nearing 45% and seen 170 median days after HSCT. It is important to recognize that close to 40% of patients that respond to the initial episode of late posttransplant CMV infection will develop a second CMV episode within a median of 11–12 weeks. Three months after HSCT, patients with positive CMV-pp65 antigenemia; post-engraftment severe lymphopenia of less than 100 lymphocytes/mm^3, especially those with helper T-cell lymphocytopenia of less than 50 cells/mm^3; presence of GVHD; and those with undetectable CMV-specific T-cell responses are at higher risk for late CMV end-organ disease. Furthermore, after 100 days following transplantation, presence of CMV viremia or pp65 antigenemia and severe lymphopenia endorsed by less than 300 lymphocytes/mm^3 is considered strong predictors for late CMV disease and death

[p]Most frequently detected viruses in symptomatic HSCT or SOT recipients with URTI are picornaviruses (~40%), such as rhinovirus and enterovirus, whereas coronavirus and influenza are isolated in nearly 20% of such patients, each. Influenza URTIs similar to RSV and unlike parainfluenza virus infections have the potential for progression to the lower respiratory tract. Viral pneumonitis is a serious complication in patients following allogeneic stem cell transplantation. It is important to recognize that hosts' immune response to influenza infection garners a high IFN-gamma state resulting in a transient increased susceptibility for secondary bacterial infections like pneumococcus, *S. aureus*, and *Pseudomonas* spp. The resulting superimposed bacterial pneumonia may precipitate life-threatening sepsis and respiratory failure. Furthermore, RTVIs are recognized as fostering enhanced susceptibility for invasive fungal lung disease during early and late transplant periods

[q]Serologic evaluation of the donor and recipient for latent CMV infection is the cornerstone during pretransplant assessment. Dissonance between D+ and R- CMV serology is the most important complicating factors during early and late posttransplant period. Antiviral prophylaxis, preemptive and empiric therapy approaches are based on CMV serologic disparities

[r]It is standard to provide prophylaxis for HSV and VZV during preparatory conditioning regimen and continue during the early post-HSCT period. Prophylaxis may have to be extended in patients with acute GVHD, cancer recurrence, patients undergoing high-risk transplantation procedure, and those with primary or secondary allograft compromise

[s]HHV-6 high-grade viremia by DNA analysis has been associated with central nervous system (CNS) dysfunction, although viral interstitial/alveolar pneumonitis is not an uncommon disease attributed to HHV6 infection following allogeneic HSCT. HHV6 may also present as limbic encephalitis with subcortical temporal lobe seizure activity presenting as memory loss and insomnia. Febrile partial or complete myelosuppression and/or skin rash should alert the physicians regarding HHV6 as a potential treatable cause of secondary stem cell allograft loss. Viral gastroduodenitis, colitis, and pericarditis are other clinical manifestations attributed to HHV6 infection in this vulnerable population. An association with post-HSCT HHV6 viremia with delayed monocyte and platelet engraftment, increased platelet transfusion requirements, risk for high-grade GVHD, and all-cause mortality needs further evaluation

[t]Early CMV low-grade viremia was observed by the use of ultrasensitive nucleic assays, within 3–4 weeks after high-risk allogeneic stem cell graft transplantation

[u]The incidence of adenovirus disease ranges from 3% to as high as 47% in high-risk pediatric allogeneic HSCT recipients. Patients undergoing T-cell-depleted stem cell grafts and those with acute graft-versus-host disease are also at increased risk for severe life-threatening adenovirus disseminated disease, which is a well-recognized complication in patients with persistent peripheral blood lymphocyte counts of <300 cells/mm^3. Infection involves respiratory (viral pneumonitis), gastrointestinal (colitis, including hemorrhagic colitis) tracts, and hepatitis;patients may present with posttransplant hemorrhagic cystitis. Adenovirus dissemination represents severity of underlying immune defect and is seen in 10–20% of patients with end-organ viral disease, except in patients with adenovirus cystitis, where disseminated adenoviral disease is seldom observed

[v]Long-term (>30 days) viral shedding is not uncommon in patients following allogeneic HSCT; RSV is notable RTVI in this regard. The 80 days of median duration of viral shedding may extend to just under a year in some allogeneic transplant recipients. This potential for pronged viral shedding warrants heightened awareness and strict adherence to appropriate precautions to prevent nosocomial RSV transmission to other vulnerable hospitalized patients. In the pediatric HSCT recipients, RSV infection within 60 days after transplant, patients given systemic corticosteroids within a week prior to the onset of RSV infection and the need for assisted mechanical ventilation were significant predictors for subsequent complications and death

[w]The BK virus was first isolated in 1971; after primary childhood infection, persistent BKV infection occurs within renal tubular cells and the urothelium. Viral reactivation in the recipients of kidney and allogeneic HSCT usually presents as allograft nephropathy and hemorrhagic cystitis, respectively. Presently, reduction in drug-induced immune suppression, when possible, and supportive care are the only viable treatment option; direct antiviral drug against BKV remains elusive

[x]EBV influence over B-cell malignant clones may act through different mechanisms of transcriptional regulation and possibly variance in genetic mechanisms that eventually determined viral latency during early EBV infection and EBV-host interaction

[y]The incidence of hMPV infection was similar to the incidence of RSV or parainfluenza virus UTRIs in patients undergoing HSCT. hMPV infections are notable for low risk of progression to the LRT. Serious systemic hMPV disease including viral encephalitis has been reported. Overall, these infections are well-tolerated, albeit hMPV pneumonitis in severely immunosuppressed stem cell allograft recipients may result in serious life-threatening lung disease

(continued)

Table 1.2 (continued)

[z]Parvo B19 infection may present as pure red cell aplasia after allogeneic HSCT

[aa]hCoV similar to hMPV is a common RTV. Serotypes associated with disease in transplant population include hCoV-OC43 followed by NL63, HKU1; 229E is less common. Unlike hMPV, these infections have a higher likelihood for progressing to the LRT, which often presents as subclinical, mild to moderate viral illness. In an observation among HSCT recipients, hCoV infection resulted in a notable number (~20%) of hospitalizations. In concert with hMPV infection, despite presence of severe immune suppression, hCoV-related confirmed deaths in allogeneic HSCT recipients remain less than 5%. Approximately one-third of transplant patients with hCoV infection may have infection due to other RTVs such as human bocavirus (HBoV). HBoV is an uncommon RTV in transplant patients and often (> 80%) seen with other RTVs. HBoV rarely causes LRTI; most infections are well-tolerated despite, transplant-related severe immune suppression

[ab]John Cunningham virus (JCV)-associated progressive multifocal leukoencephalopathy (PML) is an uncommon disease in patients undergoing allogeneic HSCT. In a report from Israel, 20 of 40 patients (24%) with JCV reactivation had persistent viremia after receiving myeloablative and nonmyeloablative pretransplant conditioning. PML was diagnosed in two patients with persistent JCV viremia, 96 and 127 days after HSCT. Advanced age was a significant predictor of JCV reactivation; 70% of these allogeneic HSCT recipients with persistent viral reactivation had died. Identifying high-risk patients with persistent JCV reactivation, especially those with incremental levels of viremia, may benefit from reduced drug-induced immune suppression for prevention of JCV leukoencephalopathy. PML continues to remain a devastating, albeit rare post-transplant infectious complication. *Artesunate*, an antimalarial drug that showed potent ex vivo activity against HHV-6, however, clinical response to artesunate in HSCT recipients with JCV-PML, has not been encouraging

[ac]Candidemia is seen in patients with severe pre-engraftment neutropenia (absolute neutrophil count <500 cell/microliter) that extends longer than 5 days. The increase in non-*albicans Candida* spp. is mainly due to *C. glabrata*, although patients following HSCT are also at risk for *C. krusei* infection. Emergence of echinocandin resistance among clinical *C. glabrata* isolates is concerning. For patients with *C. parapsilosis* infection, it is recommended to use antifungal drugs other than echinocandin class. The emergence of MDR *Candida auris* infections in transplant population makes selection of empiric anti-yeast therapy more challenging

[ad]Genetic susceptibility for IA include mutations in Dectin-1 and DC-SIGN among other well recognized risk factors such as high-risk allogeneic HSCT, CMV and respiratory virus infection, and positive *Aspergillus* PCR. It was recently noted that presence of three of the aforementioned factors generated a 57% probability for developing IA. In patients with no risk factors, the probability of IA was 2%, compared to ~80% in patients with four or more such risk factors

[ae]CMV reactivation after stem cell allograft transplantation increases the risk for IFD during the late transplant period. Unlike the risk factors for early IFD such as AML (HR 3), HLA antigen-mismatched donor graft (HR 3.4); HSCT recipients with lymphoma (HR 8.5), CMV reactivation (HR 5.5), and severe neutropenia (HR 3.5) are considered prominent risk factors for late-onset IFD. Patients with pretransplant IgG responses against *Aspergillus* proteins indicating significant fungal colonization or ongoing subclinical *Aspergillus* infections before preparatory conditioning regimen has commenced needs further clinical validation. Evaluation of 5589 HSCT recipients at a comprehensive cancer center between 1985 and 1999 showed increased incidence of IA after 1992 and remained high during that decade. The authors also reported increasing frequency of non-*Aspergillus* molds such as *Fusarium* spp. and mucormycosis in the late 1990s. These non-*Aspergillus* molds were prominent in patients undergoing multiple transplants. Most cases of mucormycosis were seen during the late transplant period, especially in patients with chronic GVHD. In patients undergoing nonmyeloablative HSCT, presence of severe acute GVHD, chronic extensive GVHD, and CMV infection are prominent risk factors for IFD

[af]Invasive aspergillosis is a complication seen in patients with delayed (>2 weeks) recovery of peripheral blood granulocyte count. Patients receiving high-dose systemic corticosteroids are also at an increased risk. *Aspergillus fumigatus* remains the most prevalent mold to cause invasive human disease, including in patients undergoing HSCT. Infections caused by *Scedosporium* and *Fusarium* spp. are occasionally seen in hematopoietic stem cell allograft recipients and commonly present during the period(s) of severe and prolonged neutropenia

[ag]Routine blood cultures have low sensitivity for diagnosis of fungemia. Carbohydrate biomarker (1, 3)-β-d-glucan has emerged as a useful laboratory test for the diagnosis of invasive yeast and mold disease. Furthermore, it may be used to monitor response to systemic antifungal therapy and infection relapse

[ah]Post-HSCT recovery of antigen-specific T lymphocyte-mediated immune response against CMV and *Candida albicans* is regarded as critical during the early and the late transplant period. Most patients develop antigen-specific T-cell response early in the transplant period which is derived from clones of both donor and recipient stem cell origin. Reconstitution of immune response via antigen-specific T lymphocytes of recipient origin is weakened in patients with GVHD. Incidence of IC during the 1st year after nonmyeloablative (5%) and myeloablative transplant conditioning is lower than that for IA (14%). Echinocandin nonsusceptible *Candida* spp. infection has been recently recognized as an emerging challenge in providing care for these highly vulnerable patients

[ai]PCP is a serious OI in transplant patients with severe cellular immune defect(s). Routine anti-PCP prophylaxis breakthrough infections are rare; although in patients receiving aerosolized pentamidine, atypical upper lung PCP may occasionally occur

[aj]Invasive zygomycosis or mucormycosis may occur disproportionally more frequently in patients on voriconazole prophylaxis and those with sinuorbital invasive mold disease. In transplant patients, the overall prevalence is less than 8% among all invasive fungal infections

[ak]Nearly half of the patients with disseminated fusariosis have evidence of fungemia, and close to 80% may exhibit multiple (>10–15) papular skin lesions with a necrotic center that is indistinguishable from ecthyma gangrenosum due to *Staphylococcus aureus* or disseminated *Pseudomonas* spp. infection

[al]Dematiaceous or melanin pigmented molds are associated with chronic localized infections and prevalent in certain geographic regions. In transplant patients, disseminated infections may occur; neurotropism is an important feature of these infections, and treatment with older antifungal drugs such as amphotericin B and early generation triazole-based compounds was associated with high rates of treatment failure

[am]The cumulative incidence of CNS infection following HSCT is <1% within first 30 days, 2% within 3 months, and 5% after 5 years following transplantation. Significantly high risk of CNS infection 5 years after CBT (8%) vs. matched related HSCT (2%) is important to note for the purpose of risk stratification. CNS fungal (35%) and viral (32%) infections are prominent, whereas toxoplasmosis and bacterial infection are seen in just over 10% of the patients. Aspergillosis is common (67%) followed by *Cryptococcus neoformans* (17%). CNS infection in transplant population is associated with high mortality (59%), and low (20%) 5-year overall survival

Table 1.2 (continued)

[an]Donor-derived toxoplasmosis has been reported along with cases of brucellosis in the endemic regions, along with West Nile virus infection, rabies, Chagas disease, and rare cases of lymphocytic choriomeningitis virus infection

[ao]*Strongyloides stercoralis* (pinworm or threadworms and *Enterobius vermiculari*) in the underdeveloped countries where fecal contamination of soil and water is common; evaluation of allogeneic transplant candidates requires serologic evaluation for exposure and if present, appropriate treatment should be completed for intestinal subclinical parasitic infestation prior to the trasnplantation procedure

[ap]In patients with extensive T-cell immune defects, *Strongyloides stercoralis* may cause accelerated autoinfection. Hyperinfection pulmonary syndrome in such patients is almost always fatal. Screening serology tests for the presence of strongyloidiasis by enzyme-linked immunosorbent assay after allogeneic HSCT may be falsely negative; and stool ova and parasite examination, in the absence of accelerated autoinfection during the pretransplant, is also riddled with low sensitivity

[aq]American trypanosomiasis caused by *Trypanosoma cruzi* needs to be assessed in patients planned to undergo allograft transplant procedure from endemic regions

[ar]Leishmania is transmitted by the bite of certain species of sand flies and presents as cutaneous (common) and visceral (uncommon and severe) disease; pretransplant evaluation should include serologic testing for prior exposure to these parasites in appropriate patients with high risk for prior exposure

Abbreviations: GVHD graft-versus-host disease, *HSV* herpes simplex virus 1 and 2, *CMV* cytomegalovirus, *VZV* varicella zoster virus, *HHV6* human herpesvirus 6, *EBV* Epstein-Barr virus, *CoNS* coagulase-negative *Staphylococcus*, *CDAD Clostridium difficile*-associated diarrhea, *GPB* gram-positive bacteria, *GNB* gram-negative bacteria, *HSCT* hematopoietic stem cell transplantation, *RSV* respiratory syncytial virus, *hMPV human metapneumovirus*, *hCoV* human coronavirus hypervirulent subtypes NL63 and HKU1, *PML* progressive multifocal leukoencephalopathy, *EBV-PTLD* Epstein-Barr virus-associated B-cell lymphoproliferative disorder, *HR* hazard ratio, *IFD* invasive fungal disease, *IA* invasive aspergillosis, *IC* invasive candidiasis, *SOT* solid organ transplant, *URTI* upper respiratory tract infection, *LRTI* lower respiratory tract infections, *RTV* respiratory tract virus, *RTVIs* respiratory tract viral infections, *hCoV* human coronavirus

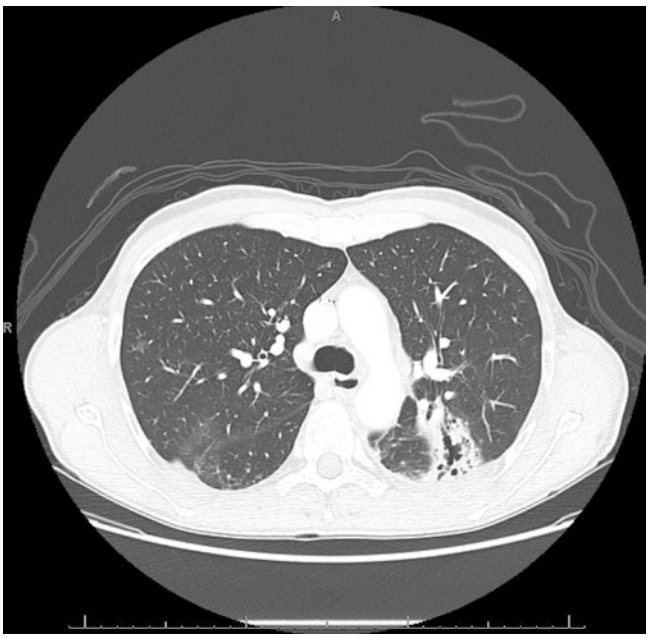

Fig. 1.1 CT scan of lungs without intravenous contrast showing necrotizing left lung *Pseudomonas* infection in a patient following HSCT. The differential for this thick-walled irregular cavitary lesion is broad and includes other bacterial infection such as *Klebsiella* spp., *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli, Nocardia* spp.; *Mycobacterium tuberculosis* and nontuberculous mycobacterial infections. Cavitary rapidly growing cancers may have similar presentation, whereas viral infections including cytomegalovirus and adenovirus seldom present with such features. Other than suppurative necrosis of the lung, ischemic necrosis, i.e. pulmonary infarction, should also be considered. Tissue invasive mold lung disease may also have comparable radiographic presentation

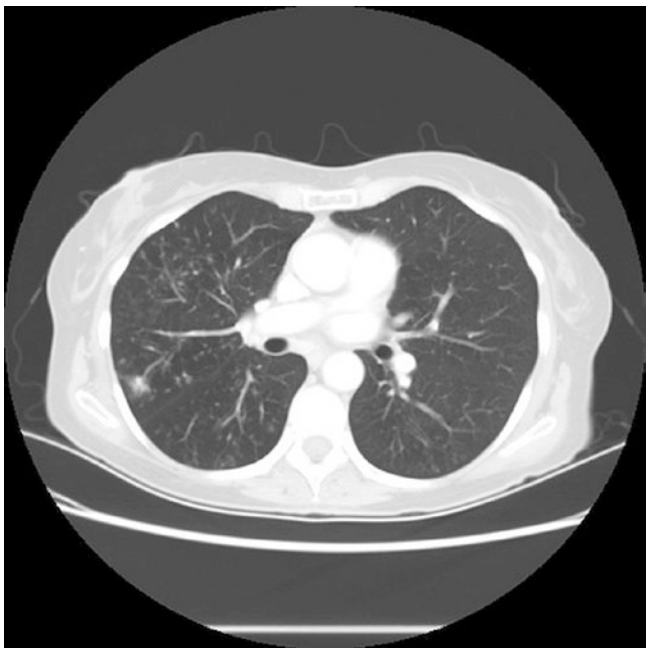

Fig. 1.2 CT scan of lungs without intravenous contrast showing tree-in-bud appearance due to pulmonary *Mycobacterium avium* complex disease mostly involving the right lung demonstrating multiple areas of centrilobular nodules with a linear branching pattern. Endobronchial tuberculosis may present with such a radiographic finding, wherein patients with acutely developed tree-in-bud infiltrates bacterial or viral (CMV) etiology may also be entertained. It is important to note that bronchiectasis is the prominent radiographic presentation of *Mycobacterium avium* complex infection in patients undergoing transplantation. Rarely carcinomatous endarteritis due to breast or gastric cancer; bronchovascular interstitial infiltration due to lymphoma, leukemia, and sarcoidosis may have similar presentation. Scedosporium lung disease and pulmonary fusariosis may occassionally have nodular peribrochovascular distribution

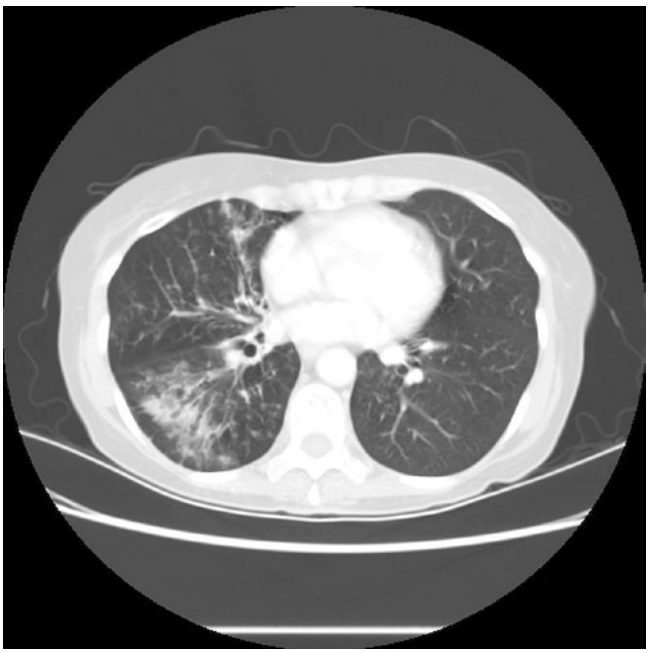

Fig. 1.3 CT scan of lungs without intravenous contrast showing right lung *Mycobacterium kansasii* pneumonia with peribronchial thickening that could be mistaken for CMV pneumonitis and *Mycobacterium tuberculosis*, among other lung infections in a patients following allogeneic HSCT

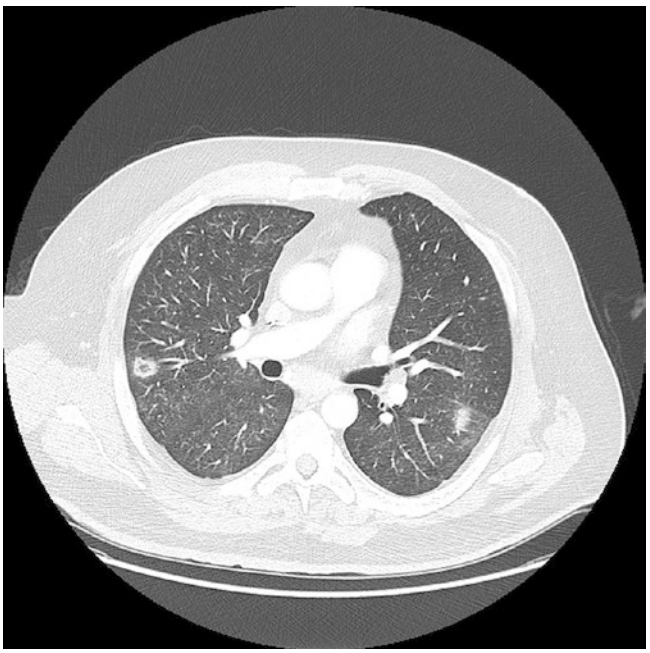

Fig. 1.4 CT scan of lungs without intravenous contrast showing bilateral nodular zygomycosis in a patient following allogeneic HSCT while receiving voriconazole prophylaxis. The right lung nodule with a central cavity cannot be radiographically excluded from other causes of nodular pneumonia such as invasive pulmonary aspergillosis, *Fusarium* spp., and other mold lung disease. Among bacteria, *Nocardia* spp. is a concern in allograft transplant recipients with such radiographic presentation. Primary lung lymphoma may have similar presentation. Rarely, patients with relapse acute leukemia in the post HSCT period may present with atypical pulmonary infiltrates

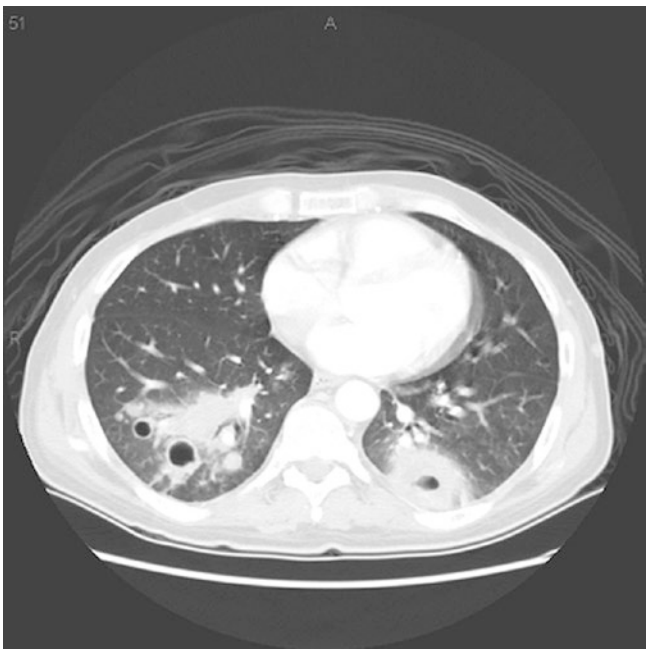

Fig. 1.5 CT scan of lungs without intravenous contrast showing cavitary pneumonia with dense consolidation involving both lower lobes in a patient with GVHD, who developed infection due to dematiaceous mold following allogeneic HSCT. In the differential diagnosis, necrotizing bacterial, clear (hyaline) and black (melanin pigmented) mold infections should also be considered along with multifocal pulmonary nocardiosis

at an additional risk for infections that are often seen in asplenic patients or those with functional hyposplenism. Patients with chronic GVHD are not only at an increased risk for systemic fungal disease like invasive aspergillosis or herpes virus reactivation herald by CMV viremia; additionally, encapsulated bacteria such as outlined in Table 1.1 may also be included in the risk profile during evaluation of such patients.

Patients receiving treatment for acute GVHD after allogeneic HSCT have heightened risk for invasive aspergillosis and infections due to other filamentous molds. Unlike the first risk period for invasive mold disease in allogeneic stem cell recipients, which coincides with the period of pre-engraftment severe neutropenia, patients with acute and chronic GVHD are seldom neutropenic.

Table 1.3 illustrates the salient features of infection risk and their association with the type of stem cell graft, pre-transplant conditioning preparatory regimens, and drugs commonly used in the prevention of GVHD. Cord blood stem cells are regarded as a major breakthrough for source that yields a steady supply of hematopoietic stem cells, especially among patients with difficult to find, immunologically (HLA-matched) compatible hematopoietic stem cell graft [18]. Cord blood stem cells have a limited number of nucleated cells that are adequate for children. In adults

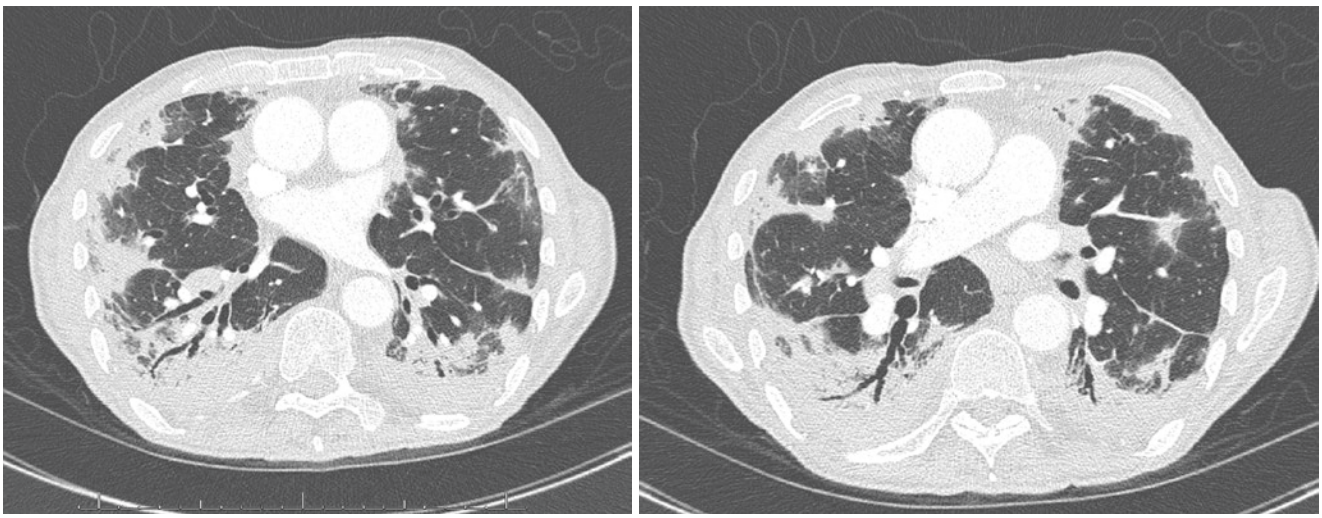

Fig. 1.6 CT scan of lungs without intravenous contrast showing cryptogenic organising pneumonia in a patient following allogeneic HSCT that may be mistaken for fibrosing subacute infection due to endemic mycosis among other causes of subacute lung infection

due to larger body surface area, transplantation with less than optimum number of stem cells complicate posttransplant period with issues such as inadequate and delayed neutrophil engraftment and peripheral blood cell count recovery, precarious graft stability, and, similar to recipients of T-cell-depleted grafts, a higher risk for infections associated with severe and prolonged neutropenia or those observed during GVHD (Tables 1.1 and 1.2). Various strategies are being explored to assuage this limitation including transplantation with cord blood grafts from more than one donor and ex vivo expansion of a single donor cord blood graft to increase the yield of nucleated cells [21]. In a review of 100 cord blood transplants at a comprehensive cancer center in Houston, Texas, the infection incidence rate ratio, which was total infection episodes per days at risk (survival after CBT) × 100, was 2.4 times higher in adult patients compared with children [22]. It was important to note that risk of infection was even greater (three times higher) in adults with neutropenia and was 1.9 times higher in patients with GVHD when compared with children undergoing CBT procedure [22].

It is considered essential to create a comprehensive infection assessment strategy that takes into account and recognizes the local issues at a particular transplant unit and its unique patient population. Such an approach requires cognizance of existing influences that may promote risk for infection including local and regional infection trends, patterns in pathogen prevalence and drug susceptibility profiles. Continued vigilance regarding emergent pathogens and ever-changing infection risk profile with advances in transplant procedures and drug-induced immune suppression are of paramount importance in providing care for the highly vulnerable transplant population.

A variety of noninfectious conditions may clinically and radiographically emulate an infectious process. Among these noninfectious maladies, those involving the skin and the lungs are the great imitators; when present, they are difficult to clinically distinguish from infections such as cellulitis or pneumonia. Two chapters in this volume are dedicated to provide an in-depth discussion on these topics.

An approach for establishing correct diagnosis for opportunistic infections is based on the maxim "when uncertain, obtain a tissue sample." A diligent adjudication is the central tenet in establishing accurate diagnosis for the immunologically vulnerable patients, in whom proclivity for atypical disease presentation further complicates ascertaining correct and timely diagnosis. Inaccurate diagnosis under the old dispensation of serologic and culture-based system may lead to inappropriate and ineffective treatment, worsening patients' morbidity, risk for further complications, and death. Therefore, focused yet comprehensive differential diagnoses, which encompasses etiology of infections and noninfectious causes that may mimic an infectious process including but not limited to drug toxicity; de novo malignancies or post transplant cancer recurrence; typical or atypical presentation of lymphoproliferative disorders; immune-inflammatory diseases like GVHD; and tissue infiltrative processes such as solid allograft rejection among others may greatly improve the guidance for an optimized management approach in patients undergoing lifesaving, stem cell and solid organ allograft transplantation.

Table 1.3 Relationship between infection risk and HSCT variables

Stem cell source, preparatory conditioning regimens, and GVHD prophylaxis	Immune defects	Infections
Allogeneic vs. autologous graft	Allograft recipient exhibits gradual recovery of cellular and adaptive immune function	Pre-engraftment neutropenia, if longer than 7–14 days, increases the risk for invasive candidiasis and IMD
	Innate immune function aided by cellular and acellular antimicrobial defense is to recover early after transplantation, especially in patients undergoing conventional autologous and nonmyeloablative HSCT. It is heralded by granulocyte engraftment and posttransplant resolution of neutropenia	IFD heightened risk coincides with the peak incidence of acute and chronic GVHD
	Complements and antimicrobial peptides reconstitute early after transplantation	Severe respiratory viral infections are also problematic in patients given systemic corticosteroids and immunosuppressive therapy for GVHD
	Patients with persistent severe thrombocytopenia that may follow in high-risk allogeneic stem cell recipients may continue to exhibit reduced host defense due to suboptimum thrombin-releasable antimicrobial peptides from platelets including platelet factor 4, RANTES, connective tissue-activating peptide 3, platelet basic protein, thymosin β-4, fibrinopeptide B, and fibrinopeptide A. The impact of depleted platelet-assisted immune defense and potentially higher susceptibility for infection in HSCT recipients with severe thrombocytopenia is not certain	CMV, less commonly HHV6, and disseminated adenovirus are encountered in patients with profound defects in anti-CMV and other antiviral pathogen-specific, effector cellular immune response
	Myeloid and plasmacytoid dendritic cells are recovered within 60 days after allogeneic HSCT to pretransplant levels, unless patients develop acute GVHD, in which case this recovery is significantly delayed. However, it may take a year or longer to achieve normal functional DC cell population after undergoing allogeneic stem cell transplantation. Plasmacytoid DCs are important for regulation and maintenance of immune tolerance and defense against viruses. The myeloid DCs serve as APCs that are pivotal in eliciting pathogen-directed cellular adaptive immune response	
	Recovery of NK cells in most patients undergoing allogeneic HSCT occurs usually 45 days after transplantation. These innate immune effector cells can directly lyse virus-infected cells and provide antineoplastic immune surveillance. NK cells are an important, readily available, albeit transient source of IFNγ and GM-CSF. The chemokines such as MIP-1α, MIP-1β, IL-8, and RANTES play a critical role in adaptive immune modulation. It was notable that lack of qualitative NK cell recovery in patients with T-cell-depleted transplant may render them less effective for prolonged periods	

Table 1.3 (continued)

Stem cell source, preparatory conditioning regimens, and GVHD prophylaxis	Immune defects	Infections
Unrelated donor or mismatched stem cell graft	Unrelated donor grafts are more frequently associated with severe GVHD and/or graft rejection compared with sibling donor stem cell allograft transplants	Mismatched and unrelated donor stem cell allograft transplants carry a significant risk for serious life-threatening infections seen in the late (6–18 months) post-transplant period. CMV infection and acute GVHD contribute significantly toward this risk. The late fatal infections include pneumonia, sepsis, central nervous system infection, and disseminated varicella
	Slow reconstitution of adaptive cellular helper and cytotoxic immunity, which is further delayed in patients requiring treatment for acute GVHD	IA 6 months after transplantation was associated with chronic GVHD and CMV disease
	Humoral immune response may not fully recover in patients with chronic GVHD	*Fusarium* spp. IFD is threefold higher in patients undergoing HLA-mismatched vs. HLA-matched HSCT; most cases occur 48 median days after transplantation. The trimodal distribution similar to IA coincides with pre-engraftment neutropenia; 60 days and over 1 year after transplant, corresponding with the incidence of acute and chronic GVHD, respectively
	Bone marrow as the source of stem cells and treatment with high-dose corticosteroids delay recovery of functional T-cell-based immunity for 3 months or longer after transplantation	Persistent neutropenia similar to that seen in cases with disseminated *Scedosporium* spp. infection and other invasive mold disease after allogeneic HSCT was the prominent prognosticator for death in patients with fusariosis
		It has also been recognized that subclinical CMV reactivation in patients while on ganciclovir prophylaxis or preemptive therapy appears to be a potent stimulator of T-cell function after transplantation
		Other serious infections include EBV-PTLD, disseminated HHV-6, and disseminated adenovirus infections
Peripheral blood stem cell graft vs. bone marrow stem cells	Faster neutrophil engraftment	The rate of severe and proven infections following stem cell engraftment was ≥twofold higher in patients in whom bone marrow SCT was given compared with those undergoing transplantation with PBSC allografts
	Blood stem cell grafts have higher lymphocyte subset counts, which, in most part, account for fewer infectious complications during the posttransplant period	HLA-matched, related-donor peripheral blood stem cells appear to lend protection against IA during early transplant period compared with those undergoing similar bone marrow stem cell allograft transplants
	Late transplant immune suppression due to chronic GVHD may occur	The greatest benefit of PBSC vs. BMSC has been noted in the risk profile for IFD, whereas for bacterial infections such benefit is intermediate, and it is least for viral infections

(continued)

Table 1.3 (continued)

Stem cell source, preparatory conditioning regimens, and GVHD prophylaxis	Immune defects	Infections
Cord blood stem cell graft	Slower neutrophil engraftment resulting in prolonged neutropenia in adult CBT recipients continues to be a serious limitation for this stem cell donor source	Cord blood stem cell transplantation increases the risk of early (<40 days) IAs
	Adult patients require a higher number of total nucleated cells and CD34+ progenitors than are often present in a cord blood unit, yielding to instability of the allograft even after successful engraftment. To mitigate these limitations, especially in adults, strategies to expand selected subpopulations of stem cell within the cord blood unit and transplantation of multiunit CB are currently being explored	CBT recipients had a higher incidence of severe bacterial infections within 100 days after transplantation; however, 3 years after CBT, risks of severe bacterial and other infections are comparable to patients undergoing BMT or peripheral blood allogeneic HSCT
	Slower restitution of T-cell pathogen-specific, cellular immune response as cord blood T-cells are predominantly naïve and exhibit suboptimum T-cell proliferation and IFN-gamma production in response to an insult or exposure to a foreign antigen. This inherent cellular dysfunction in CBS grafts appears to reflect defect(s) in signal transduction pathway(s)	CMV infection and/or presence of acute GVHD significantly increases the risk for IA
	Furthermore, T-cell dysfunction may also arise from prominence of Treg population in CBS with potent suppressor function compared with moderate Treg population in adult donor-derived stem cell grafts	Most (>90%) IFD similar to bacterial infections are seen within 100 days after transplantation
	Hypogammaglobulinemia and other B-cell dysfunction may occur in patients with chronic GVHD	Nearly half of the early fungal infections may be noted within the first 30 days after CBT
	Risk of graft rejection and severe acute GVHD have been comparable to that observed following PBSC or BMSC transplants; this is despite high degree of HLA antigen donor-recipient disparity in most adult patients undergoing CBT	CMV and varicella zoster virus infections after 100 days following CBT are mostly seen in patients with chronic GVHD
	Graft-versus-leukemia/lymphoma effect in CBT recipients has also been comparable to conventional stem cell graft transplants	Patients who recover peripheral blood lymphocyte count following successful CBT engraftment are at a significantly low risk for serious systemic infections
T-cell-depleted stem cell graft	Higher risk for graft rejection may be an issue	These patients have a higher risk of infections during the prolonged pre-engraftment neutropenia
	Slower reconstitution of cellular and humoral immunity	The risk factors for IA noted in allogeneic HSCT recipients include T-cell-depleted or DC34-selected stem cell grafts, treatment with systemic corticosteroids, GVHD, presence of severe lymphocytopenia, and neutropenia
	CD8 cells recover rapidly, whereas helper T-cells and B lymphocyte recovery remain significantly stunted for 1 year or longer after T lymphocyte-depleted stem cell graft transplantation	CMV infection and end-organ disease; LRTI due to RTVs are now recognized as important predictors for IA and other IFD during post-engraftment period
	Natural killer cells also make early and sustained recovery after transplantation	
	Despite T-cell-depleted PBSC grafts having higher numbers of mononuclear cells and granulocyte-macrophage units compared with BM grafts, recovery in B lymphocyte and T-cell subpopulations has not been dissimilar, in either group	
	These patients also exhibit a subnormal level of primed T-cell repertoire. Prominent lymphocyte population in such stem cell grafts is composed of naïve/unprimed T-cells. Primed T lymphocytes including activated helper T-cells that are an important and sustained source of IFN-gamma, a critical cytokine in targeted intracellular neutralization of various pathogens	
	Hypogammaglobulinemia has not been an issue in patients undergoing T-cell-depleted vs. conventional stem cell transplantation	

Table 1.3 (continued)

Stem cell source, preparatory conditioning regimens, and GVHD prophylaxis	Immune defects	Infections
Nonmyeloablative stem cell transplantation	Faster neutrophil engraftment following reduced intensive preparatory regimen	Patients with chronic lymphocytic leukemia (138 episodes/100 person-years) and recipients of matched unrelated donor graft (128 episodes/100 person-years) had higher risk of infection after NMT
	Blood stem cell recipients have higher lymphocyte subset counts and account for fewer infectious complications during posttransplant period	Nearly half of the CMV viremia is noted between 31 and 100 days after transplantation. CMV infection as expected is mostly encountered after the resolution of neutropenia
	Substantially reduced incidence of GVHD, especially severe grade III–IV acute GVHD	Close to 80% of IFI are late transplant infections that are diagnosed 100 days after NMT and associated with unacceptably high mortality (~80%). Presence of GVHD and treatment with systemic corticosteroids significantly increases the risk for IFD in such patients
	Late transplant immune suppression due to chronic GVHD may occur	
	B-cell dysfunction, when present, is often represented as deficiencies of immunoglobulin subclasses rather than severe hypogammaglobulinemia	The risk of IA after NMT appears to increase with time, while well-under 10% within 1 year after HSCT, the overall risk increases to around 10% at 2 years and close to 15% 3 years after transplantation. Patients with GVHD involving the intestinal tract show a significant risk for IA after NMT
	As in all transplant recipients including those undergoing autologous SCT, B-cell hyporesponsiveness is clinically demonstrated as reduced immunogenicity for convention vaccines. Response to protein conjugate vaccines tends to be superior compared with response elicited by pure polysaccharide and other complex sugar immunogens. Superior conjugate vaccine construct requires restitution of cellular immune response and a functional antigen presentation process	GVHD treatment with daclizumab further enhances the risk for IA. Daclizumab is a humanized monoclonal antibody that binds to CD25, the alpha subunit of the IL-2 T-cell receptor resulting in severe iatrogenic drug-induced cellular immune suppression
	Adults with rapid engraftment of NMT become full donor T-cell chimeras within 6 months after transplantation. In contrast to children, quantitative B-cell recovery in adults is usually delayed until 1 year after HSCT. It was interesting that immune reconstitution occurs faster in children undergoing NMT who exhibit extended duration of mixed hematopoietic chimerism, whereas in adults, reconstitution is more gradual despite rapid donor stem cell engraftment and T-cell chimerism	

(continued)

Table 1.3 (continued)

Stem cell source, preparatory conditioning regimens, and GVHD prophylaxis	Immune defects	Infections
Total body irradiation and chemotherapy-induced mucositis	Radiation exposure and highly active antineoplastic drugs kill rapidly proliferating cancer cells. The rapidly dividing normal orointestinal epithelial cells also sustain unintended damage that may clinically present in patients with severe and potentially life-threatening mucositis	Patients with severe mucositis, especially those with mucosal ulcerations, have threefold higher risk for α-hemolytic streptococcal bacteremia compared with those without ulcerative mucositis following HSCT. In such patients, presence of oral ulcerations significantly increases the length of hospitalization by nearly 1 week
	Various strategies including recombinant human keratinocyte growth factor among others are being explored to mitigate this serious debilitating complication commonly seen in the early posttransplant period	Similarly, presence of orointestinal mucositis has been associated with the risk for neutropenic enterocolitis or typhlitis and CDAD
	Initial phase of chemotherapy-induced stomatotoxicity is infiltration of tissue with inflammatory cells and vascular congestion, followed by epithelial cell damage resulting in ulceration; risk for bacterial and less often yeast invasion resulting in systemic infection. Patients who survive this phase are expected to make full recovery	The risk of fungemia due to *Candida* spp. may also be increased in such patients
	Divergent cytokine response plays an important role in the risk, severity, and duration of mucositis as does hosts' genetic predisposition	Patients with intestinal VRE colonization and mucosal disruption heighten the risk for systemic invasion and risk of VRE bloodstream infection
		Later TBI complication between 12 and 136 months after treatment is mostly noninfectious and includes restrictive lung disease (~8%) and altered pulmonary diffusing capacity (~12%); pulmonary complications had been statistically higher in patients with GVHD and those who underwent high-dose (15 MV vs. 9 MV) energy beam radiation therapy. Ocular complications are noted in nearly 30% of patients on long-term follow-up and include cataract and dry eye syndrome (~15% each), whereas keratitis is seldom seen
Antithymocyte globulin	ATG is polyclonal human antilymphocyte globulins that result in multifaceted immunomodulation and are shown to reduce the incidence of solid organ graft rejection and GVHD following allogeneic HSCT	The incidence of EBV-related complications was twice as high (~7%) in patients undergoing non-HLA-matched vs. HLA-matched allograft stem cell transplants. This risk was significantly higher (>20%) in patients given antithymocyte globulin versus those in whom this treatment was not given (<2%). In HSCT recipient with persistent EBV reactivation, just above 80% developed EBV-related PTLD suggested targeted surveillance
	ATG in vivo depletes proinflammatory cytotoxic T-cells in the peripheral blood via complement-dependent cell lysis, and peripheral lymphoid tissue T-cell depletion occurs via cell activation and apoptosis	Febrile illness, CMV infection, and hematologic abnormalities are known complications in patients treated with ATG
	ATG downregulates expression of the α-chain of the IL-2 receptor (CD25), which is expressed on activated T lymphocytes thereby interrupting an important signal for cell proliferation	
	Modulation of key cell surface molecules such as integrins and intercellular adhesion molecules that facilitate and regulate lymphocyte interactions with the endothelium. Chemotaxis is effected by interference with CXCR4 and stromal cell-derived factor-1α-driven lymphocyte migration	
	ATG induces apoptosis in B-cell lineages	
	It promotes and expands functionally immunosuppressive regulatory T-cells	

Abbreviations: *GVHD* graft-versus-host disease, *CMV* cytomegalovirus, *DC* dendritic cells, *NK* natural killer, *PML* JC virus-associated progressive multifocal leukoencephalopathy, *PTLD* Epstein-Barr virus-associated B-cell lymphoproliferative disorders, *IFD* invasive fungal disease, *CDAD Clostridium difficile*-associated diarrhea, *CBT* cord blood stem cell transplantation, *IA* invasive aspergillosis, *IC* invasive candidiasis, *Treg* regulatory T-cells, *HSCT* hematopoietic stem cell transplantation, *IMD* invasive mold disease, *HHV6* human herpes virus 6, *RANTES* regulated on activation, normal T-cell expressed and secreted, *APC* antigen-presenting cells, *IFNγ* interferon gamma, *NTM* nonmyeloablative transplant, NST, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *CBS* cord blood stem cells, *BMSC* bone marrow stem cells, *PBSC* peripheral blood stem cells, *LRTI* lower respiratory tract infection, *SCT* stem cell transplant, *HLA* human leukocyte antigen

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Infections in Heart, Lung, and Heart-Lung Transplantation

2

Andrés F. Henao-Martínez and José G. Montoya

Historical Perspective

We have conceived the human heart as the main source of our deep emotions and feelings. A place where our very conscious resides as portrayed by Edgar Allan Poe in his famous *The Tell-Tale Heart* short story: "I felt that I must scream or die! And now—again!—hark! Louder! Louder! Louder! Louder!" Dr. John Gibbon Jr. used for the first time in 1953 a heart-lung respirator to keep a patient alive while performing heart surgery. Dr. Norman Shumway at Stanford developed and perfected the first surgical technique leading to heart transplantation surgery. After Dr. Christian Barnard's first orthotopic heart transplant in December 1967, and Dr. Shumway first heart transplant in the United States in January 1968, heart transplantation became a standard therapeutic option for life-threatening congestive failure and started to be performed in the hundreds over the next following years at different centers. Heart transplant surgery faced complications due in part to rejection and infection. However, the development of more selective immunosuppressive therapy and improvements in prevention, detection, and treatment of infections allowed for heart transplant surgery to increase rapidly worldwide.

Four thousand and ninety six heart (3529 adults) transplants were reported to the International Society of Heart and Lung Transplant Registry (ISHL) in 2011 [1]. The landscape of infection affecting heart transplant patients has been shaped by different factors: (A) implementation of more selective calcineurin-based immunosuppressive protocols, (B) lessened immunosuppressive induction regimens, (C) the institution of antimicrobial prophylaxis resulting in a significant decrease or delay in the emergence of major infections episodes including *P. jirovecii* (PCP), *Nocardia* spp., *Listeria spp.*, *Toxoplasma gondii*, cytomegalovirus, toxoplasmosis, cytomegalovirus (CMV), herpes simplex virus (CMV), varicella zoster virus (VZV), and invasive fungal infections, (D) introduction of novel diagnostic technology facilitating earlier recognition and treatment of infections, (E) expansion in the criteria to select donors and recipients to include various scenarios dealing with HBV, HCV, and HIV infections [2], and (F) shift toward predominantly Gram-positive bacterial infections and multiresistant bacteria in recent years [3–5].

A Stanford team lead by Dr. Bruce Reitz performed a Lung transplantation as a combined heart-lung transplant procedure in 1981 [6]. Shortly after, thoracic surgeons optimized the single- and double-lung transplant procedures. Improvement of surgical techniques, especially bronchial anastomosis and evolution of flush perfusion lung preservation, decreased the perioperative bronchial complications substantially. Similarly to heart transplantation, improvements in immunosuppressive regimens, antimicrobial prophylaxis, and graft preservation led to enhancement in survival among lung transplant recipients. In contrast to cardiac, lung transplantation has faced the challenge of infections unique to the transplant of this organ. Mold infections of the anastomotic site, host versus graft disease, and serious infections with *Mycobacterium abscessus*, *Chlamydia* spp., bronchiolitis, and *Burkholderia cepacia* complex are among infectious complications rarely observed in other transplant patients [7].

Transplantation of thoracic organs has improved the quality of life and prevented the death of thousands of

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A. Safdar (ed.), *Principles and Practice of Transplant Infectious Diseases*, https://doi.org/10.1007/978-1-4939-9034-4_2

individuals worldwide. Graft survival and life expectancy have been markedly improved in these patients due to the introduction of more optimal immunosuppression, antimicrobial prophylaxis, and diagnostic technology allowing the earlier diagnosis and treatment of infection and rejection. Finally, further control of infection is likely to result from implementation of new approaches to assess the net state of immunosuppression in these patients.

Epidemiology

Infection was recognized as a major threat to thoracic transplantation from the early inception days [8]. There are several factors predisposing thoracic transplant recipients to infections: (A) factors present before transplantation: age, presence of comorbidities (e.g., chronic kidney disease, diabetes mellitus, cancer, etc.), nutrition status, latent infections, colonization with healthcare-associated organisms, and occult community-acquired infections; (B) factors during the surgery: duration of the transplant procedure, graft injury including ischemic time, colonization or latent infection of the graft, surgical instrumentation (e.g., mechanical ventilation, invasive devices such as catheters, drains, Foley catheters, etc.), ICU stay, and need for re-interventions; and (C) factors present after transplant: degree of immunosuppression, CMV infection, and rejections (Table 2.1).

Table 2.1 Clinical features modifying infection risk in transplantation

Before transplantation
Age
Comorbidities: diabetes mellitus, chronic kidney disease, cancer, etc.
Nutrition status
Latent infections or occult community-acquired infections
Colonization with healthcare-associated organisms
During transplantation
Duration of the transplant procedure
Graft injury
Ischemic time
Anastomosis site in lung transplant
Denervation of allograft (e.g., diminished cough reflex)
Lymphatic drainage disruption
Colonization or latent infection of the graft
Surgical instrumentation (e.g., mechanical ventilation)
ICU stay
Need for re-interventions
After transplantation
Immunosuppression
CMV infection
Rejections

Heart Transplant Infections

A total of 4096 heart transplants were performed in 2011. Heart transplant recipients have an average age of 54 years and are predominantly man (76%). They have a significant history of smoking (46%) and hypertension (45%) and have cardiomyopathy (54%) followed by coronary artery disease (37%) as the leading causes of transplant [1]. The historical (pediatric and adult transplants between 1982 and 2011) 1-year, 5-year, and 10-year survival rates are 81%, 69%, and 50%, respectively. Overall median survival is 11 years, but it increases up to 13 years for those surviving the first year after transplantation. Although not associated with increased posttransplant mortality, infections before transplant can affect up to 25% of heart transplant candidates. Being bronchitis and soft tissue infections, the more commonly present [9]. Despite no major changes in the distribution of causes of death since 1994, infections remained a predominant factor of mortality during the first 3 years after transplant. It contributes with up to almost 20% of causes of death [3]. The global incidence of infections in heart transplant ranges between 30% and 60% and the associated mortality between 4% and 15% [10]. The incidence of infection measured as major infectious episodes per patient has steadily declined from 2.83 in the early 1970s to 0.81 in the early 2000s [3, 8, 11]. The most frequent type of infection is bacterial (44%), followed by viral (42%), fungal including *Pneumocystis jirovecii* (14%), and protozoa (0.6%). Unfavorable functional outcomes are observed in patients who developed infections in the first year of transplant, mainly associated with bloodstream, CMV, and lung infections [12]. Pulmonary and central nervous system (CNS) infections are independent predictors of mortality among heart transplant recipients. Reactivation of latent parasitic infections residing in extra-cardiac tissues in the host or transmitted in the transplanted heart is an important consideration. The classic example is the reactivation of *Trypanosoma cruzi*. Chagas disease is a vector-borne illness transmitted by triatomine bugs, and it is endemic in Latin America. The ethnicity or origin of either the donor or the recipient from these regions should raise the concern for possible reactivation. Chagas reactivation was documented in 38.8% of cases in a cohort of Brazilian heart transplant recipients, where Chagas cardiomyopathy was the second most common indication for transplant (34.9%) [13]. Chagas can also reactivate from the transplanted heart procured from a seropositive donor and transplanted into a seronegative recipient. Although with a substantial decreased on its prevalence in the most recent eras, toxoplasmosis is another important consideration in this setting. Similarly to Chagas, *Toxoplasma gondii*—also

with a predilection to invade the myocardium—can be transmitted by reactivation of quiescent cysts in the recipient or the transplanted heart [14].

Lung and Heart-Lung Transplant Infections

By 2011, 3640 adults received lung transplantation, the highest reported number of procedures up to that date, driven mainly by the increase of double-lung transplants. Double-lung transplant is indicated for septic lung diseases (e.g., cystic fibrosis). Around 66% of recipients were aged 45–65 years old. The most frequent indications for transplant were COPD (34%), followed by interstitial lung disease (ILD) (24%), bronchiectasis associated with cystic fibrosis (CF) (17%), and α1AT deficiency-related COPD (6%) [15]. The overall (from 1994 to 2011) 1-year, 5-year, and 10-year survival rates among lung recipients are 79%, 53%, and 31%, respectively. Overall median survival is 5.6 years. Lung transplants from CMV seronegative donors have better survival rates than from CMV seropositive donor. Thirty-day mortality was led by graft failure (24.7%) and non-CMV infections (19.6%). During the remainder of the year, non-CMV infections were the leading cause of death (35.6%). Infection is still prominent as the cause of death following the first year of transplant after bronchiolitis obliterans syndrome (BOS)/chronic lung rejection or graft failure [15]. Other infections complications historically present among the ten primary causes of death within the first year include sepsis, pneumonia, and fungal infections [16]. High lung allocation score (LAS) at the time of transplantation is associated with a lower 1-year survival and higher rates of infections among lung transplant recipients [17].

Sixty-three adult Heart-Lung transplantations were reported to the ISHL registry in 2011. Sixty-six percent of recipients were in the group range from 18 to 49 years old. Sixty-three percent of the indications were for congenital heart disease and idiopathic pulmonary arterial hypertension. Heart-lung transplant for CF was higher in Europe and other centers compared to North American. When compared to lung only transplants, short-term survival was worse, but long-term survival was better for the heart-lung transplant recipients. Their 1-year, 5-year, and 10-year survival rates were 63%, 44%, and 31%, respectively. The median survival was 3.3 years and 10 years for those surviving the first year. Similarly, they have graft failure (27%), technical complications (21.9%), and non-CMV infections (17.8%) as leading causes of death during the first 30 days posttransplant. Non-CMV infections (35.1%) were the top cause of death after 1 month and within 1 year of transplant. After the first year, BOS/late graft failure and non-CMV infections were the predominant causes of death [15]. Among other risk factors for mortality in lung transplantation are cystic fibrosis, nosocomial infections, and mechanical ventilation before transplant [18].

Infections in lung transplant recipients are predominantly bacterial (48%), viral (35%), fungal (13%), and mycobacterial (4%) [19]. In 60%, the infection site is pulmonary. Risk factors for infection vary by the type of organism. Mechanical ventilation (MV) for >5 days immediately following transplant surgery and isolation of *Staphylococcus aureus* (SA) from airway cultures in the recipient were considered risk factors for invasive SA infections in a retrospective study of patients with lung and heart-lung transplants [20]. Likewise, risk factors for the development of healthcare-associated infections with Gram-negative organisms, *Aspergillus*, *Legionella*, and MRSA (methicillin-resistant *Staphylococcus aureus*), include prolonging MV, renal failure, use of ATG (antithymocyte globulin), and recurrent rejections episodes [21]. Additionally, α-1-antitrypsin deficiency and repeat transplantation are also risk factors for nosocomial infections. *Mycobacterium tuberculosis* transmission from lung donors with latent infection has been documented in highly endemic areas [22]. Colonization with MDR organisms (*Pseudomonas aeruginosa*, *Burkholderia*, *Acinetobacter*, nontuberculous mycobacteria (NTM), and *Scedosporium*) before transplant—especially important in CF patients—can predict the development of challenging infections to treat after transplant [23].

Pretransplant Evaluation of Recipients and Donors

Pretransplant Screening of Recipients

Patients should undergo a comprehensive evaluation of potential infectious complications associated with transplantation. A detailed medical history including previous vaccinations, history of past infections, exposures (geographical, occupational, animal, etc.), travel, and foreign-born status among others should be obtained.

Clinicians shuold perform routine serologies for the detection of pathogen-specific IgG for CMV, HSV, EBV (VCA), VZV, hepatitis B (HBsAg, HBsAb, HBcAb), HIV, hepatitis C, and syphilis. Toxoplasma IgG should also be performed in heart and heart-lung transplant candidates. Additionally, we recommend to obtain UA, urine culture, CXR, and tuberculin skin test (TST), or a Quantiferon assay. In lung and heart-lung transplant candidates, sputum should be cultured for bacterial, fungal, and AFB studies.

Some centers advocate the screening of patients for colonization with MDR (multidrug resistant) bacteria such as MRSA and VRE (vancomycin resistant *Enterococci*),

which it may have an impact on the type of antibacterial prophylaxis used preoperatively or the empirical antibiotics should sepsis develop in the immediate postoperative period. In potential lung recipients, previous respiratory colonization with MDR *Pseudomonas*, especially in CF patients, should not exclude them from transplant [24]. On the other hand, if colonization with *B. cenocepacia* (genomovar III) in CF is present transplant is relatively contraindicated [25, 26].

Checking for endemic fungi such as *Coccidioides immitis* or for the parasites *Trypanosoma cruzi*, *Strongyloides stercoralis*, and *Leishmania* spp. is indicated in the presence of the appropriate risk factors [27–31].

Histoplasma capsulatum has reactivated during immunosuppressive therapy [32]. Infections after solid organ transplantation (SOT) are rare and attributable to transmission from the donor [33]. Furthermore, latent histoplasmosis can be present with negative serologies and treatment after transplant carries a good outcome. Therefore the role of screening for histoplasmosis is of questionable significance [34].

Pretransplant Screening of Donors

The type of evaluation may change if the donor is alive or deceased depending on the available time to collect the samples. Similarly to recipients, donors should undertake a comprehensive assessment including a complete history, assessment of risk factors, exposures, immunizations, and previous or current infections. Donors should be screened for HIV, hepatitis B/C, syphilis, and tuberculosis. Furthermore, we recommend to obtain serologies for CMV, EBV, HSV, VZV, and *Toxoplasma gondii*, and for HTLV-1/HTLV-2 in endemic areas. In high-risk donors, the use of nucleic acid amplification tests (NAAT) for HBV, HCV, and HIV should be considered. Additionally, blood cultures to document an occult bacteremia are recommended. In lung transplant donors, we recommend obtaining respiratory cultures through bronchoscopy to detect colonizing organisms and target them to prevent invasive infections in the donor. Culturing the media of the allograft during acquisition or processing have been advocated to reduce the risk of mycotic aneurysms among kidney transplant recipients, which may apply to other SOT [35]. Screening of donors for endemic mycosis is not well established. On the other hand, heart transplant donors should be screened for Chagas if the donor was born in Latin America [29]. Finally, it is important to highlight the increase recognition of emerging, unusual viral infections such as West Nile virus, lymphocytic choriomeningitis virus, rabies, and different human coronaviruses [34, 36]. Testing for those organisms should be done based on individual assessments. Table 2.2 describes and summarizes the diagnostic workup recommend among donors and recipients.

Table 2.2 Infectious screening during transplantation

Diagnostic workup among donors and recipients
Routine tests obtained among donors and recipients:
Viral test: HIV Elisa, hepatitis C antibody, HBV (HBsAg, HBcAb total, HBsAb), IgG antibody for CMV, HSV, EBV VCA, VZV
Bacterial: Treponemal antibody (e.g., EIAs, FTA-ABS), QFN assay or PPD
Parasite: Toxoplasmosis IgG (routinely indicated for heart transplant patients)
Other screening to consider among donors or recipients in the presence of specific risk factors:
Viral: NAAT for HIV, HCV, HBV in high-risk donors. HTLV-1/HTLV-2 in donors from endemic areas
Bacterial:
Recipients: UA, urine culture, CXR, and sputum culture. *Optional*: To consider screen for colonization with MDR organisms (MRSA or VRE)
Donors: Blood cultures, allograft media culture, and bronchoscopy with culture from respiratory specimens in lung donors
Parasite: Ortho EIA and Abbott Prism Chagas test to screen for *Trypanosoma cruzi* in donors or recipients from Latin America. *Strongyloides stercoralis* and *Leishmania* spp. serologies should be obtained in recipients in the presence of appropriate geographic risk factors
Fungal: EIA for coccidioidal antibodies or complement fixing antibodies for cocci

Abbreviations: NAAT Nucleic acid amplification test, *CXR* chest X-ray, *MDR* multidrug resistant, *EIA* enzyme-linked immunosorbent assay

Prevention of Infections

Immunizations

Immunization should be optimized before transplantation since the recipient will have better chances to mount an adequate immune response [37]. The advisory committee on immunization practices (ACIP) [38] and the guidelines for immunizations in solid organ transplantation [39] recommend inactivated influenza vaccine annually. Tetanus, diphtheria, and acellular pertussis (Tdap) should be administered to all adults who have not previously received Tdap or have an unknown status. Varicella vaccination with two doses in patients without evidence of immunity or a single dose of zoster vaccination, inactivated polio vaccine, hepatitis A/B, HPV (three series through 26 years of age), and meningococcal and pneumococcal vaccines should be administered [38]. It is remarkably important to vaccinate all household members as well. BCG and rabies vaccines can be considered under some extenuating or exposure-related indications. See Table 2.3.

Avoidance of Exposures

Education of the patient and the family members is a cornerstone to establishing effective preventive measures. Emphasis should be enforced about hand hygiene and food handling.

Table 2.3 Immunizations recommendations during transplantation

Recommended vaccines among heart, lung, and heart-lung recipients
Annual inactivated influenza vaccine
Tdap (should be administered to all adults who have not previously received Tdap or have an unknown status)
VZV (two series) in patients without evidence of immunity
Zoster vaccine should be given in varicella-positive candidates age ≥60 years and considered in candidates aged 50–59 (>4 weeks before transplant)
Inactivated polio
Hepatitis A series
Hepatitis B series
HPV (three series through 26 years of age)
Pneumococcal: Pneumococcal conjugate 13-valent (PCV13) followed by pneumococcal polysaccharide 23 (PPSV23) vaccine 8 weeks later (If PPSV23 was received first; PCV13 should be given at least 1 year after)
Meningococcal conjugate vaccine
Under special circumstances: Rabies and BCG

Additionally, potential sources of bacteria, fungi (e.g., *Aspergillus*), and toxoplasmosis such as plants and flowers, cleaning pet's litter or cages, eating uncooked meat, acquiring new pets, construction areas, farming, barnyard activities, and smoking marihuana should be avoided. If those recreational or occupational exposures are unavoidable; appropriate gear, such gloves, must be worn. Education about possible community exposures is also important. Close contacts with persons with fevers or rash potentially infected with VZV, herpes zoster, or influenza should be circumvented as well. Patients should cook all meals thoroughly, wash all fruits and vegetables, and shun all unpasteurized products. Safe sex practices are recommended. If any foreign travel is planned, seeking evaluation in a specialized travel clinic is advisable.

Prophylaxis

Guidelines for the management of surgical antimicrobial prophylaxis list cefazolin (2 g, 3 g for patients with weight >120 Kg every 4 h) as the recommended regimen for heart, lung, and heart-lung transplantation surgery. Clindamycin (900 mg every 6 h) or vancomycin (15 mg/kg) can be substituted as alternative agents in beta-lactam allergic patients [40, 41]. This recommendation can be adjusted individually, based on local hospital surveillance data or previous knowledge of colonizing organisms (e.g., addition of aztreonam, gentamicin, or a single-quinolone dose). However, the widespread use of quinolones may increase the resurgence of antimicrobial resistance. The antibiotic should be administered within 60 min before surgical incision (within 120 min for vancomycin or quinolones) and to be continued for 24–48 h in heart transplants and 48–72 h and no longer than 7 days in lung and heart-lung transplant recipients. Recommendation to continue antibacterial prophylaxis until chest and mediastinal tubes are removed lacks sufficient evidence. Redosing will depend on the procedure duration and associated blood loss.

The recipient does not need treatment if a localized infection was present in the donor, except during meningitis where concomitant bacteremia often coexist. In meningitis and bacteremia, it is prudent to treat the recipient for 2–4 weeks [34].

Indications for antifungal prophylaxis in heart transplant recipients are not clear. A systemic review showed no benefit of antifungal therapy to prevent invasive fungal infections in transplants recipients other than liver [42]. Although a prospective cohort of heart transplant recipients showed targeted prophylaxis—an echinocandin for a median of 30 days with the presence of at least one risk factor for invasive aspergillosis (IA) (reoperation, cytomegalovirus disease, posttransplantation hemodialysis, and another patient with IA in the program 2 months before or after the procedure)—was highly effective and safe in preventing IA episodes [43], no consensus exists for universal antifungal prophylaxis in heart transplant recipients. Most centers have adopted antifungal prophylaxis including inhaled amphotericin B, oral itraconazole, or IV targeted echinocandin prophylaxis.

In lung and lung-heart transplant recipients, fungal prophylaxis should be considered, especially if pretransplantation respiratory cultures either from the donor lung or recipient airways shows *Aspergillus* or *Candida*. One approach is to use inhaled amphotericin B (50 or 100 mg in extubated or intubated patients, respectively) daily until 4 days after transplant and then weekly until hospital discharge in patients with no known colonization [44, 45]. If a mold has been isolated, voriconazole is recommended up to 4 months after transplant. Although evidence and efficacy need to be confirmed, combination antifungal prophylaxis therapies is used at some centers [46].

Pneumocystis jiroveci prophylaxis is done with trimethoprim-sulfamethoxazole (TMP-SMX) for 6 months, up to 1 year. Some centers extend the PJP prophylaxis to lifelong. TMP-SMX also confers protection against *Toxoplasma*, *Nocardia*, and *Listeria* species infections. Alternatively, dapsone, inhaled pentamidine, or atovaquone can be used in patients with a history of sulfa allergy. TMP-SMX is recommended at many centers for lifelong in toxoplasmosis seronegative recipients of seropositive cardiac donors (*Toxoplasma* D+/R−) [11].

CMV prevention is recommended to all D+/R− and R+ patients. There are two common strategies for CMV prevention: antiviral prophylaxis and preemptive therapy. Both approaches possess similar success rate and their advantages and disadvantages [47]. Guidelines recommend valganciclovir or intravenous ganciclovir as the preferred antivirals. Oral ganciclovir is an option in heart transplant patients, although it possesses a low oral bioavailability and therefore the theoretical risk of increased resistance. Often, CMV immune globulin is used as an adjunctive agent. In heart recipients, prophylaxis is recommended for 3–6 months in D+/R− and 3 months in R+. In lung and heart-lung recipients, the duration of prophylaxis is 12 months and 6–12 months in D+/R− and R+ recipients, respectively [48]. In D−/R− patients, otherwise not receiving CMV active

agents, antiviral prophylaxis against other herpes viruses, such as HSV and VZV, should be considered. Use of oral CMX001 (oral liposomal formulation of cidofovir) in hematopoietic-cell transplants reduced CMV-related events and may have a potential role in preventing CMV in other transplant settings [49]. Refer to Table 2.4 for a list of prophylaxis recommendations.

Table 2.4 Antimicrobial prophylaxis

Prophylaxis in heart, lung, and heart-lung transplant
Bacterial[a]:
Preferred: Cefazolin 2 g (3 g for patients with weight >120 Kg). Redose every 4 h for extended procedure time and significant blood loss
Alternative: Vancomycin 15 mg/kg or clindamycin, 900 mg IV
CMV prophylaxis[b]:
Valganciclovir, 900 mg PO once daily
IV ganciclovir, 5 mg/kg IV once daily
Oral ganciclovir (heart transplant), 1 gr PO three times a day
Consider adjuvant therapy with CMV immune globulin
Pneumocystis jiroveci:
TMP-SMX, one single tablet a day or one double-strength tablet three to seven times a week for 6–12 months
Alternatively, dapsone (100 mg PO daily); inhaled pentamidine (300 mg/dose monthly) or atovaquone (1500 mg PO once daily) can be used
Other: In D−/R− patients, otherwise not receiving CMV prophylaxis, consider acyclovir to prevent HSV/VZV reactivation
Prophylaxis in heart transplants
Parasitic:
Consider lifelong TMP-SMX in toxoplasmosis mismatch recipients (D+/R−)
CMV prophylaxis:
Doses as above. Duration: 3–6 months in D+/R− and 3 months in R+ recipients
Fungal (optional):
IV echinocandin daily for 30 days in the presence of IA risk factors
Prophylaxis in lung and heart-lung transplants
Bacterial:
Consider the addition of aztreonam, gentamycin, or a single-quinolone dose in the presence of previous respiratory cultures positive for Gram negatives
CMV prophylaxis[b]:
Doses as above. Duration: 12 months in D+/R− and 6–12 months in R+ recipients
Fungal:
Negative pretransplant respiratory cultures: Inhaled *amphotericin B*, 50 or 100 mg in extubated or intubated patients, respectively, daily until 4 days after transplant and then weekly until hospital discharge
Positive pretransplant respiratory cultures for *Aspergillus*: *voriconazole*, 6 mg/kg every 12 h for 2 doses; followed by maintenance dose of 4 mg/kg every 12 h, is recommended up to 4 months after transplant. Maintenance dose can be achieved with oral voriconazole 200 mg PO every 12 h

Abbreviation: IA Invasive aspergillosis

[a]The antibiotic should be administered within 60 min before surgical incision (within 120 min for vancomycin or quinolones) and to be continued for 24–48 h in heart transplants and 48–72 h and no longer than 7 days in lung and heart-lung transplant recipients

[b]Doses of valganciclovir, ganciclovir, and other antibiotics may require adjustment for renal function

Risk of Infection Posttransplantation

<1 Month

This period is characterized more commonly for nosocomial, bacterial infections. Thus, the bacterial organisms present are often MDR (e.g., VRE, MRSA). In heart transplant recipients, skin and soft tissue infections (SSTI), surgical site infection, and mediastinitis are of concern during this period. Likewise, lung and lung-heart transplant recipients may develop infections related to previous respiratory colonization (*Pseudomonas, Aspergillus*). Other significant infections include aspiration pneumonitis, healthcare- and ventilator-associated pneumonia, catheter-related bloodstream infections (CRBSI), nosocomial UTIs, and *Clostridium difficile* colitis. Donor-derived infections during this period can be present and will include HSV, lymphocytic choriomeningitis virus (LCMV), rhabdovirus (rabies), West Nile virus (WNV), and HIV. *Toxoplasma gondii* and *Trypanosoma cruzi* are also serious donor-derived infections in heart transplant recipients that can develop within the first 6 months posttransplantation [50].

1–6 Months

During this period, reactivation of latent infections usually occurs. Hence, bacterial infections such as those caused by *Nocardia asteroides*, *Listeria monocytogenes*, and *Mycobacteria tuberculosis* typically occur. Additionally, fungal infections by *Aspergillus* spp., *Cryptococcus neoformans*, and *P. jirove*ci and parasitic by *Toxoplasma gondii*, *Leishmania* spp., *Strongyloides*, and *Trypanosoma cruzi* can also be seen. Viral infections present during this period include herpesviruses (HSV, VZV, CMV, and EBV) and adenovirus.

>6 Months

Development of infections after 6 months are predominantly community-acquired pneumonia and urinary tract infections. Other diseases include *Aspergillus* and *Mucor* species, *Nocardia*, *Rhodococcus*, and late viral infections including CMV, hepatitis B and C, JC polyomavirus infection, post-transplant lymphoproliferative disorder (PTLD), HSV encephalitis, and viral community-acquired infections (e.g., coronavirus, West Nile virus, influenza).

Monitoring

Infections

It is important to recognize transplant recipients as a patient population with increased susceptibility to infections and

have a low threshold to perform diagnostic workup in the presence of any concerning signs or symptoms. Infections monitoring is also done in a structured way when preemptive therapy for CMV is in place (as opposed to universal prophylaxis). Protocols vary by the transplant center but, usually, implies a weekly CMV PCR or pp65 Ag monitoring [51]. Likewise, monitoring of cell-mediated immunity (CMI) using a Quantiferon-CMV assay may be useful predicting late-onset CMV disease once CMV prophylaxis has been stopped [52]. CMI also have been monitored for EBV using an enzyme-linked immunoSpot assay [53].

Immunoglobulin G (IgG), C3, IgG2 levels, and NK cell counts have been proposed as an attempt to identify the risk of infection in heart transplant recipients within the first year [54].

Drug-Drug Interactions

Significant drug-drug interactions exist among antimicrobial and immunosuppressive agents. Patient medication list should be reviewed carefully. CTP3A4 strong inducers such as nafcillin reduce tacrolimus serum concentrations. In contrast, azoles such as fluconazole can result in increased levels of tacrolimus or cyclosporine. For voriconazole, the dose of tacrolimus needs to be reduced by two-thirds [55] and the cyclosporine dose by 50% [56]. Rifamycins can have an opposite drug-drug interaction by decreasing the concentrations of prednisone, cyclosporine, tacrolimus, sirolimus, and mycophenolate mofetil (MMF) [57, 58]. Likewise, tacrolimus administration along with quinolones may cause QT prolongation [59].

Infections in Heart Transplantation

Infecting Microbial Agents

Bacterial

In heart transplant patients, bacterial infections have similar clinical manifestations commonly observed in other patient populations. However, clinical signs may be subtle or absent (e.g., afebrile). They are the most frequent type of infections in this setting, reaching up to 50% of all infections [3]. The most common are pulmonary infections followed by bacteremias, mediastinal, and skin infections. *Staphylococcus aureus*—predominantly methicillin-resistant—can cause SSTI, ventilator-associated pneumonia, mediastinitis, CRBSI, other forms of bacteremia, and osteomyelitis. In contrast, coagulase-negative *Staphylococcus* is more commonly associated with CRBSI. Among Gram-negative bacteria, *Pseudomonas aeruginosa* is common, usually of pulmonary origin. *Escherichia coli* is the primary causal organism of UTIs. Extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae*, *Escherichia coli*, *Klebsiella oxytoca*, and *Citrobacter freundii* are also found in 2.2% of heart transplant recipients [60].

Nocardia species are well recognized as an opportunistic pathogen in this setting. Although relatively rare in heart transplant recipients (frequency <1%), *Nocardia* is only second in frequency in heart transplant after lung transplant recipients [61–63]. Pertinent-independent risk factors associated with the development of this infection in SOT include high-dose steroids, history of CMV disease, and high levels of calcineurin inhibitors [62]. With the almost universal prophylaxis with TMP-SMX, *Nocardia* infection is less common and often present late, usually after 1 year posttransplant [63]. When they occurred, they affect the lung predominantly, which is the port of entry for disseminated infections and CNS invasion. Also, it can cause skin nodules and abscesses. *Listeria monocytogenes* can also be seen in heart transplant recipients and can count for a significant proportion of the bacterial meningitis cases in this setting [64]. Additionally, myocarditis and myocardial abscesses with this organism have also been documented [65]. *Mycobacterium tuberculosis* and nontuberculous mycobacteria (NTM), although, documented to occur in heart transplantation, are rare in the United States [66, 67]. However, it is important to recognize that the development of tuberculosis (TB) can be more prevalent in some endemic regions and often present with extrapulmonary involvement [68, 69]. *Legionellosis* and *Rhodococcus equi* with mainly pulmonary manifestations (pneumonia, pulmonary infiltrates, or cavitation) are another significant infections among heart transplant recipients [70].

Fungal

Fungal infections excluding PCP represent around 4.0% of all the infections. From them, invasive mold infections (IMI) are a significant contribution to morbidity and mortality among heart transplant recipients. The incidence in this population can reach 10 per 1000 person-years, and its associated mortality is approximately 17% [71]. *Aspergillus* represents up to 65% of all IMI. Its median time of onset is about 46 days, although late presentation (>90 days) has been more recently recognized associated with receipt of sirolimus in conjunction with tacrolimus for refractory rejection or cardiac allograft vasculopathy [72]. The most common clinical presentation for aspergillosis includes fever, cough, and single or multiple pulmonary nodules [73]. Extrapulmonary manifestations include spondylodiscitis, infective endocarditis, mediastinitis, endophthalmitis, and brain and cutaneous abscesses [74–78]. Dissemination tends to affect the CNS in a good proportion of the cases. Mucormycosis is the second most frequent mold affecting heart transplant recipients. *Mucor*, along with other non-*Aspergillus* molds (e.g., *Scedosporium*, *Ochroconis gallopava*), are associated with disseminated infections, CNS involvement, and poorer outcomes [79, 80]. *Pneumocystis jiroveci* (PCP)—although with a marked reduction in inci-

dence with the introduction of universal prophylaxis—is still a significant pathogen and cases may occur late after heart transplant. Cryptococcosis, although infrequent among SOT patients, has its higher incidence in heart transplant recipients [81]. Usually, its manifestations present late and affect the lungs and the CNS predominantly. Histoplasmosis and coccidioidomycosis occurred typically in the first year after transplant. Antigenuria was the most sensitive diagnostic test in SOT for histoplasmosis [82]. Finally, *Candida* infections are an important cause of morbidity and mortality as well. Rate of colonization is higher than in the general population [83]. *Candida* most commonly causes an oral mucosa infection. Although there has been a decline of invasive infections over time, these do occur and typically in the form of bloodstream infections secondary to catheter-related infections, tracheobronchitis, or disseminated disease [84]. Additionally, other confined end-organ injuries such as endophthalmitis and esophagitis can also be seen.

Viral

CMV infection is of critical importance among SOT. In heart transplant recipients, CMV has been inconsistently associated with cardiac allograft vasculopathy [85]. Furthermore, CMV leads to upregulation of pro-inflammatory cytokines, increase procoagulant response, left ventricular dysfunction, allograft rejection, and an increase of opportunistic infections [86]. The greatest risk for developing CMV disease is CMV-negative recipients of CMV-positive organs (D+/R−), followed by D+/R+ and D−/R+. A clinical report estimated that the rate of *infections* in heart transplant ranges between 9% and 35%, and *disease* is present in around 25% of patients [87]. The clinical manifestations are not unique to heart transplant recipients and include a CMV syndrome (fevers, myalgias, arthralgias, malaise, leukopenia, and thrombocytopenia). CMV-associated end-organ injury in this setting includes most frequently pneumonitis and gastrointestinal disease [10]. Other manifestations comprise myelosuppression, hepatitis, and pancreatitis. In contrast to the high frequency observed in AIDS patients, chorioretinitis in heart transplant patients is relatively rare [87]. Guidelines on CMV diagnosis and managements are discussed in more detail in Chap. 55 and also have been published elsewhere [88]. Other herpes viruses are of important consideration as well. EBV-associated T-cell PTLDs are more frequent in heart transplant recipients (0.4%) than in other SOT patients [89]. PTLD is a significant contributor to morbidity and mortality in the pediatric heart transplant population [90]. Human T-lymphotropic virus type I (HTLV1), human herpes virus (HHV)-6, HHV-7, and HHV-8 might play a role in EBV(−) T-cell PTLDs as well. Herpes viruses can manifest, as in other hosts, as mucocutaneous lesions for HSV, herpes zoster for VZV, infectious mononucleosis in the case of EBV, Kaposi sarcoma for HHV-8, and encephalitis for HHV-6/7. Hepatitis, colitis, pneumonitis, and gastrointestinal disease have also been attributed to dissemination with certain herpes viruses. Herpes viruses can present with disseminated skin lesions (with or without vesicle formation) and fever of unknown origin.

Adenovirus has been associated with rejection, ventricular dysfunction, coronary vasculopathy, and the need for retransplantation. The current standard treatment for adenovirus is cidofovir, but outcomes are not optimal [91].

Chronic hepatitis without an identifiable cause should prompt testing for hepatitis E virus (HEV). Chronic HEV infection leads to the rapid development of fibrosis. HEV testing should be done with RNA PCR due to a delay in the antibody response. We recommend decreased immunosuppression and ribavirin therapy for 3 months [92, 93]. Other less common manifestation that should be considered under the correct epidemiologic risk factors include HTLV-1/HTLV-2-associated myelopathy, rabies, lymphocytic choriomeningitis virus, subacute measles encephalitis, mumps (associated parotitis, orchitis, vestibular neuritis, and allograft involvement), dengue virus, orf virus, human coronavirus, and influenza [36].

Parasitic

Cardiac transplant itself is one the predictors for development of toxoplasmosis [94]. Other associated risk factors include negative serum status before transplant, diagnosis of cytomegalovirus (CMV) infection, and high-dose prednisone. Toxoplasmosis can be transmitted by the donor heart (D+/R−, especially during the first 3 months) or can reactivate from the recipient (>3 months). Most of the infections developed during the first 6 months posttransplant and are predominantly primary infections. About 22% of infected patients had a disseminated infection carrying an estimated 17% mortality. Toxoplasmosis can manifest otherwise with myocarditis, encephalitis, pneumonitis, or chorioretinitis. Diagnosis requires identification of tissue cysts surrounded by an abnormal inflammatory response, detection of *Toxoplasma* DNA in body fluids by PCR, or positive *Toxoplasma*-specific immunohistochemistry in affected organs. Posttransplant serological tests are not helpful for diagnosis and may be misleading since results may change or not regardless of the presence of toxoplasmosis [95]. The preferred treatment regimen is a combination of pyrimethamine with sulfadiazine [96].

Advanced Chagasic cardiomyopathy is a primary indication for heart transplantation in some centers [13]. *Trypanosoma cruzi*, the causal organism of Chagas disease, can be transmitted up to 75% of the time from infected heart donors (D+/R−) [97]. Additionally, Chagas disease can reactivate from the donor once immunosuppression is

in place (R+). The reactivation rate can range between 22% and 90% in recipients with chronic chagasic cardiomyopathy undergoing heart transplant [98–100]. Additional risk factors for reactivation include rejection episodes, neoplasms, and use of MMF [98]. The mean onset of symptoms is approximately 112 days [101]. Once manifested, Chagas can present with nonspecific symptoms such as fever, malaise, anorexia, hepatosplenomegaly, and lymphadenopathy. Myocarditis, pericarditis, and encephalitis are also seen. Reactivation can mimic rejection and exhibits congestive heart failure, AV block and skin manifestations such as nodules and panniculitis. Increased eosinophil count and anemia can be indirect indicators of reactivation [102]. Diagnosis is made with the visualization of circulating trypomastigotes in peripheral blood. Additionally, blood and tissue PCR can be used. Tissue amastigotes can be seen in biopsy H&E preparations (Fig. 2.1). Finally, serologies are a crucial aspect in the diagnosis especially if seroconversion have been documented. In asymptomatic individuals, when the diagnosis of Chagas has been established in the donor, monitoring should be instituted with weekly blood *T. cruzi* PCR and microscopy [29]. Preferred antitrypanosomal therapy consists on benznidazole. Nifurtimox is an alternative treatment option. Posaconazole has anti-parasitic activity but carries high failure rates [103, 104]. GI disease with *Isospora* (*Cystoisospora*) *belli*, *Cryptosporidium*, *Cyclospora*, and *Microsporidia* has been reported to affect SOT recipients. Microsporidiosis can manifest with disseminated disease: fever, keratoconjunctivitis, CNS involvement, cholangitis, cough, and thoracic/abdominal pain [94]. Other rare parasitic infections affecting heart transplants include leishmaniasis, strongyloidiasis, and free-living amoebas [94, 105].

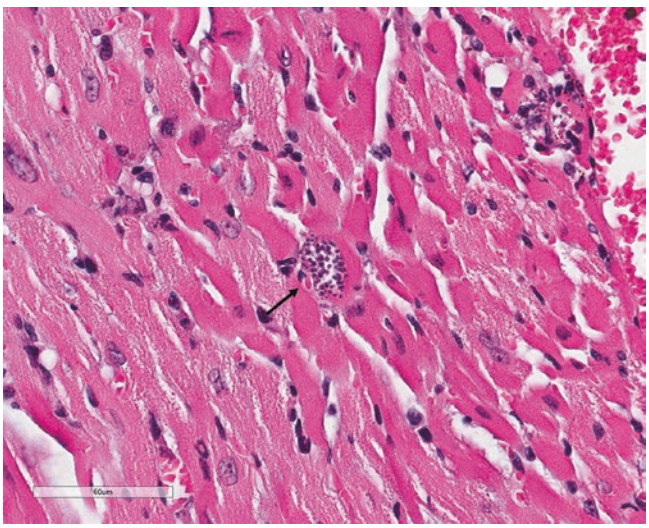

Fig. 2.1 *Trypanosoma cruzi* amastigote in heart tissue (H&E stain, 400×)

Sites and Types of Infection

Skin, Soft Tissue, and Bone

The rate of surgical site infections (SSI)—sternal wound infections—in patients receiving antimicrobial prophylaxis ranged from 5.8% to 8.8% following heart transplant procedures [41]. Heart transplantation itself is an independent risk factor for SSIs. Other risk factors include age, prophylaxis with ciprofloxacin alone, positive wire cultures, female gender, previous left ventricular assist device (VAD) placement, BMI >30 kg/m^2, previous cardiac procedures, and inotropic support for hemodynamic instability [41, 106]. Similarly to other hosts, *Staphylococcus* species are the predominant organism causing SSTIs. MRSA can reach up to 21% of the cases. Gram-positive organisms: VRE (*E. faecalis*), coagulase-negative staphylococci, and other *Enterococcus* species are other etiologic agents. Candida and selected gram negatives such as *Enterobacteriaceae*, *P. aeruginosa*, and *Stenotrophomonas maltophilia* can cause SSIs as well [107]. Sternal osteomyelitis often complicates deep SSI. Additionally, sternal wound infections by NTM and fungi such as *Aspergillus* and *Scedosporium* have been documented [108, 109]. Herpes zoster is also an important consideration and source of morbidity. Herpes zoster (HZ) is found as a complication in 19–22% of the patients with a median time of presentation ranging from 0.73 to 2.10 years [64, 110]. Close to half may develop postherpetic neuralgia. Multi-dermatome involvement, zoster ophthalmicus, and meningoencephalitis are also described. Exposure to MMF is an independent risk factor. Conversely, CMV prophylaxis reduces the risk for HZ.

Bloodstream

Bloodstream infections (BSIs) are a risk factor for mortality among heart transplant recipients. Likewise, SOT recipient status is an independent risk factor for developing bacteremia [111]. In heart transplant recipients; the rate of BSI ranged between 16% and 24%. The median onset is about 51–191 days, and the sources are in order of frequency: lower respiratory tract, urinary tract, and CRBSI. Gram-negative bacteria were more commonly isolated. They are in order of appearance *E. coli*, *P. aeruginosa*, and *K. pneumoniae*. More common Gram-positive bacteria were *S. aureus*, *S. epidermidis*, *E. faecalis*, and *L. monocytogenes*. Directly attributable mortality is 12.2%. Among the identifiable independent risk factors to develop BSI are hemodialysis, prolonged intensive care unit stay, and viral infections [112, 113]. Infective endocarditis (IE) is seen more frequently among heart transplant recipients than in the general population. With IE occurred, it most commonly involves the mitral and tricuspid valves and *Staphylococcus aureus* and *Aspergillus* are the main etiologic organisms. The main predisposing factors in this setting are believed to be the frequent use of vascular indwelling cathe-