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Post-transplant infectious complications and therapeutic approaches

Zümer Duman, Oytun Erbaş

Institute of Experimental Medicine, Gebze-Kocaeli, Türkiye

ABSTRACT

Infections are a clinical condition that we are constantly exposed to in our daily lives, and they can sometimes be fatal. Infections caused by the disruption of a protective mechanism in the body, particularly when immunosuppressive drugs are used to prevent organ rejection after organ transplantation, carry more life-threatening risks. In this review, we discussed how human immune systems react to various infectious agents, as well as common infections and treatment approaches in organ transplants such as kidney, liver, heart, and lung transplants.

Keywords: Infection, organ transplantation, posttransplant infection, transplantation.

In general, infection occurs when microorganisms that cause disease invade the body tissues of a living being, multiply, and the host tissues respond to infectious microorganisms and the toxins they produce. Infections have a wide range of transmission, location, and impact. Some diseases occur when a person interacts with and is exposed to an external source; these are known as exogenous infections *(Clostridium tetani, Neisseria gonorrhoeae,* etc.). Many infectious diseases in humans can occur when a microorganism that should be in the person's microbial flora proliferates in a different body area than where it should be; for example, candidemia, which occurs when *Candida* species found in the urogenital tract and colon pass into the blood.[1] Foreign body infection (FBI) can be caused by a foreign body in the nose, eyes, skin, or elsewhere, or it can be caused by an infection of a vascular graft or a prosthesis. The latter is a broader term for medical FBI, also known as biomaterial-associated infection.[2] Another sub-branch is Orthopedic Device Related Infection (ODRI),[3] which is a biomaterial-related infection of an orthopedic implant. It can be seen as a result of the use of orthopedic implants for medical purposes such as screws, plaques, and prostheses. Periprosthetic infection, often known as an infection associated with arthroplasty, is another type of infection that can be brought on by ODRI if the orthopedic implant is a prosthesis.[4] As can be seen, the notion of infection alone creates a complicated network of interwoven relationships.

To prevent the transmission and development of infection, humans have three fundamental defense systems. The first is 'natural barriers,' which include skin, mucus, and stomach acid, and the second is 'non-antigen-specific (natural) immune defense (innate),' which includes fever, interferon, complement system, neutrophils, macrophages, and natural killer (NK) cells, and at last 'antigen-specific adaptive immunity,' which includes antibodies and T lymphocytes. Only until the agent has overcome all of these defensive barriers does the infection occur, and each infectious agent is subjected to a unique immune response.[1]

THE IMMUNE RESPONSE TO BACTERIAL INFECTIONS

The complement system is one of the fastest and most essential defense mechanisms against pathogens.[1] Recognition molecules on bacterial cell surfaces trigger the alternating and lectin pathways of the complement system, whereas the classical pathway is activated by subsequently

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Correspondence: Zümer Duman.
e-mail: zumerduman@hotmail.com

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formed antibody-antigen complexes. The division of two core complement proteins, C3 and C5, performs the fundamental tasks of complement.[5,6] All recognition processes converge on the production of convertase enzymes on the surface of bacteria. First, C3 transducers degrade the primary protein C3 to create C3b, which releases a reactive thioester bond, allowing C3b to covalently connect to the hydroxyl groups of carbohydrates on the bacterial cell surface.[6,7] When the amount of C3b molecules on the surface increases, it efficiently triggers and facilitates phagocytosis by immune cells. Labeling bacterial cells with C3 products also induce an adaptive immune response by causing bacteria to be transported to lymphoid organs and enhancing antigen delivery to acquired immune cells.[6,8-10] The accumulating C3b molecules also affect the structure of the C3 transducer. When the local density of C3b is high, C3 transducers transition to C5 transducers, changing the substrate from C3 to C5.[6,11] It induces the release of the peptide C5a, a powerful chemoattractant that causes an oxidative burst that enhances the collection of phagocytes at the site of infection by activating C5. Furthermore, C5a-mediated activation of basophils and mast cells causes histamine synthesis followed by vasodilation. Simultaneous C5b production activates a membrane attack complex (MAC; C5b-9). This destroys Gram-negative bacteria rapidly.[12] Gram-positive bacteria are likely protected from MAC-related mortality since their strong peptidoglycan outer layer stops the MAC from accessing the cell membrane.[6,13]

Neutrophils are another type of defensive mechanism. Pathogen detection and subsequent neutrophil ingestion to infection sites are critical components of host defenses against bacterial disease. Neutrophil uptake is a multi-stage process that includes extravasation of bloodstream neutrophils to areas of distal infection and/or injury, mobilization of neutrophils from bone marrow reserves, and enhanced hematopoiesis when required. Invasive pathogens and their signature pathogen-associated molecular patterns (PAMPs) are identified by host pattern recognition receptors (PRRs) that contain toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) proteins. Receptor ligation induces the production of chemokines such as tumor necrosis factor (TNF), granulocyte-colony stimulating factor (G-CSF), or granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as various proinflammatory host cytokines such as interleukin (IL)-8, IL-1 alpha (α), and IL-beta (β), chemokine (CXC motif) ligand 1 (CXCL1; GROα), CXCL2 (MIP2α), CXCL (ENA78). These compounds operate as chemoattractants, promoting neutrophil uptake into infected tissues. To kill trapped bacteria, neutrophils engage both oxygen-dependent and oxygen-independent mechanisms.[14] Their secreted prostaglandins and leukotrienes increase vascular permeability, induce edema, and trigger pain receptors.[1] Bacterial pathogen phagocytosis results in the generation of antimicrobial reactive oxygen species (ROS) such as superoxide radicals, hydrogen peroxide, hypochlorous acid, hydroxyl radicals, and chloramines. Additionally, cytoplasmic granules interact with bacterium-containing phagosomes to enrich the vacuole lumen with antimicrobial peptides and proteases. Therefore, the strong antimicrobial activity of neutrophils is a combined effort of highly proteolytic and degrading enzymes, cationic compounds, and ROS.[14]

Macrophages, as opposed to neutrophils, have a longer lifespan. Activated macrophages with proinflammatory properties in infection produce a number of proinflammatory mediators, including TNF-α, IL-1, IL-6, and type 1 interferon (IFN-I), which assist in the activation of numerous microbicidal processes and contribute to the clearance of invasive pathogens.[15-17] Activated macrophages can also mediate the adaptive immune response to severe infection by secreting IL-12 and IL-23, which promote the polarization of T helper (Th) 1 and Th17 cells, respectively, or by secreting IL-4 and IL-13, which aid in the differentiation of Th2 cells for extracellular infections. Macrophages may destroy bacteria using a variety of substances, including antimicrobial proteins such as ROS, nitric oxide (NO), and defensin. One study found that macrophage elastase, also known as matrix metalloproteinase-12 (MMP12), destroyed both Gram-negative and Gram-positive bacteria within macrophages.[18] Following bacterial ingestion, intracellular MMP12 migrates to macrophage phagolysosomes and binds to the bacterial cell

wall, disrupting bacterial membranes and resulting in bacterial death.[19] Macrophages may also work with platelets to fight pathogens. When infected with *Bacillus cereus* or methicillin-resistant *Staphylococcus aureus (S. aureus)* (MRSA), Kupffer cells rapidly capture these bacteria and activate platelets under basal conditions, resulting in a continuous release of GPIIb from the Kupffer cell surface, allowing the bacteria to be enclosed through "touch and go" adhesion.[20]

THE IMMUNE RESPONSE TO VIRAL INFECTION

The immune response is the most effective and, in many cases, the only way to control viral infections. In viral infections, the primary purpose of the immune response is to eliminate both the virus and the host cells that contain the virus.[1]

Interferons are cytokines produced in response to viral and microbial infections, with the most remarkable property being the capacity to block viral growth nonspecifically by inducing an "antiviral state" in cells.[21] Interferons are classified into two types: IFN-Is, also known as viral IFNs, which comprise IFN-α (leukocytes), IFN-β (fibroblasts), and IFN-omega (ω). Type 2 IFN (IFN-II) is often referred to as immune IFN-gamma (IFN-γ). Viral IFNs are produced in response to virus infection, whereas IFN-II is produced in response to mitogenic or antigenic stimuli. In cell culture, most virally infected cells can produce IFN-α/β. IFN-γ, on the other hand, is produced solely by immune system cells such as NK cells, CD4+ Th1 cells, and CD8+ cytotoxic suppressor cells.[22-24] Natural IFN-α producing cells are assumed to be dendritic precursor cells (pDCs).[25,26] According to a study, purified CD4+CD11c-type 2 dendritic cell precursors (pDC2s) from human blood released up to 103 times more IFN than other blood cells when a microbial or viral threat was detected in cell culture.[26]

Natural killer cells are lymphocytes that belong to the innate lymphoid cell family. The primary functions of NK cells include the direct death of target cells via the release of granules containing the cytotoxic proteins perforin and granzymes, as well as the secretion of the marker cytokines IFN-γ, as well as the TNF, GM-CSF, and chemokine (C-C motif) ligand 3 (CCL3) and 4 (CCL4). As direct effectors and immunoregulators a result, NK cells support host defenses.[27] Through studies using animal models, the function of NK cells in virus defense has been thoroughly investigated. Analysis of the NK cell response to the herpesvirus, murine cytomegalovirus, in particular, revealed crucial insights on how NK cells can precisely detect virus-infected cells and help to viral infection control.[27,28]

Macrophages become active during viral infection and cause inflammation, which prompts an antiviral response and the pathogen's eradication.[29] Macrophage activation is mediated by intracellular signaling events starting with the recognition of single- or double-stranded viral ribonucleic acid (RNA) as PAMPS through PRRs, including TLRs; cytoplasmic retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs); and melanoma-differentiation-associated gene 5 (MDA5, also known as Ifih1 or Helicard); and NOD-like receptors (NLRs).[29-33] The PAMP-PRR connection triggers an antiviral response by generating cytokines such as IFN-Is, IL-1β, and inducible nitric oxide synthase (iNOS), causing the infected cell to undergo apoptosis.[29,30,34]

THE IMMUNE RESPONSE TO FUNGI AND PARASITES

Primary immune responses to fungal infections begin with the binding of fungal cell wall polysaccharides to TLRs and the Dectin-1; supplied by neutrophils, macrophages, and antimicrobial peptides. The Th17 and Th1 responses of CD4 T cells increase neutrophil and macrophage activation. Patients with low neutrophil or CD4 T cell responses (for example, acquired immunodeficiency syndrome; AIDS patients) are more vulnerable to fungal infections.[1] For some fungi infections (such as mucormycosis and aspergillus), defensins and other cationic peptides may be important; nitric oxide may also be significant for *Cryptococcus*[35] and other fungi.[36] The removal of a fungus with opsonin can be facilitated by antibodies.

Since parasites have distinct forms and settle in different tissues during their life cycle, antiparasitic immune responses cannot be generalized; for example, *Plasmodium* species settle in hepatocyte and erythrocyte cells, but

Leishmania species settle in macrophages. Immunoglobulin (Ig) E (IgE), eosinophils, and mast cells are very effective against worms (nematode and cestode). Macrophages phagocytize extracellular parasites such as *Leishmania* species. Extracellular parasites can be phagocytized and killed by neutrophils via both oxygen-dependent and oxygen-independent processes. Eosinophils, on the other hand, congregate around parasites; they bind to IgG or IgE on the surface of larvae or maggots (such as helminths and *Schistosoma mansoni)*, secrete a major basic protein (MBP) into the intercellular space, and degranulate as a result of the fusion of intracellular granules with the plasma membrane. On parasites, MBP has a toxic effect.[1]

INFECTIOUS COMPLICATION AFTER KIDNEY TRANSPLANTATION

The most recent U.S. Public Health Service guidelines on donor's kidneys with elevated risk refer to kidneys from donors whose tests for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) were negative but whose risk of exposure to the viruses was enhanced due to behavioral risk factors. The risk of HCV and HIV transmission from these donors is low (0.1-0.3%), and the risk of HBV transmission is <1.0%. Understanding the potential complications for recipients based on donor type is critical for providing the best treatment possible to these patients.[37]

Urinary tract infection (UTI) is a pathological invasion of the urothelium defined by clinically specific signs and symptoms as well as an inflammatory response triggered by an infectious pathogen (especially bacterial agents and *Candida* species). Urinary tract infections are the most important and prevalent infection in adults, and the most common pathological condition in patients undergoing kidney transplantation (KTx), with a much greater prevalence in these patients than in the general population.[38-40] These infections not only have a negative impact on patient well-being, but they also increase the risk of further complications in patients undergoing organ transplantation, particularly with regard to potential drug interactions, the development of resistant bacteria,[41] and the potential impact on severe sepsis, long-term graft survival, and even death.[40,42,43] Even a minor amount of UTI in the post-transplant period can result in a reduction in graft function as determined by the glomerular filtration rate (GFR).[44] Therefore, UTI prevention and early detection are critical to reducing the risk of life-threatening complications and graft loss.[45] The true impact of UTIs in this context, however, is still being contested, and certain aspects, such as morbidity and mortality from UTIs, remain contentious. After a KTx, UTIs might appear as symptomatic infections or as asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of more than $>10^5$ bacteria colony-forming units per milliliter (CFU/mL) in a urine culture with no local or systemic symptoms.[46] Symptomatic UTI is characterized as either uncomplicated (with local urinary symptoms such as dysuria and urgency but the presence of $>10^5$ CFU/mL without systemic symptoms) or if urinary symptoms are associated with systemic symptoms (allograft pain, fever, chills).[40,44,47] The European Association of Urology has traditionally proposed a classification based on the severity of UTIs that distinguishes six different degrees of infection severity [cystitis, mild-to-moderate pyelonephritis, severe pyelonephritis, systemic inflammatory response syndrome (SIRS), severe urosepsis, and uroseptic shock]. The general consensus is that all transplant recipients with asymptomatic bacteriuria should be treated within the first three months after transplantation, even though UTI may not be clinically specific since acute pyelonephritis (APN) can develop into a risk for bacteremia, urosepsis, and allograft rejection. The initial treatment of empirical antibiotics should be followed by a specific course of antibiotics based on the pathogen and sensitivity pattern detected in the urine culture. Uncomplicated UTIs can be treated as an outpatient, and common antibiotic regimens include ciprofloxacin 250 mg twice daily, levofloxacin 500 mg once a day, amoxicillin 500 mg three times a day, and nitrofurantoin 100 mg orally twice daily.[48] The duration of medication should be varied based on the patient's characteristics and the time of transplantation (10-14 days after transplantation, 5-7 days after six months),[49] and the dosage should be adjusted in patients with impaired graft function. For the risk of APN or other complications, the graft

requires hospitalization and intravenous (IV) therapy, which comprises both Gram-negative and Gram-positive organisms based on function (piperacillin-tazobactam 4.5 g IV every 6 hours, meropenem 1 g IV every 8 hours, cefepime 1 g IV every 8 hours).[48] Urine culture samples should be taken before beginning empirical antibiotic treatment in uncomplicated UTI, and appropriate treatment should be initiated based on the results of the treatment urine culture. There is no agreement on the ideal period, and general recommendations advocate treating all patients with complicated UTIs for 14-21 days, and then switching to oral medication after the symptoms have resolved. Patients experiencing relapses or recurrent UTIs (three or more attacks in a year) should be assessed for potential predisposing factors (structural and functional abnormalities of the urinary tract), and treatment duration may be extended (up to three months). In other circumstances, patients can switch to prophylactic antibiotics after only a brief duration of antibiotic therapy.[40,48,49] Due to the possibility of substantial graft and patient complications, the majority of patients get treatment. Despite this, some research warns against using this strategy unless the patient has a urological or neutropenic condition.[50] Fluconazole is the preferred medication; however, the dosage of 200-400 mg is taken orally daily and calcineurin inhibitors may need to be adjusted after 14 days. Due to the restricted urine concentrations, lipid formulations should not be used for amphotericin B (0.3-1 mg/kg/day IV) nephrotoxicity. Alternative treatments (flucytosine, voriconazole, echinocandins) may be considered in specific cases, particularly in the treatment of transplant pyelonephritis. Guidelines classify UTIs as sporadic (fewer than three attacks per year) or recurrent (more than three attacks per year) based on the frequency of symptoms.[40,51]

The BK virus (BKV) is an icosahedral, envelope-free, double-stranded deoxyribonucleic acid (DNA) virus from the polyoma virus (PV) family. This virus, which was isolated in 1971, is a substantial risk factor for KTx dysfunction and allograft loss. Unfortunately, treatment options for BKV infection are limited, and there is no effective prophylaxis. Although excessive immunosuppression remains the primary risk factor for BKV infection after transplantation, other risk factors have been identified, including male sex, older recipient age, previous rejection status, degree of human leukocyte antigen (HLA) incompatibility, duration of prolonged cold ischemia, BKV serostatus, and ureteral stent placement. Routine BKV screening has been demonstrated to prevent allograft loss in patients with BK viruria or viremia. Since therapy options for BK virus nephropathy (BKVN) are limited, the aim of screening is to allow for early detection of viruric or viremic patients and intervention before overt nephropathy develops. Prospective screening studies have revealed that BKVN is mostly an early complication of KTx, with the majority of cases occurring within the first year. The BK virus can be found in both blood and urine. After BKV reactivation, the virus is first detected in the urine and viremia emerges a few weeks later. Patients have been reported in a few isolated cases to have viremia without viruria, but this is unusual. Compared to BKV viruria, the positive predictive value (PPV) for BKV is higher (50-60%).[52] For this reason, screening for BKV has become the primary screening approach at many institutions. Real-time polymerase chain reaction (PCR) is used to assess BKV viral loads; a BKV-specific sequence is amplified by a fluorescent probe, and the number of amplicons produced is compared to a standard curve created by serial dilutions of a known BKV DNA concentration. Immunosuppression reduction is a core part of BKVN treatment. There are many different management strategies, and discontinuing the anti-metabolite may require reducing the dosage of the calcineurin inhibitor (CNI) to much lower levels of 25-50% (tacrolimus 3-4 ng/mL and cyclosporine 50-100 ng/mL or less) or switching from tacrolimus to cyclosporine.[53] The most typical strategy is to stop using an anti-metabolite such as mycophenolate mofetil (MMF). However, one study[54] suggests that tacrolimus and cyclosporine, both of which inhibit anti-BKV Tcell responses *in vitro*, may pose a barrier to this treatment. Other options for treatment include leflunomide, cidofovir, ciprofloxacin, rapamycin, or intravenous immunoglobulin G (IVIG).[55] Rapid viral decrease was related to steady or improving GFR regardless of treatment approach.[56]

The Parvovirus B19 (PVB19) is a small, non-enveloped, single-stranded DNA virus in the *Parvoviridae* family, identified in 1975 and first related to human disease in 1981. The PVB19 infection causes a variety of clinical syndromes (fifth disease, transient aplastic crisis, pure red cell aplasia, and hydrops fetalis) as well as the development of additional disorders.[57] Approximately 10% of KTx recipients had PVB19 DNA quantifiable in plasma samples without clinical symptoms in the first year following transplantation. However, symptomatic infection is quite rare.[58] Since there is no specific antiviral medicine for PVB19 infection, treatment is mostly symptomatic. Kurtzman et al.[59] published the first effective treatment of PVB19 human infection with IVIG in 1989, and it soon became the treatment of choice. Unfortunately, the optimal dose and duration of IVIG treatment in PVB19 infection have not been determined; also, long-term resolution of the infection has been documented in some patients without IVIG treatment. The American Society of Transplantation suggests lowering immunosuppression at the time of diagnosis and using IVIG at 400 mg/kg/day for five days.[60] In actual practice, however, there is no agreement on the best way to treat PVB19 infection.[61]

Infection with cytomegalovirus (CMV) is a common complication among KTx recipients. It usually occurs within the first year of transplantation, and when it does, it has both immediate and long-term implications for the patient and the graft.[62] The direct effects, which are associated with high rates of viral replication and occur in the form of CMV infection, are well recognized. However, the indirect impacts are more difficult to identify and are induced by the interaction of low rates of viral replication with the immune system. During a time when viral preventive and surveillance measures were not widely used, the incidence of CMV infection was high (60% infection and 30% disease).[63] Both donor and recipient CMV sero-pairing, and the usage of antilymphocyte antibodies, were significant risk factors for CMV disease.[64] This determined the patients' risk of infection, and they were classed as having a high, medium, or low risk of infection. This classification is still used to organize the prevention strategy.[65] Indirect effects have been linked to increased morbidity (opportunistic infections), graft loss, and long-term mortality.[66-73] Antiviral drugs that are effective in cytomegalovirus control (ganciclovir and valganciclovir), improved diagnostic methods, and the use of CMV prevention strategies (universal prophylaxis and early treatment) represented an important milestone in improving transplant care and outcomes, lowering the risk of CMV infection, which is associated with the risk of acute rejection, mortality, and long-term graft loss.[67,68,73-76]

One of the leading causes of life-threatening infections in immunocompromised hosts is invasive aspergillosis (IA). The one-year incidence of IA in KTx recipients is 0.65%, and it is associated with a high 12-week mortality rate ranging from 16 to 39%.[77-80] According to the most recent Infectious Diseases Society of America (IDSA) guidelines, the most prevalent agent is *Aspergillus fumigatus*, and voriconazole monotherapy is elective therapy, including clinical manifestations affecting the central nervous system (CNS).[81] Aspergillus fumigatus has developed a global resistance to triazoles in recent years.[82] In parts of Europe, IA caused by azole-resistant *Aspergillus fumigatus* may account for one-fifth of cases and has a significant mortality rate.[83] If resistance is suspected, azole monotherapy should be avoided, and empirical combination therapy (voriconazole plus an echinocandin or liposomal amphotericin B [L-AmB]) is recommended in areas with 10% environmental azole resistance, and L-AmB should be used as the primary treatment in the case of CNS.[80,81,84,85]

Pneumocystis jirovecii (P. jirovecii) is an opportunistic pathogen that causes severe respiratory infection in immunocompromised hosts.[86] Without prophylaxis, the incidence of *P. jirovecii* pneumonia (PCP) varies from 0.6 to 14% in KTx recipients, with a mortality rate of up to 50% despite aggressive antibiotic treatment.[87,88] Several studies have examined at the link between PCP and mortality,[87,89] however, the impact of PCP on graft rejection and overall graft outcomes has received less attention. Certain infections, including CMV and BKV, have been linked to acute rejection in the early post-transplant period.[90-93] Given that appropriate infection prophylaxis and treatment regimens can be applied to address the

immunological complications that occur later, this is a significant clinical challenge. However, the clinical effects of PCP are still unknown.[94]

INFECTIOUS COMPLICATION AFTER LIVER TRANSPLANTATION

Liver transplantation (LTx) has proven increasingly successful over the years, with great patient outcomes and low mortality, giving patients with poor prognoses a better chance of survival. The longevity of the graft and the patient has continued to improve as a result of breakthroughs in medical and surgical treatment, particularly the introduction of induction therapy and better immunosuppressive regimes. These medicines are used to prevent or treat rejection by inhibiting T-lymphocyte activation through diverse mechanisms. Since this problem has virtually disappeared, infectious complications are now a common source of morbidity and mortality following transplantation. The majority of bacterial infections arise after transplantation; individuals on the waiting list might colonize with the community *(Aspergillus spp., Nocardia spp., Cryptococcus, S. aureus*) or hospital-acquired organisms that are frequently resistant to multiple drugs, including MRSA. Bacterial and fungal infections are frequently connected with surgical complications (e.g., incisions, the presence of a central line, or complications related to intubation) in the first six months following transplantation. Bile leakage can result in peritonitis or an intra-abdominal abscess, and early graft injury can result in a liver abscess.[62,95]

The bacteria *S. aureus* has emerged as a significant infection that complicates the clinical course of LTx recipients.[96,97] *Staphylococcus aureus* is a commensal organism that colonizes the skin and mucous surfaces, producing infections when the skin or mucosal barriers are breached.[98] The anterior nostrils are the primary reservoir of *S. aureus* and can function as an endogenous source of infection in colonized patients. Therefore, nasal carriage has been linked to an increased risk of infection in hemodialysis patients, intensive care unit patients, surgical patients, LTx recipients, HIV-infected patients, and long-term care facility patients. Patients colonized with MRSA may be at higher risk than patients colonized with methicillin-susceptible *S. aureus* (MSSA). However, MRSA carriers frequently have poorer clinical conditions than other patients, so differences in infection rates may also be related to differences in host characteristics. Patients using tacrolimus and corticosteroids may benefit from taking cefoxitin as an antibiotic as the first line of defense.[99]

Pseudomonas aeruginosa (P. aeruginosa), one of the most fatal bacteremia agents, is a Gram-negative bacilli that does not ferment lactose.[100] Aside from its extreme virulence, it is naturally resistant to some routinely used drugs and can acquire resistance to other bacteria. As a result, it causes a wide spectrum of life-threatening acute and chronic infections, particularly in immunocompromised patients. *P. aeruginosa* bacteremia is still a life-threatening complication following LTx and cannot be treated due to the high occurrence of antibiotic resistance. The prevalence of *P. aeruginosa* bacteremia among LTx recipients ranged from 0.5 to 14.4%, with mortality rates as high as 40%. Approximately 35% of all cases of bloodstream infections (BSIs) are caused by *P. aeruginosa* bacteremia, of which 47% are multidrug-resistant and 63% are extensively drug resistant. Hypotension, mechanical ventilation, and increased disease severity, particularly hypotension, are known to affect the mortality of transplant recipients with *P. aeruginosa* bacteremia. Alteration in DNA gyrase A genes and overexpression of proteins involved in efflux systems, such as KPC-2-type carbapenemase, NDM-1, and VIM-2 type metallo-lactamases (MBL), lead to *P. aeruginosa* resistance to a wide spectrum of antibiotics in transplant recipients with *P. aeruginosa* bacteremia. Due to complex mechanisms of drug resistance, *P. aeruginosa* causes high morbidity and mortality in the bacteremic transplant patient. In the early post-transplantation period, early diagnosis and treatment with enough early targeted coverage for *P. aeruginosa* BSI are essential to improving the prognosis for LTx patients.[101]

Acinetobacter baumannii (A. Baumannii) has emerged as a highly drug-resistant pathogen in recent years, capable of causing a wide spectrum of illnesses such as bacteremia, pneumonia, UTI, and peritonitis.[102] Previous research has found that *A. baumannii* bacteremia affects 0.8-15.9% of LTx recipients.[102-110] According to Nie et al.,[111] 3.7% of LTx recipients had an intra-abdominal

infection caused by *A. baumannii*. The total death rate among Acinetobacter-infected LTx recipients ranges from 50 to 90%.[109,110] According to a recent study, antibiotics based on fosfomycin in various combinations can successfully cure this drug-resistant bacteria.[112]

Cytomegalovirus infection is frequent in LTx recipients, with an overall incidence of CMV disease of up to 29%[113] and up to 44-65% in the donor (D+)/recipient (R-) risk group without prophylaxis.[114-116] With an incidence of 2-17% following LTx, CMV hepatitis is a serious consequence of CMV infection.[113,117,118] However, when pre-ganciclovir was utilized, CMV hepatitis affected 64% of high-risk (D+/R-) LTx patients.[115] Cytomegalovirus hepatitis or intragraft CMV infection following LTx is not always linked with a high degree of antigenemia in the blood, implying that CMV can infect the liver even with low viral loads.[118] However, CMV hepatitis has no effect on patients' long-term outcomes, but biliary complications have been reported to be prevalent.[113,118,119] In addition to clinical disease, there is a greater knowledge of the indirect impacts of CMV, such as a higher risk of acute or chronic allograft rejection and the development of additional infections.[113,114,120-122] In patients with LTx, CMV is likely to increase the risk of invasive fungal and bacterial infections, and correlations between CMV and other viral infections have been documented.[121-123] For example, CMV can collaborate with other viruses to hasten the development of HCV.[122,123] Prophylaxis and preventative therapy are the two main approaches to preventing CMV disease following LTx. Cytomegalovirus prophylaxis involves administering antiviral medicines similar to ganciclovir or valganciclovir to people who are at risk of developing CMV disease. CMV prophylaxis has been shown to minimize the incidence of CMV disease, initially after LTx and later in general solid organ transplantation.[116,124] To prevent primary infections, this strategy is advised for all D+/R- recipients, but it is now commonly utilized for other patients as well.[125] Prophylaxis is routinely administered for three months after transplantation. Preventive treatment is based on detecting CMV reactivation prior to the beginning of clinical signs. This approach is primarily advised for intermediate or low-risk individuals, such as R+ recipients. A preventive method, however, has been successfully utilized for high-risk patients (D+/R-).[126] Early administration of antivirals, ganciclovir or valganciclovir, based on viral load monitoring, primarily using sensitive quantitative nucleic acid testing such as quantitative CMV-PCR methods, can avoid the onset of CMV disease.

The number of HCV-positive individuals in Europe is around eight million.[127] The most frequent indication for orthotopic LTx is chronic hepatitis C (CHC), which when left untreated can progress to cirrhosis and eventually end-stage liver disease (ESLD); according to 2011 United States data, CHC accounts for between 28 and 40% of all LTx.[128] In Italy, HCV-related ESLD accounts for 30-40% of LTx.[129] Following LTx, HCV infection recurs virtually invariably, and in roughly 70% of patients during the first year after LTx, histologically proven CHC develops.[130] Donor and recipient age, graft quality, immunosuppression, HCV and IL-28B genotypes, viral load, and CMV infection have all been linked to higher risk and severity of HCV infection recurrence.[127,131] Aggressive HCV treatment prior to the onset of cirrhosis or hepatic decompensation may eliminate the necessity for transplantation or lower the risk of relapse following LTx.[127,131,132] HCV recurrence after LTx might cause liver disease to progress more quickly: 20-30% of patients with relapsed HCV develop cirrhosis of the graft liver within five years, with significantly lower allograft and patient survival rates.[133,134] Currently, all patients with the associated decompensated disease and many cirrhotic patients are contraindicated for IFN-based regimens.[135] After LTx, IFN-based HCV therapy is poorly tolerated because of serious side effects (particularly anemia and infections), which have a negative impact on patient outcomes. Therefore, although significant progress has been made in the treatment of HCV in immunocompetent patients, immunocompromised LTx recipients' results are still far from optimal[132] and there is a continuing need for efficient and well-tolerated anti-HCV medication both before and after LTx.[136]

Invasive aspergillosis (IA) is still uncommon (1 to 8%), despite the 42% frequency of fungal infections in LTx recipients.[137,138] Although

pulmonary aspergillosis is the most prevalent clinical form, 10 to 25% of all cases of IA have CNS involvement, possibly without hematogenous dissemination,[137] resulting in nearly 100% mortality if CNS involvement is present, despite an overall case-fatality rate of 60% in IA.[139] Poor CNS penetration of antifungal drugs traditionally used in IA such as amphotericin B may be the cause of high mortality. Voriconazole is a triazole that outperforms other antifungal medicines in the treatment of cerebral aspergillosis since it crosses the blood-brain barrier and delivers fungicidal drug concentrations within the CNS that exceed the inhibitory concentrations required for *Aspergillus* species. However, there is hesitation to use voriconazole in liver transplant units for LTx recipients since of drug interactions with CNIs, immune reconstitution inflammatory syndrome, and drug interactions that cause hepatotoxicity, with 34% of patients needing frequent treatment interruption.[140-144] Aside from this hesitant treatment, other antifungal medicines (amphotericin B, voriconazole, itraconazole, 5-fluorocytosine, caspofungin, etc.) are used in combination.[145]

COMPLICATIONS AND TREATMENT AFTER HEART TRANSPLANTATION

Heart transplantation (HTx) is a treatment option that, while it's successful in extending and improving the quality of life in patients with refractory heart failure, includes a number of complication concerns that can have a negative impact on recipient outcomes. Some are directly connected to graft characteristics or graft interaction with the host immune system, whilst others are dependent on donor characteristics and, in particular, the side effects of immunosuppressive medicines.[146,147] The majority of difficulties occur within the first few months of surgery, which is compounded by surgical stress and patient weakness at the time of transplantation. Long-term adverse outcomes, on the other hand, might be risky and difficult to control.[148]

Nocardial infections, which have become common in HTx recipients, arise later than other bacterial infections (i.e., six months after transplantation) and are frequently a reflection of the degree of posttransplant immunosuppression. *Nocardia transvalensis* is an uncommon human nocardial infection.[149] Slow growth in culture is a common feature of Nocardia, and it has clinical implications due to its enhanced resistance to numerous antibacterial agents.[150] Traditionally, a long course of sulfonamides is the first line of treatment, but resistance has been reported, particularly among transplant recipients. In some cases, minocycline,[151] piperacillin-tazobactam combination with ciprofloxacin, or imipenem combined with amikacin[152] have been effective. The optimal duration of antibiotic therapy is debatable. Six months of treatment in non-immunocompromised individuals is frequently followed by complete recovery with no relapse. AIDS patients, on the other hand, are treated for the rest of their lives due to the high relapse rate. The optimum period of treatment in less immunocompromised patients, such as solid organ transplant recipients, has not been established.[153]

Immunosuppression and systemic inflammation after transplantation may promote the reactivation of latent virus (donor or recipient origin) and disrupt the host-virus balance against viral replication. Typically, this imbalance can result in an undesirable outcome, favoring both direct CMV cytotoxic effects and so-called indirect CMV effects, which are thought to be a result of the virus's complex immunomodulatory and proinflammatory events: cardiac allograft vasculopathy (CAV) is a common example of a CMV infection's indirect consequence.[154] In order to prevent acute CMV disease and syndrome in solid organ recipients, two different approaches are advised: universal prophylaxis with antiviral drug administration for a set amount of time to all patients at risk of infection, and preventive treatment with antiviral drug administration only to patients with laboratory indicators of CMV infection above a certain threshold but before its clinical manifestation.[155] Although universal prophylaxis is known to almost fully suppress CMV replication in the early posttransplant phase, this strategy may select drug-resistant CMV strains and expose more patients to medication toxicity. Whereas under a preventive strategy, there may be time for subclinical CMV replication, this strategy

greatly reduces the number of patients needing antiviral treatment.[148]

The most frequent etiologic agents in HTx are viruses, followed by bacteria. Infections with the varicella-virus zoster (VZZ) are frequent after HTx, however research on this virus has lagged behind CMV assays. There is no specialized series investigating this infection in HTx. Due to cellular immunosuppression brought on by prophylaxis and rejection therapy, VVZ infection in transplant recipients may be more severe. In one case study, immunosuppressive therapy included three drugs: cyclosporine or tacrolimus plus azathioprine or mycophenolate mofetil and steroids. Patients recovered without extra medicine if they did not develop any specific complications while receiving this therapy approach.[156]

The Hepatitis B virus is a latent virus that lives in the body. Reactivation of HBV can present with a variety of clinical symptoms, ranging from asymptomatic viremia to fulminant hepatic failure, and has primarily been examined in individuals following cytotoxic chemotherapy or immunosuppressive therapy for hematologic malignancies and autoimmune diseases.[157] It can, however, be transmitted from other organ transplants in addition to liver transplants (such as latent in the donor). Adefovir[158] and lamivudine[159] have been used in several studies to treat chronic HBV.

Infection is still the most common complication among transplant recipients, accounting for around 20% of mortality in the first year following transplantation and being a major source of long-term morbidity and mortality. In solid organ transplantation, where immunosuppressants are prescribed indefinitely, clinicians and patients regularly weigh the risks of graft rejection and infection.[160] In this immunocompromised population, *Aspergillus* spp., an opportunistic pathogen, can cause severe infections such as sinusitis, tracheobronchitis, pneumonia, necrotizing cellulitis, brain abscess, or disseminated disease. *Aspergillus* spp. has been identified as the most common cause of invasive fungal infection in HTx recipients, causing pneumonia[161] with a high attributable mortality rate ranging from 53 to 78%.[162-164] Although invasive pulmonary aspergillosis (IPA) is a serious disease in this population, little is known about its natural history. In one study, patients were kept alive with fungal prophylaxis (micafungin or fluconazole) and amphotericin B, amphotericin B+caspofungin or voriconazole+caspofungin depending on the complication developing in the patient.[165]

The prevalence of PCP varies by type of solid organ transplantation. In the absence of prophylaxis, PCP can arise in approximately 2 to 10% of HTx recipients;[88] nonetheless, an attack rate as high as 41% has been reported.[166,167] It has been demonstrated that combining echinocandins with trimethoprim/sulfamethoxazole decreases the risk of death.[168]

Pneumocystis carinii (PC) pneumonia is a leading cause of death and morbidity in immunocompromised individuals, including AIDS patients and solid organ allograft recipients.[149,169,170] This variation can be explained, at least in part, to variances in the spread of PC infection among the general population in different geographical areas.[171,172] Despite the high prevalence of PC pneumonia in immunocompromised patients, little is known about its epidemiological characteristics, transmission process, and sources. It is also unknown whether cases of PC pneumonia in immunocompromised subjects are the result of the reactivation of latent infection or are caused by a recent infection.[173] The conventional treatment for PC pneumonia is intravenous TMP-SMX at a dose of 20 mg/kg per day. This medication delivers the fastest clinical response. 25% of patients experience adverse responses, which might include skin rashes, elevated creatinine, and transaminase levels, hyponatremia, and bone-marrow depression.[170] Although pentamidine is an alternative medication, it has the potential to cause nephrotoxicity, pancreatitis, hypoglycemia, hyperglycemia, and pancytopenia.[174] A new choice is an atovaquone. Clinical response should be anticipated after 3-4 days of TMP/SMX and 5-7 days of pentamidine in the treatment course of 14-21 days. Antimicrobial resistance does not seem to be linked to a lack of response. After 4-5 days of treatment, some[175] switch to pentamidine in situations of persistent fever and deteriorating respiratory condition, while others advise additional therapies such as corticosteroids.[170]

Toxoplasma gondii (T. gondii),[176] obligate intracellular protozoa, has been shown to

infect one-third of the world's population, according to seroepidemiologic investigations. Heart transplant recipients are at an especially high risk of serious sequelae since tissue cysts of the parasite most frequently develop in skeletal muscle and the myocardium. In immunocompetent humans, primary infection is mostly asymptomatic, and chronic parasite latency is maintained by an adaptive T-cell response involving IFN-γ responses mediated by IL-12.[177] T-cell-mediated IFN-γ responses and chronic infection, on the other hand, have been demonstrated to play an important role in the development of CAV, which is currently one of the most significant barriers to long-term survival among HTx patients.[178] Furthermore, if a patient is immunocompromised, there is a significant chance of reactivation, as occurs soon after an HTx (through medicine) to prevent rejection. Transmission of *T. gondii* from seropositive donor to the seronegative recipient has been shown to approach 80% in cases of mismatch. Given the immune response to *T. gondii* and the response to the known pathophysiology of CAV, there is concern that recipients who are *T. gondii* seropositive or who get an HTx from a seropositive donor to a seronegative recipient may have worse long-term outcomes.[179]

Sternal wound infection is still a severe complication following cardiac surgery, with incidence ranging from 1 to 10%. Although the majority of wound infections are superficial and self-limiting, deep sternal infection and acute mediastinitis can be fatal, particularly in HTx recipients who are given immunosuppressive drugs in the postoperative phase. Not only has sternal wound infection been observed in recent clinical trials comparing newer immunosuppressive medications after HTx,[180,181] but the frequency of wound infection has nearly never been studied in single-center studies of clinical outcomes after HTx. Nonetheless, sternal wound infection is a significant cause of morbidity and, in some cases, mortality in these patients. Surgical interventions are used to try to correct it.[182]

INFECTIONS AFTER LUNG TRANSPLANTATION AND TREATMENT

In lung transplant (LTx) recipients, CMV is the most prevalent opportunistic infection. In addition to acute morbidity, several studies have demonstrated that CMV, particularly CMV pneumonia, is related to an increased risk of chronic graft dysfunction shown as bronchiolitis obliterans syndrome (BOS) and poor post-transplant survival.[183] Therefore, CMV prevention remains a critical target for improving long-term LTx outcomes. Although centers routinely administer three months of prophylaxis to at-risk patients following LTx, a considerable proportion of patients acquire infection or illness after prophylaxis is discontinued, highlighting the need for more effective approaches to CMV prevention.[184] A number of early single-center studies suggest the advantage of extending prophylaxis, although concerns about expense, late-onset CMV disease, viral resistance, and bone marrow damage limit interest in extended durations. Several recent investigations, including a multicenter, prospective, randomized, double-blind clinical study, have revealed considerable benefits in continuing CMV prophylaxis beyond three months.[185] Although certain issues remain, the therapeutic implications of these studies imply that prolonged valganciclovir treatment for up to 12 months is obviously advantageous for CMV prevention following LTx.[186,187]

The influenza virus produces annual outbreaks of viral respiratory illnesses that cause major morbidity and mortality. It is particularly dangerous in transplant recipients, causing pneumonia, superinfection, and rejection, and is associated with a high fatality rate.[188] The estimated incidence of influenza among LTx recipients is 1 to 4.1%, however, this is likely an underestimate since the majority of these studies only examined individuals with respiratory symptoms.[189,190] Although most LTx recipients complain of respiratory problems, these may not be present at the beginning of the disease. Progression to viral pneumonia is well described and secondary bacterial pneumonia is not uncommon, although most patients recover from their infection. The most serious issue is that influenza infection is linked to the development of obliterative bronchiolitis, a form of chronic rejection.[189,191] Treatments with oseltamivir give successful results.[192]

In healthy individuals, respiratory syncytial virus (RSV), a respiratory virus acquired in the community and belonging to the Paramyxoviridae family, is typically linked to a moderate, self-

limiting respiratory infection. Infection can cause severe pneumonia and respiratory failure in solid organ transplant recipients.[193] Despite antiviral medication, the acute mortality rate from RSV has been reported to be 10 to 20% in LTx recipients. Additionally, RSV infection has been linked to the later development of BOS.[193,194] There have been studies in which patients were given oral or IV ribavirin for a low-cost and effective treatment.[195,196]

Immunosuppressive medication limits antiviral host immunity, which allows Epstein-Barr virus (EBV) viral replication and B cell transformation, leading to post-transplant lymphoproliferative disorder (PTLD) after LTx. The mechanisms by which EBV survives include latency, evasion of cytotoxic T-cell responses, and down-regulation of host immunity to EBV. The clinical manifestation of EBV can emerge early post-transplant in lung allograft or late-onset with a higher likelihood of dissemination. Advances in monitoring through EBV viral load have offered a tool for earlier detection; however, the sensitivity and specificity of EBV load monitoring after LTx may require further optimization. Once PTLD has developed, adequate histopathologic classification, prognosis, staging, tissue diagnosis, and therapy advice are required. A general treatment paradigm for PTLD has been devised, and it is based on risk factors such as EBV-naive status, clinical presentation, and disease stage and localization. In general, clinical management includes decreasing immunosuppression, using anti-CD20 therapy, and inhibiting plasma cells, followed by chemotherapy for refractory PTLD.[197]

Lung transplant recipients are a unique subset of individuals who are susceptible to invasive aspergillosis since the transplanted organ is constantly exposed to the environment and its possible infections. Invasive *Aspergillus* pneumonia, which occurs disproportionately in lung transplant recipients and may indicate early stages of infection, is a separate infectious agent from *Aspergillus* airway colonization and isolated tracheobronchial infection (without parenchymal disease).[198] Lung transplant centers have used a variety of strategies to reduce the incidence and mortality of IA in LTx recipients, including prophylaxis, mycological surveillance, and early empirical treatment, but the evidence for these strategies is limited to uncontrolled case series and expert opinion.[199]

Due to its prevalence and proclivity to acquire treatment resistance, *P. aeruginosa* is a significant infection for LTx recipients. It is a prevalent colonizer, infecting more than 30% of LTx patients, and is the leading cause of post-transplant pneumonia, accounting for a quarter of all cases.[200,201] Pre-transplant *P. aeruginosa* colonization is very common in individuals with structural lung diseases, particularly cystic fibrosis.[202] Up to 45% of these strains are multidrug resistant.[203] Post-transplant airway colonization with *P. aeruginosa* is linked to the development of BOS, a leading cause of death in LTx recipients.[201,202] Although multidrug-resistant *P. aeruginosa* infections constitute a significant challenge, survival rates are comparable independent of its presence,[204] and pre-transplant colonization with multidrug-resistant *P. aeruginosa* is not an absolute contraindication to transplantation.[205] If a transplant patient has a history of *P. aeruginosa* colonization, at least two antipseudomonal drugs should be continued for two to three weeks after transplantation, based on past antibiotic susceptibility results.[206] Colistin and aminoglycosides are frequently used medicines for the prophylaxis and treatment of multidrug-resistant *P. aeruginosa*. However, they cause cumulative nephrotoxicity, especially when used with CNIs. Newer medicines, such as ceftolozan-tazobactam or ceftazidime-avibactam, may be alternatives, but their role in LTx recipients is unknown.[207,208] In case series, inhaled colistin and aminoglycosides were used as supplementary therapy to intravenous agents for the prevention and treatment of post-transplant infection with multidrug-resistant *P. aeruginosa* in LTx recipients.[209,210] More research is needed, however, to determine its efficacy and safety.[211]

Nocardiosis is a serious infection that affects LTx recipients. The incidence of nocardiosis in LTx recipients is 1.9-3.5%, the highest among all solid organ transplant recipients.[212] In a retrospective study of 473 LTx recipients, nocardiosis occurred 34 months after transplantation on average.[213] The incidence of *Pneumocystis* prophylaxis

with trimethoprim-sulfamethoxazole has decreased,[214] although there have been reports of breakthrough nocardiosis in trimethoprim-sulfamethoxazole-susceptible isolates.[213] The most prevalent signs are subacute nodular or cavitary lung lesions. Furthermore, nocardiosis has a proclivity to involve the CNS, most commonly in the form of single or multiple brain abscesses. Patients may or may not experience neurologic symptoms, thus if a patient has nocardiosis outside the CNS, a radiographic assessment of the brain is required. Common infections as well as skin and soft tissue infections have been described.[212] Nocardiosis must be isolated from samples acquired from suspected infection sites in order to be diagnosed.[211] It is essential to isolate the correct species of Nocardia since antimicrobial susceptibility varies greatly between species and isolates. It is advised that selective media incubation be extended, molecular methods are utilized according to specific species, and clinicians communicate with the clinical microbiology laboratory. The antimicrobial regimen is determined by the infecting isolate's susceptibility pattern, as well as the location and severity of the infection. Trimethoprim-sulfamethoxazole is the preferred drug if the isolate is susceptible. Trimethoprim-sulfamethoxazole alone can cure mild to moderate infections; however, severe infections, central nerve involvement, or disseminated disease necessitate the use of at least two drugs (typically imipenem-cilastatin or amikacin in addition to trimethoprim-sulfamethoxazole). The suggested duration of treatment is 6-12 months or longer, depending on the location and amount of infection, as well as the degree of immunosuppression. Trimethoprim-sulfamethoxazole may be effective in preventing primary and relapse nocardiosis; however, the appropriate dose and duration are unknown.[215]

The incidence of *Clostridium difficile (C. difficile)* infection (CDI) in LTx recipients is 1.9-22.9%, the highest among all solid organ transplant recipients. Aside from the immediate post-transplant period, CDI has a second peak after 24 months.[216] Infection with *C. difficile* has been linked to an increase in mortality among LTx recipients.[216,217] The diagnosis and treatment of *C. difficile* infection are essentially the same as for non-transplant individuals. Among the CDI prevention strategies are lowering unnecessary antibiotic usage through antimicrobial stewardship programs, reducing the use of gastric suppressive drugs, preventing prolonged hospitalization, and enhancing adherence to contact precautions when necessary.[218] The role and safety of probiotics in lung transplant recipients have been identified.[211,219]

In conclusion, the immunosuppressive medications used to prevent organ rejection are the primary cause of all these infections. Treatment is also challenging due to the large variety of infection types, the development of drug resistance in some agents over time, and the variance in each patient's reactions. These reasons contribute to the ongoing development of innovative treatment modalities in medicine. However, in order to tackle the problem completely, instead of immunosuppressive drugs, peaceful drugs targeting only the parts connected to organ rejection should be developed. This approach can improve the quality of life for many patients while also increasing survival rates.

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