GLOBAL SCIENCE LIBRARY

Frontiers in Transplantation

REVIEW ARTICLE

Diagnosis and management of graft versus host disease, infection, malignancy and rejection in transplant recipients

Vaughn E Whittaker and Rainer WG Gruessner*

Department of Surgery, State University of New York, SUNY Downstate Health Sciences University, Brooklyn, NY, USA

Introduction

Modern Transplantation aims to lengthen the duration and quality of the life of the patient whilst minimizing the side effects of the highly effective immunosuppressive regimen designed to prevent rejection. Minimizing side effects such as infections, malignancy, graft versus host disease (GvHD) are key to ensuring this goal as well as prolonging graft survival. With new and emerging infections such as Sars-Cov-2 infection, this becomes even more urgent and important.

In manipulating the complex mammalian immune system to prevent rejection, other unwanted side effects have emerged. As the science of transplantation matures, preventing rejection has largely been overcome. The emphasis is now on prolonging more effectively patient and graft survival while minimizing these morbidities. One of the earliest lessons of transplantation in the sixties is the sustained suppression of the immune system was cardinal to prolonging both patient and graft survival.

Today transplantation has made many advances that success rates approaching 94-96% is the standard and the expected by regulatory agencies and payors. This has been the result of learning from early failures. High dose corticosteroid and azathioprine [1] was the bedrock of early successful allogeneic renal transplantation. The use of these non-selective immunosuppressive regimens had the benefits of increased graft and patient survival but was associated with increased infections often with unusual, opportunistic pathogens [2]. Furthermore, immunosuppressed transplant recipients were noted to have an increased susceptibility to malignancy [3].

Few branches of medicine have achieved the status of being initially experimental to being standard of care in less than a lifetime. Since the initial reports of allogeneic renal transplants, solid-organ transplantation has become mainstream. Kidney, liver, heart, and lung transplants are now standard-of-care therapies for end-stage renal, hepatic, cardiac, and pulmonary disease, respectively. Pancreas and pancreatic islet-cell transplants restore the beta-cell function in patients with diabetes mellitus. The small bowel has also been successfully transplanted as a treatment for patients with short gut syndrome. Rapid and sustained development and advances in critical care, organ procurement and preservation, surgical techniques, anesthesia management, tissue typing, immunosuppressive therapy, and the use of antibacterial, antifungal, and antiviral agents for both prophylaxis and treatment of posttransplant infection has made this possible. (Table 1) lists some of the major advances in the management of graft versus host (GvHD), infection, malignancy and rejection in transplant recipients.

The breath and scope of immunosuppressive regimen available allows for truly personalized medicine in the twenty first century as it relates to creating optimal acceptance of the graft and preventing rejection and side effects. The practice remains challenging to finely balance each patient from being under immunosuppressed and rejecting their organs or over suppressing their immune function and leaving them susceptible to opportunistic infections and malignancies. This chapter reviews the complications (namely, graft versus host disease (GvHD), infection including covid-19, malignancy and graft rejection) of solid-organ transplantation on either side of this delicate balance. Special attention is directed toward opportunistic infections and unusual malignancies that occur in the immunosuppressed patient population.

Graft versus Host Disease (GvHD)

Graft-versus-host-disease (GvHD) is the constellation of clinical findings when transplanted donor allogeneic cells with immune competence attack histocompatibility antigens expressed on tissues of transplantation recipients [4]. It has an incidence of 0.1-2.0% with a mortality rate as high as 75%. It is much more common in patient with bone marrow transplant but still occurs in patients with solid organ transplants [5,6]. The terminology, which has just been subject to a consensus statement and largely refers to bone marrow transplant but is applicable to solid organ transplantation. There is acute GvHD and chronic GvHD. Acute GvHD has inflammatory response in primarily three organs: the skin (inflammatory maculopapular erythematous skin rash), the liver (high bilirubin), and gastrointestinal including anorexia with weight loss, nausea, vomiting, diarrhea, severe pain, and GI bleeding [7-10]. Systemic manifestations such as fever may also be present. The consensus statement concerning a unified method of documenting and diagnosing GvHD is a good resource in distinguishing acute versus chronic GvHD [4].

The condition occurs typically occurs 2 to 6 weeks post solid organ transplant as typified in liver or intestinal transplant recipients but may occur up to 4 months following the transplant[11]. The mechanism is thought to be related to the engraftment of T cells from the donor graft [11]. There is no standard treatment for GvHD.

Hematopoietic cell transplant is associated with graft versus leukemia effect and the new immune cells can remove residual leukemic cells. The mechanism of this effect may be spontaneous or through the infusion of donor cells [1]. The mechanism of this curative effect is the ability of donor T cells to induce graft versus leukemia effect against the malignant cells [2].

Treatment options have included almost complete withdrawal of immunosuppressive agents, steroid therapy, antibody therapy and different types of plasmaphereses. The greatest experience is in bone marrow transplant recipients in whom aside from steroid therapy, extra-corporeal photopheresis has also shown positive treatment

Table 1: Major advances in management of rejection, infection, and malignancy in transplant recipients

Topic	Major advances	Reference
Graft vs Host Disease	Different Types of Plasmapheresis [13]	[7]
	Desensitization protocols for patients with DSA [114,146,147]	[72,103,104]
Graft rejection	Flow cytometry, Luminex-based cross-match [117,148]	[73,105]
	Induction therapy and biologics reduce rejections [119,120,149]	[75,76,106]
Fungal infection	Caspofungin and voriconazole [41,150]	[25,107]
Viral infection	PCR for CMV and EBV detection [60]	[31]
	Preemptive CMV therapy [60,151]	[31,108]
	Liver transplants for patients with HBV or HCV [74,78]	[41,43]
	Improved outcomes for recipients with HIV	[46, 47]
Malignancy	Chemotherapy and rituximab beneficial for PTLD [94]	[56]
	HHV-8 and posttransplant Kaposi sarcoma [152]	[109]
	Liver transplant for patients with HCC [110]	[69]

DSA: Donor-Specific Antibody; PCR: Polymerase Chain Reaction; CMV: Cytomegalovirus; EBV: Epstein–Barr virus; HBV: hepatitis B virus; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; PTLD: Posttransplant Lymphoproliferative Disease; HHV: Human Herpes Virus; HCC: Hepatocellular Carcinoma.

effect. This involves subjecting the peripheral blood to phototherapy to induce apoptosis in mononuclear cells. A consensus statement on the role of extracorporeal photopheresis in the management of T-Cell lymphoma, graft-versus-host disease and organ transplant rejection reports 60% response rates and complete response 14-26% [12]. The postulated mechanisms involve the following: (1.) reduced stimulation of effector T cells; (2.) deletion of effector T cells; (3.) induction of regulatory T cells; (4.) increased anti-inflammatory cytokines; and (5.) reduction of proinflammatory cytokines. Photopheresis seems to downregulate the T-cells alloreactivity that plays a significant role in the pathogenesis of GvHD after bone marrow transplant with hemopoietic stem cells [13]. Additional studies and pursuing these therapies with a view to share the results to add to the current cohort of patients who are being treated with this modality is the current recommendation based on a Cochrane review and other reviews which shows improved outcomes [13-15].

Infections

Infections is one of the achilles heel of transplantation since its inception. It is a natural consequence of suppressing the host immune system in order to maintain organ function and prevent rejection. The development of immunosuppressive therapies has been impressive, leading to the widespread use of solid-organ transplantation as the primary therapy for end stage organ failures including heart, lung, liver, intestines, pancreas and renal. Like a double-edged sword, this success is also associated with infectious complications. Up to 80% of solid-organ transplant recipients experience an infectious complication during the first year posttransplant, and infections remain a major cause of morbidity and mortality in the transplant population [16]. More recent studies from the Swiss group showed the infections in the first-year post-transplant. Bacterial infections accounting for 63% of infections [17].

The relationship between infections and organ transplantation has also taken a new twist. The emergence of highly effective therapeutics for hepatitis C [18] and controlling HIV [19-21] has changed the attitudes towards the use of these organs with a greater emphasis on organ utilization from these donors and realignment of risk profile. The emergence of the covid-19 pandemic [21,22] has also changed the calculus for transplant recipients and some centers are even using organs from patients who had previous covid infection or even have current covid infection that is not present in the broncho-alveolar aspirates. The outcome of this is still not known for the long term and is an emerging area. However, it is an interesting new relationship between transplant and infections.

The range of potential pathogens that can cause disease in the immunosuppressed host is wide and includes viral, bacterial, fungal and other opportunistic infections. Common endogenous and nosocomial flora are involved, as well as “opportunistic” or “atypical” pathogens. These differentials must be considered in solid-organ transplant recipient who has evidence of infection. There is a spectrum of infections which are predictable based on timeline post-transplant. Other considerations include the organ transplanted, the type and level of immunosuppression, the need for antirejection therapy, and the potential incidence of surgical complications.

The first year represent the highest risk timeline for infection. This is associated with the most intense period of immunosuppression and/or after antirejection therapy, particularly for recurring AR episodes. Vidal et al. have characterized periods posttransplant during which certain infection patterns may be seen [16]. Infectious complications in the first month posttransplant are typically caused by endogenous or nosocomial flora that would cause disease in an immunocompetent host [23], including (a) bacterial surgical site infections; (b) postoperative or ventilator-associated pneumonia; (c) urinary tract infections (UTIs) associated with prolonged indwelling urinary catheters; (d) intraabdominal infections related to surgical complications; and (e) central venous catheter infections.

The infections may be classified as those that affect the graft and those that are systemic in nature. Systemic viral infections such as polyoma virus or BK and CMV virus commonly affect the graft as well. CMV may affect other organ systems other than the transplanted graft. These infectious patterns may be categorized into an *early cluster* of viral agents occurring with peak frequency between 2 and 3 months posttransplant and a *late cluster* more commonly occurring between 4 and 9 months posttransplant. The early cluster includes CMV [24], adenoviruses [25], hepatitis B virus (HBV) and hepatitis C virus (HCV), and human herpes virus (HHV)-6. The late cluster includes varicella zoster and polyoma viruses. Epstein–Barr virus (EBV) may cause disease throughout the first year posttransplant [26]. The opportunistic fungi can similarly be observed to cluster with *Candida* and *Aspergillus* species (spp), causing infections in the first 2 to 3 months posttransplant [26], whereas *Cryptococcus*, histoplasmosis, coccidioidomycosis, and *P. jiroveci* most often occur later during the first year [27].

After the first 6 to 12 months, most transplant recipients exhibit patterns of infectious disease morbidity that mirrors the rest of the general population, with frequent respiratory infections secondary to pneumococcal infections and influenza, as well as uncomplicated UTIs. However, opportunistic infections can occur anytime. Increased immunosuppression secondary to AR treatment may slightly increase transplant recipients’ susceptibility to, and alter the temporal pattern of, various pathogens. When assessing immunosuppressed transplant recipients for infectious diseases, the clinician must always maintain a high index of suspicion. The typical localizing signs of infection and inflammation may be blunted, or even absent, because of the anti-inflammatory action of immunosuppressive regimens. Newer techniques involving CRISPR-Cas13 technology in a point of care method may be used to detect infections with BK polyoma DNA and Cytomegalovirus DNA from samples of recipient blood and urine including CXCL9 messenger RNA (detects graft rejection) rejection with elevated levels of these markers [28].

Preoperative assessment of the donor and recipients underlying infections, predisposing disease processes such as diabetes, are key elements of assessing the risk for infection that could manifest after administration of exogenous immunosuppression. For the donor, apart from the serologies including HIV, Hepatitis B and C, the most important evaluation is the determination of Sars-CoV-2, CMV and EBV status, because those three agents are most easily transmitted to a seronegative recipient or those not vaccinated with the covid-19 vaccine [28,29].

For the recipient, a thorough pretransplant history and physical examination are essential to minimize the risk of infectious complications secondary to a latent or indolent infectious process. Routine viral studies should be obtained including SARS-CoV-2, vaccinations updated, and prophylaxis administered where indicated (e.g., gut decontamination in liver transplant candidates with end-stage liver disease or prophylactic antibiotics in patients with cystic fibrosis).

Bacterial infections

Bacterial infections are the most common in the first month post-transplant. This is the same for the general surgery population who has undergone non-transplant surgeries. The site of surgery, the presence of catheters, lines, endotracheal tubes, or breaks in skin will determine the risk of a nosocomial bacterial infection. The urinary tract, the incision site, the lung and blood stream are the most common sites of infections. The risk of nosocomial bacterial infections is directly related to host factors (including underlying diseases such as diabetes or cirrhosis, obesity, and chronic pulmonary disease) as well as to technical and management factors (including the length and technical aspects of the procedure, the development hematoma or seroma, and the need for prolonged urinary catheterization, mechanical ventilation, or central venous catheterization).

Renal transplant and bladder drained pancreas recipient recipients are particularly prone to urinary tract infections. Bacteriuria may be detected in up to 56.7% of renal transplant recipients [30], with an

attendant increased risk of systemic sepsis and wound infection. The most common pathogens are Gram-negative aerobes, enterococci, and *Candida* spp. The risk factors associated with an increased incidence of UTIs include prolonged catheterization, and hemodialysis.

Urinary Tract Infections in transplanted patients is often asymptomatic. As a result, diagnosis in transplant recipients is based on clinical suspicion, urinalysis and culture results. The typical findings of dysuria, hesitancy, and frequency may be absent; fever or an elevated white blood cell count may be the only sign. Treatment is often empiric and, because of the risk of bacteremia, and should consist of intravenous administration of a third-generation cephalosporin or a quinolone, particularly during the first months posttransplant. Once the offending organism has been identified and antimicrobial sensitivity data are available, treatment can be targeted.

Recipients of solid-organ grafts excluding kidney and bladder-drained pancreas with long dwelling urinary catheters, an increased risk of bacterial or fungal UTIs is not seen.

Surgical site infections are potentially another source of major morbidity, occasional graft loss and mortality in solid-organ transplant recipients. These wound infections are classified according to the structures involved. Infections above the fascia are superficial, infections below the fascia are deep, and combined infections involving elements of both the superficial and the deep compartments of the wound [31].

Prophylactic antibiotics is given to all solid-organ transplant recipients, immediately before start of their operation. Antibiotic should be administered within an hour of skin incision, to decrease the risk of surgical site infections. In pancreas, bowel, lung, and liver transplant recipients, significant degrees of wound contamination may occur, so antibiotics are typically administered for 24 to 72 hours posttransplant, although data to support this practice are lacking [32]. Despite this lack of data, there is a potential downside to this practice in inducting resistant organisms. The American Society of Transplantation Infectious Disease Committee encourages restraint and care to avoid resistance organisms and to exercise good antimicrobial stewardship especially in asymptomatic patients [3]. In renal transplant recipients, the surgical site infection rate is very low (1% to 2%) and is comparable to the wound infection rate for other clean-contaminated procedures in immunocompetent patients [31]. Diabetics and morbidly obese patients are exceptions and additional measures may need to be taken to modulate their increased risk of infection such as incision drains. However, other transplant procedures are associated with higher rates of infection. The wound infection rate after heart transplants is typically below 8%. The rate of wound infections is slightly higher after lung and heart–lung transplants [33]. The rate after liver transplants of superficial wound infections is 6% to 8%; of deep wound infections (most commonly an intra-abdominal abscess secondary to a biliary leak), 15% to 20% [31]. The rate of wound infections after pancreas transplants is high: 10% to 40%, superficial; 15% to 22%, deep; and 8%, combined [34]. Such wound infections confer substantial morbidity, are associated with mortality in some cases, and require a very aggressive approach to diagnosis and therapy.

Pathogenic microorganisms are predictable, according to the type of procedure. In renal transplant recipients, wound infections are caused by the endogenous flora of the skin (Gram-positive aerobes) and the bladder (Gram-negative aerobes), with occasional *Candida* spp and enterococci.

In heart transplant recipients, wound infections are almost always due to skin flora such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, although some fungal and unusual pathogens are found.

Lung transplants introduce respiratory flora and the potential for grave infections with *Pseudomonas aeruginosa*.

In liver transplant recipients, wound infections are typically associated with either skin or biliary flora, although any preexisting cirrhosis and end-stage liver disease may result in colonization with drug-resistant nosocomial pathogens.

In pancreas transplant recipients, wound infections are invariably polymicrobial, with gram-positive, fungal, and resistant gram-negative pathogens frequently present. Treatment generally requires opening of the wound, reexploration, and/or administration of broad-spectrum antimicrobial therapy (with carbapenem or extended-spectrum penicillin, a β-lactamase inhibitor, and vancomycin) and often antifungal coverage.

Wound infections are often understated, and findings may be limited to fever, elevated white blood cell count, or wound drainage with a deceptively innocuous appearance. Any wound drainage should be examined by Gram stain and culture; any suspicion or evidence of infections should result in opening of the superficial wound. Additionally, imaging should be undertaken to rule out infections in the deep surgical space; if a fluid collection is identified, percutaneous drainage or prompt exploration is needed. Prolonged, broad-spectrum antimicrobial therapy is used, and immunosuppression is significantly reduced in the face of potentially life-threatening infections.

The development of postoperative pneumonia varies with the type of transplant and is associated with a high death rate (20% to 60%). Renal transplants are associated with the lowest incidence of postoperative pneumonia (1% to 2%); lung transplants, the highest (22%). The most common pathogens are Gram-negative aerobes, staphylococci, and *Legionella* spp. Frequently, *Candida* spp or CMV may be identified along with bacterial pathogens, particularly in the first 2 to 3 months posttransplant.

Factors predisposing to the development of pneumonia in solid-organ transplant recipients include prolonged mechanical ventilation, thoracic surgery, pulmonary edema, and intense immunosuppression or AR treatment. Lung transplant recipients are at increased risk, because of their lungs' preexisting colonization with endogenous flora as well as the loss of the mucociliary clearance function associated with denervation [35]. The evaluation of suspected pneumonia in lung transplant recipients should be thorough, including bronchoscopy with biopsies and BAL to rule out rejection, as described below. Pleural effusions should be drained and cultured, because the progression of an infected effusion to empyema in lung transplant recipients is associated with a very high mortality rate.

Bacteremia in the transplant population, as in the general hospital patients, may occur secondary to seeding along a vascular access device or as a result of hematogenous spread from another source; or it may be primary (without a source being identified). UTIs, wound infections, and pneumonia are risk factors for the development of bacteremia, as is prolonged vascular catheterization. Other risk factors include receiving a deceased donor graft, leukopenia, and antirejection therapy. Bacteremia in immunosuppressed patients may present as fever, leukocytosis, leukopenia, or hypotension without other significant manifestations. Consequently, routine blood cultures should be part of any workup for fever in this population. Suspicion of bacteremia should prompt removal and culture of intravascular devices and judicious search for a source of other sites of infection. The mortality rate of bacterial sepsis and septic shock in transplant recipients exceeds 50%. Consequently, the use of broad-spectrum antimicrobial therapy, an aggressive approach to source control, and the minimization of immunosuppression are indicated.

There are several atypical bacterial infections that occur in the solid-organ transplant recipients, including mycobacteria such as *Mycobacterium tuberculosis*, *Nocardia* spp, and *Listeria monocytogenes*. Such infections are associated with high rates of morbidity and mortality. Mycobacterial infections are 50 to 100 times more frequent in the transplant population than they are in the general population and are fatal in 30% of cases. Infections are typically due to reactivation of latent disease or transmission from the transplanted graft. Their diagnosis is complicated by the typical lack of reaction to skin testing seen with immunosuppression. Consequently, a high index of clinical suspicion is needed. If mycobacterial pulmonary infection is suspected, bronchoscopic evaluation with biopsy, acid-fast staining, and culture should be performed. Treatment consists

of multidrug therapy with isoniazid, ethambutol, pyrazinamide, and rifampin. Preventative strategies should be considered in patient populations in whom infections are common, in patients with a history of significant exposure without subsequent therapy, and in patients with a history of serious or inadequately treated infections.

Nontuberculous mycobacteria (NTM) such as *Mycobacterium avium complex*, *M. ulcerans*, and *M. xenopi* are environmental mycobacteria that rarely caused disease in humans until the AIDS epidemic of the 1980s. NTM infections typically manifest as insidious pulmonary or soft tissue infections in immunosuppressed patients. If NTM infections are suspected, repeat isolations by bronchoscopy or tissue biopsy are required to improve the chance of diagnosis. In addition to acid-fast staining, a special culture for an atypical mycobacterium should be obtained. Besides continuing antimicrobial treatment, wide debridement of the infected site is often required to eradicate such infections [36].

Listeria monocytogenes infection may be associated with pneumonia, bacteremia, or most worryingly, cerebromeningitis in the transplant population. In renal transplant recipients, *Listeria* spp have been associated with a 26% mortality rate. Consequently, if listeriosis (pulmonary or meningitis) is suspected in any immunosuppressed patients, a thorough evaluation must be performed. Empiric therapy for meningitis should include suitable targeted coverage, such as ampicillin plus an aminoglycoside [37]. The extended-spectrum penicillins also provide adequate coverage.

Nocardial infections most commonly apparent with pulmonary symptoms and signs, but disseminated disease may involve the skin, eyes, and brain, alone or in concert. The clinical manifestations are nonspecific and include fever, chills, malaise, occasional cough, dyspnea, headache, or mental status change. Such infections have a mortality rate of 25% to 50% and must be aggressively diagnosed and treated [37]. The diagnosis is made by microscopic examination of sputum or lung (or occasionally brain) biopsy tissue, or by aspiration of a skin nodule using routine, Kinyoun, and Ziehl-Neelsen staining. Treatment consists of high-dose intravenous TMP-SMX, generally in combination with an aminoglycoside, such as amikacin, with continued treatment with oral TMP-SMX, if possible, for life. Concurrently, immunosuppression should be abridged, particularly during treatment of aggressive, disseminated infections.

Fungal infections

Fungal infections are more common in solid-organ transplants recipients compared to the general population. This has been ameliorated by the broad use of antimicrobial prophylaxis. It is associated with an increased incidence of resistance to azoles as well. Fungal infections are far more common after liver and pancreas transplants, with an incidence of 40% [38] compared to renal transplants (5%). Fungal infections in transplant patients are deadly with an attendant mortality rate, associated with invasive disease, of 30%-50%. They occur early in transplant within the first three to four months, when immunosuppression is the greatest. The source of most fungal pathogens is the oral cavity, the gastrointestinal (GI) tract, or the environment.

Preventive strategies with the use of topical nystatin or clotrimazole is often used as first line to manage overgrowth of the oral and GI tract. Invasive candidial disease is more common in patient with risk factors such as diabetes, neutropenia, intense immunosuppression, and prolonged administration of antibacterial antibiotics, particularly broad-spectrum agents. Long-term TMP-SMX prophylaxis has not been associated with fungal infections. Despite prophylaxis, invasive candidiasis does occur, most often in transplant recipients with a perforation of the GI tract, an anastomotic breakdown, a deep surgical-site infection, or a concomitant GI infection, such as CMV gastroenteritis or colitis.

Resistant *Candida* species such as *C. glabrata* and *C. krusei* are being seen increasingly with the widespread use of triazoles such as fluconazole. The newer agents such as the echinocandins and amphotericin B have become necessary to treat these more invasive strains of fungal infections. These more invasive species are associated with increased morbidity in the immunosuppressed population [38]. Caspofungin is an echinocandin that acts to block the synthesis of 1,3-β-D-glucan, an essential element of the fungal cell wall. It is well tolerated, with a side effect profile that compares favorably to amphotericin B. Note that caspofungin and amphotericin B appear to act in an additive manner, and cross-resistance has not been identified [39]. Clinical trials of caspofungin versus amphotericin demonstrated equivalent outcomes in the treatment of candidemia [39]. In solid-organ transplant recipients, caspofungin will be an important drug in treating serious fungal infections, particularly because it lacks the nephrotoxicity of amphotericin. Two of the more recently released triazole drugs, itraconazole and voriconazole, also possess activity in vitro against *Aspergillus spp*; however, the combination of voriconazole and caspofungin has not been shown to enhance clinical efficacy [40].

Disseminated *aspergillus* disease is found in over 50 % of cases, with a mortality rate in excess of 80% [41]. Most patients with aspergillosis present with what appear to be a bacterial pneumonia. In high-risk lung or liver transplant recipients, or in lower risk patients whose supposed pneumonia fails to respond to appropriate antibiotic therapy, an aggressive diagnostic approach is urgently needed. The diagnosis of aspergillosis is established initially by microscopic examination of samples obtained via bronchoscopy and BAL for the presence of filamentous hyphae. Agents approved by the U.S. Food and Drug Administration (FDA) against invasive aspergillosis include liposomal amphotericin B, itraconazole, voriconazole, posaconazole, and caspofungin. Voriconazole remains an effective therapeutic agent [42]. Dissemination to the central nervous system (CNS) may result in brain abscesses, which in the past were nearly uniformly fatal, but more recently have been successfully treated with newer antifungal agents (such as voriconazole) and neurosurgical resection [43].

Infections due to several other fungi occur in solid-organ transplant recipients, including *Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, Histoplasma capsulatum*, and *Zygomycetes*, *Mucor*, and *Rhizopus* spp. Infections caused by those fungi occur in specific settings and present as specific clinical courses that should be considered by the clinician caring for immunosuppressed patients.

Cryptococcus neoformans is the second leading cause of invasive fungal infections in liver transplant recipients. This pathogen may cause pneumonia or meningitis, and patients with pulmonary disease often have CNS involvement as well. A high index of suspicious should be maintained and it is recommended that immunocompromised patients with cryptococcal infection should undergo lumbar puncture even if asymptomatic neurologically. Skin nodules are occasionally seen. The diagnosis is confirmed by India-ink staining and by testing for cryptococcal antigen in cerebrospinal fluid or sputum. Treatment consists of amphotericin B followed by oral fluconazole bearing in mind there is increasing resistance to fluconazole over time [44].

Coccidioides immitis is endemic in the southwestern United States and in Mexico. There is a significant since of the fungal infection between 7% and 9% of solid-organ transplant recipients residing in that area develop coccidioidomycosis, with an associated mortality rate of 25% in pulmonary cases and of up to 70% in disseminated cases. The presentation of disease is variable, as multiple organ systems may be involved. The diagnosis must be made by microscopy, antigen detection, or tissue culture. Lifelong fluconazole prophylaxis for solid-organ transplant recipients who reside in endemic areas is advocated in some centers, this has not been validated by long term studies. A beneficial adjunct in tackling this disease is a reduction of calcineurin inhibitor dosage. The treatment is prolonged amphotericin B administration or azole therapy [45].

Histoplasmosis and blastomycosis infections occur in endemic areas in the Midwest United States, the Mississippi and Ohio River valleys. Invasive disease, either reactivation of latent fungi or a new

infection, occurs in up to 2% of solid-organ transplant recipients, with the highest incidence in those areas. Invasive disease spreads from the lungs to the skin and bone marrow. Biopsy and samples for culture analysis may be obtained from skin lesions or from a bone-marrow aspirate. Amphotericin B or itraconazole are appropriate therapeutic agents [27].

Mucor and *Rhizopus* spp in the *Zygomycetes* class are soil fungi that, when inhaled, may cause a highly morbid, invasive rhinocerebral infection in profoundly immunosuppressed patients and in diabetic patients with poor glycemic control. The diagnosis is established by biopsy; aggressive surgical debridement is the treatment of choice with adjuvant antifungal therapy (amphotericin B with the occasional addition of 5-flucytosine, itraconazole, or rifampin). The mortality rate associated with those types of infections is in excess of 50% [46].

Pneumocystis jiroveci pneumonia (PCP) is a common cause of pneumonia in immunosuppressed patients. PCP is associated with profound defects in cellular immunity and normally is seen with CD4-positive T-cell counts lower than 200 per μL. Those indices are historically seen with OKT3 therapy for AR which is currently not in use. Prophylaxis with TMP-SMX or atovaquone (if sulfa allergic) makes PCP a rare entity; however, transplant recipients who have a respiratory illness but did not receive prophylaxis (e.g., because of allergy or noncompliance) should be evaluated promptly for PCP. Untreated PCP has a very high mortality rate. The diagnosis is generally established by bronchoscopy and BAL, with methenamine silver staining of washings, or by transbronchial biopsy. Normal findings should not delay further evaluation and therapy which should be started empirically (the characteristic alveolar and interstitial changes seen on a chest radiograph are late findings). This consists of intravenous TMP-SMX or inhaled pentamidine. Dapsone is used in patients with a sulfa sensitivity.

Covid-19 (SARS-CoV-2)

The remarkable success of immunosuppressive therapy has made it a challenging for transplant recipients to fight infections. The covid-19 pandemic has laid bare the susceptibility of these patients to the SARS-CoV-2 virus [47]. The rapid development of effective vaccines has been met with enthusiasm, skepticism and hesitancy [48].

Transplant patients have been noted to be at increased risk of severe complications from the viral infection. Transplant recipients should be vaccinated in order to provide protection against acute severe disease [49]. When administered the vaccine they are also noted to mount a less effective immune response to the spike protein which is the major mechanism whereby the vaccines act [50-54].

The FDA in August 2021 recommended a third dose or booster dose for immunosuppressed patients in order to achieve an adequate immune response [55,56]. This measure based on convincing evidence of a more robust antibody response will help to provide much needed protection to the immunocompromised host.

As a result of work done to monitor the immune response, it was found that a booster dose of the vaccine is essential to provide adequate immune response in the immunosuppressed. This has been supported by the CDC and FDA panels. The transplant surgery literature also supports this practice overwhelmingly.

In order to protect these patients, as more is learnt, they will need to continue to employ social distancing, masking, frequent and effective handwashing and quarantining as part of the combined strategies to protect from adverse outcome. As we learn more and make use of therapeutics such as convalescent plasma, monoclonal antibodies and antiviral agents these patients at high risk for adverse outcome with these viral infections. With the booster dose of these vaccines, the benefits of the vaccine enjoyed by the immunocompetent should be like those immunosuppressed. Guidelines have been developed but this will be evolving as we learn more about the virus in transplant recipients [57]

The vaccine even though it shows high efficacy in the general population, has some side effects which have been reported such general malaise, fever and soreness at the injection sites. Poor antibody response is one of the downsides of the vaccine. However, hematuria has been reported as a rare side effect [53].

Viral infections

Viral infections have frequently been recognized as important causes of morbidity and mortality in solid-organ transplant recipients. Viruses that are endemic and of little clinical concern in the general patient population may produce overwhelming life-threatening infections in the host with suppressed cellular immunity. The recent appreciation of the immunomodulatory effect of several opportunistic viral pathogens gives even more reason for continued development of effective prophylaxis, diagnosis, and treatment modalities for this class of infectious agents. The development of new mRNA viral technology is promising as a mechanism for future development anti-infectives against viruses such as CMV. There has been clinical trials which shows high efficacy of the mRNA virus against CMV viruses [58]. Immunosuppressed transplant recipients may develop serious viral infections by reactivation of latent virus, by transmission of the virus from the donor graft or via blood transfusion, or by exposure to the virus in the environment.

Pathogens known as the HHVs are important in the solid-organ transplant population (Table 2). Those viruses commonly cause disease during periods of greatest immunosuppression, particularly early posttransplant and after antirejection therapy. They include many of the most important viral pathogens facing immunosuppressed patients, including CMV, EBV, the herpes simplex viruses (HSVs), and the varicella zoster virus (VZV).

CMV infections affect 30% to 75% of solid-organ transplant recipients, primarily within 2 weeks to 3 months posttransplant. The highest hazard for CMV infections is in a CMV-seronegative recipient receiving a graft from a CMV-seropositive donor (the D+/R-graft) [59]. Lung and heart–lung transplant recipients have the highest rate of CMV disease (50% to 80%). The most severe CMV disease is also a primary infection in the D+/R-population. A superinfection (due to concurrent reactivation of an endogenous strain and transmission of a serotypically distinct strain of CMV) is typically intermediate in severity, whereas reactivation of latent disease is most often comparatively mild [59]. The range of clinical disease is vast: from asymptomatic infections (detected solely by a change in anti-CMV titer or by shedding of virus or viral DNA in blood, urine, or sputum) to tissue-invasive disease (which may affect the lungs, liver, or intestine). Clinically, a mild infection produces

Table 2: Human Herpes Viruses (HHVs)

Virus	Eponym	Clinical syndromes
HHV-1	Herpes simplex virus-1	Mucocutaneous disease
		Primarily oral–labial symptoms
		Ocular keratitis
		Herpes simplex virus encephalitis
HHV-2	Herpes simplex virus-2	Mucocutaneous disease
		Primarily genital symptoms
		Ocular keratitis
HHV-3	Varicella zoster virus	Chickenpox, shingles
		Pneumonitis, encephalitis
HHV-4	Epstein–Barr virus	Infectious mononucleosis
		Hepatitis, pneumonitis
		Posttransplant lymphoproliferative disease
		Burkitt lymphoma
HHV-5	Cytomegalovirus	Mononucleosis, pneumonitis
		Hepatitis, gastroenteritis, retinitis
HHV-6	Roseola (6B)	Childhood febrile exanthema
		Mononucleosis, encephalitis
		Pneumonitis, disseminated disease
HHV-7		No clear clinical entities
HHV-8	Kaposi agent	Cutaneous lymphomas

a mononucleosis-like syndrome, including fever, malaise, and myalgias, often accompanied by leukopenia. More severe disease clinically manifests with differing signs and symptoms, depending on the site(s) of invasive infection. GI ulceration with occasional hemorrhage is seen in GI disease. CMV pneumonitis may produce respiratory insufficiency and failure. CMV hepatitis may lead to liver failure and to severe pancreatitis and can occur leading to critical deterioration of clinical course. CMV retinitis may produce vision changes, leading to blindness.

Given the high prevalence and significant morbidity of CMV disease, prophylaxis with ganciclovir, valacyclovir, or valganciclovir for 3 to 6 months posttransplant is common, particularly in high-risk patients. Additional prophylaxis routinely is begun with initiation of antirejection therapy. Several randomized clinical trials have shown ganciclovir prophylaxis to be superior to acyclovir prophylaxis in preventing both reactivation and primary CMV disease in solid-organ transplant recipients [60].

A second approach to this problem is the routine close monitoring of at-risk patients with protocol antigenemia or polymerase chain reaction assays followed by empiric (so-called preemptive) therapy with ganciclovir, if levels rise above a predetermined threshold. This approach, though somewhat more cumbersome, has led to reductions in the burden of CMV disease in liver transplant recipients [60]. Prophylaxis, surveillance with empiric therapy, or a combination of both based on calculated risk is currently practiced in most transplant centers. Ganciclovir prophylaxis is used for lung, heart–lung, and heart transplant recipients as well [61], but data on surveillance, preemptive therapy, and efficacy in such recipients are limited. However, there is evidence that there is a tendency toward less CMV disease with the use of mTOR inhibitors [62].

Foscarnet (trisodium phosphonoformate) is used in those rare instances where ganciclovir-resistant strains of CMV are isolated. The data that clearly establish the efficacy of foscarnet in treating CMV disease are limited to CMV retinitis; efficacy equivalent to ganciclovir was observed, but foscarnet was associated with a higher rate of adverse effects (e.g., nephrotoxicity) [59].

The HSVs (HSV-1 and HSV-2) commonly cause mucocutaneous disease of the oropharynx (HSV-1) and the genitalia (HSV-2). In profoundly immunosuppressed patients, they may cause widespread disease, including hepatitis, encephalitis, and pneumonitis. Most such infections are thought to be reactivation of latent virus [63]. The diagnosis is established by identification of the virus by immunofluorescent monoclonal antibody staining or by Tzanck smear. Culture and rising anti-HSV antibody titers provide evidence as well. Treatment consists of acyclovir; most epidermal lesions respond to oral therapy, but any evidence of disseminated disease requires high-dose intravenous acyclovir and minimization of immunosuppression.

Epstein Bar Virus (EBV) infections are commonly detectable in solid-organ transplant recipients. The most common manifestations include the typical mononucleosis-type syndrome, pneumonitis, and hepatitis. PTLD, the disease syndrome most associated with EBV has a biphasic pattern. Early presentation in the first year of transplant is EBV+ in over 90% of cases. Late PTLD which occurs 7-10 year is associated with EBV seronegativity in half the cases (50%) [64]. The diagnosis of EBV infections is made by detection of heterophile immunoglobin M antibodies in serum or by following titers of antibodies to viral capsid antigen. Polymerase chain reaction is also used to monitor viral activity and response to therapy. Treatment consists of acyclovir (or ganciclovir, when a CMV infection is also suspected). Reduction in immunosuppressives (RIS) is the best intervention to be validated [65]. In disseminated disease it is essential. In a Cochrane review with the use of Belatacept there was an increased incidence of PTLD in EBV naive recipients compared to patients receiving calcinuerin inhibitors [66].

VZV commonly emerges from latency in immunosuppressed transplant recipients and causes an episode of shingles [67]. More rarely, VZV may cause disseminated infections, such as pneumonitis and encephalitis. Pediatric transplant patients are routinely innoculated with the varicella vaccine which has markedly reduced this type of disease; the vaccine is recommended pretransplant for all pediatric and nonimmunosuppressed transplant candidates. VZV infections are treated with acyclovir; with severe disseminated disease, immunosuppression is reduced in addition [68]. No evidence supports the efficacy of anti-VZV immune globulin for treating severe VZV disease in immunocompromised patients.

Co-infection with HHV-6 and association with severe CMV disease has been reported but understanding causality in this context is difficult. Treatment of neurologic diseases related to HHV-6 includes ganciclovir and foscarnet, either alone or in combination [69]. HHV-7 is not yet clearly associated with clinical syndromes that pose major problems in solid-organ transplant recipients. HHV-8 is linked to the development of Kaposi sarcoma in transplant recipients (vide infra).

Viral hepatitis is fast becoming a less significant problem in transplant recipients. In the past it was more significant particularly for liver transplant recipients who may have developed end-stage liver disease as a result of HBV or HCV infections. Primary HBV or HCV infections may occur during the transplant operation itself, because of donor graft or blood transfusion transmission. However, with the advent of highly effective agents to treat hepatitis C infections many patients can be treated prior to transplant with agents that are easily tolerated. In addition, patients can be transplanted with organs which are from Hepatitis C donors and then treated if they become viremic. This has effectively transformed transplantation giving increased access to high quality organs which were previously discarded due to hepatitis C infections. There is a consensus statement that is a useful guide to the use of these organs which is in rapid evolution soon becoming the standard of care [18,70,71].

Would-be donors positive for hepatitis B surface antigen (HBsAg) and/or anti-hepatitis B core antibodies (HBcAbs) are often excluded from donating any organ or tissue [72]. Organs other than the liver have been transplanted from isolated HBcAb-positive donors, without evidence of transmission, but the risk for transmission is very low from a review of the literature [73]. HCV-positive donors are normally allowed to donate their livers and kidneys to recipient who are also HCV-positive. Liver transplant candidates with HBV or HCV disease are transplanted; currently, their graft and patient survival rates, particularly in the short term, are comparable to those for recipients without HBV or HCV disease. HBV disease is no longer a contraindication to a liver transplant; however, the use of lamivudine and HBV-immune globulin (HBIG) has significantly reduced the burden of recurrent HBV disease [74] and has allowed hundreds of patients with end-stage liver disease secondary to HBV to undergo successful transplants. Continuing HBV prophylaxic therapy appears to be the optimal duration strategy in ensuring low or absent viral levels [74].

In the past up to 25% of Hepatitis C positive transplant recipients accelerate to cirrhosis within 5 to 10 years posttransplant, likely related to immunosuppressive therapy and rejection [75]. As mentioned earlier, the availability of effective therapeutic allows for transplant recipients to be cured and avoid this fate [76]. The care of transplant candidates with HCV includes extending the use of these antiviral therapeutics [77], increasing donor pool, tailoring antiviral treatment pre-and posttransplant, and offering a living donor transplant [78]. Very effective interferon free regimen which obtains high sustained viral response within eight weeks to twelve weeks of therapy has proved effective in managing hepatitis C whose cost which was initially prohibitive but has been increasingly honored by insurance companies [79]; is much cheaper than organ transplant. These drugs are currently available for clinical use with very promising results even in those co-infected with HIV [80]. These drugs have expanded the pools of organs available even for those who are not infected with hepatitis C. They are then treated post operatively. These patients

are getting increased access to livers, kidneys, hearts, lungs and pancreata [79].

The transmission of HIV via an organ transplant from an HIV-positive donor have been described over two decades ago [81]; HIV-positive status will not be contraindication to either donating or undergoing a transplant after passage of the HOPE Act and the enactment of appropriate policies to support the practice [82]. However, solid-organ transplant recipients infected with HIV have been identified and have enjoyed long-term survival posttransplant [82], given the success of long-term multidrug therapy for HIV. With the introduction of highly active antiretroviral therapy (HAART), the transplant community has now recognized HIV infections as a chronic condition. In fact, end organ failure develops in HIV-positive individuals as they age and/or from the side effects of their antiviral treatments. Short-term outcomes in HIV-positive transplant recipients have been good even in those co-infected with Hepatitis C [83]: the HIV load remains suppressed, CD4-positive T-lymphocyte counts are stable, and the risk of opportunistic infection is acceptable. However, major challenges in the care of HIV-positive transplant recipients include high graft rejection rates and multiple drug interactions between HAART and maintenance immunosuppression [83]. With the HOPE act HIV+ donors are increasingly being used to transplant patients who are also HIV positive. Initial review of the results is promising with excellent patients and graft survivals [84].

The polyomavirus, including BK, JC, and SV40, is an omnipresent pathogen that has no clinical significance in immunocompetent hosts. BK virus (BKV) is tropic-specific for human transitional and renal tubular epithelial cells. Primary infection occurs early in life; BKV establishes lifelong latency in the host's renal cells. Reactivation takes place when the host's immune system is compromised, such as during pregnancy or posttransplant immunosuppression. The diagnosis is made by detecting free viral particles in the urine, blood, or intranuclear viral inclusion-bearing cells (decoy cells) in urine cytology specimens. BKV nephropathy (BKN) has been increasingly recognized as an important entity in kidney transplant recipients since the mid-1990s; currently, it is seen in 1% to 9% of them within the first year posttransplant. Depending on the severity of renal tubular injury, clinical presentations of BKN can include fatigue, fever, mild hydronephrosis, or marked graft dysfunction. In bone marrow transplant recipients, hemorrhagic cystitis has been described. The diagnosis of BKV reactivation is made by urinary cytology, quantitative PCR analysis to measure the viral load in urine or plasma, and kidney biopsy [85]. The mainstays of caring for patients with BKN are to reduce immunosuppression and to closely monitor disease progression. Given the lack of specific antiviral agents against BKV, low-dose cidofovir or leflunomide or fluoroquinolone has been used, with no appreciable effect, in patients with persistent BKN [86].

Human papilloma viruses may cause disease through the development of tissue-specific growth leading to benign or malignant processes, including cervical cancer, cancer of the vulva and perineum, condyloma acuminatum, laryngeal polyposis, and nonmelanotic skin cancer (vide infra). Respiratory syncytial virus may produce a fulminant pneumonia in both adult and pediatric transplant recipients. The diagnosis is made by nasopharyngeal washing. More severe cases should be treated with ribavirin.

Parasitic infections

Numerous common parasitic infections are seen in immunosuppressed solid-organ transplant recipients. *Toxoplasma gondii* presents as a brain abscess with neurologic changes [87]. It is seen late posttransplant, whereas a brain abscess in the early posttransplant period is more likely to be fungal [88]. Heart transplant recipients seem to be at greatest risk, possibly due to the presence of *T. gondii* cysts in donor myocardial tissue. Positive Toxoplasma is a not a contraindication for organ donation. However, if the heart donor was seropositive for *T. gondii*, the recipient normally undergoes prophylactic treatment with pyrimethamine and sulfadiazine for 3 to 6 months posttransplant. Treatment of *T. gondii* infections consists of pyrimethamine and sulfadiazine; the mortality rate is high in transplant recipients who exhibit CNS disease as high as 55% at 90 days [84].

Malignancy

The key to managing malignancy post transplantation in solid-organ transplant recipients is risk recognition and proactive surveillance and screening due to a distinctly increased risk. For those patients who have had prior malignancies but are now being considered as candidates for transplanted, updated recommendations are available [89]. The Israel Penn International Transplant Tumor Registry initiated and has maintained an extensive data collection that tracks the epidemiology of tumors in transplant recipients [90]. The increased incidence of malignancy is multifactorial, probably due to a combination of the activation of latent viruses with oncogenic potential, the direct oncogenic effect of immunosuppressive drugs such as cyclosporine, and, perhaps, environmental factors [91]. Strong but indirect evidence points to the loss of immunologic surveillance as a mechanism of increased oncogenesis. The most common neoplasms in solid-organ transplant recipients are skin cancers, PTLD, lung cancer, Kaposi sarcoma, and carcinoma of the cervix. Of those neoplasms, lung cancer appears to occur at the same frequency as in the general population; the other neoplasms occur at increased incidence in solid-organ transplant recipients. PTLD presents the greatest challenge in terms of attendant high morbidity and mortality rates.

Posttransplant lymphoproliferative disorder

PTLD encompasses a very broad range of pathologies, from simple lymphoid hyperplasia to very aggressive monoclonal B-cell lymphomas. EBV infections play a central causal role. In particular, primary EBV infections posttransplant (EBV D+/R-match) and immunosuppression markedly increase the risk of PTLD [26]. Other risk factors include active CMV disease [59], CMV D+/R-match, and increasing intensity of immunosuppression.

PTLD have a bimodal distribution pattern most commonly early: typically, in the early post-transplant (1-3 months) associated with high level of intense immunosuppression such as treatment of acute rejection with anti–T-cell therapy for acute rejection and late (years after transplant). PTLD is least common in adult kidney transplant recipients and most common in pediatric small-bowel transplant recipients. The late-occurring neoplasms appear to be related to patient age, duration, and intensity of immunosuppression, and type of graft than to the more typical risk factors seen in early onset disease.

The clinical presentation of PTLD varies tremendously, as might be expected from the wide range of pathology encountered with this entity. Many patients experience fever, sweats, and myalgias as the only symptoms. Weight loss, diarrhea, and upper respiratory infection are common symptoms; some, but not all, patients have lymphadenopathy. CNS involvement, which occurs in up to 20% of patients [92], often manifests as mental status changes. GI disease may be silent or may present as abdominal pain, GI bleeding, and perforation with peritonitis, or bowel obstruction. Intrathoracic PTLD has a characteristic radiographic appearance of multiple circumscribed pulmonary nodules, which may or may not be accompanied by mediastinal lymphadenopathy. PTLD in the graft itself can present very similarly to AR; because the therapeutic approach to those two entities is diametrically opposed, a correct diagnosis on biopsy is essential.

Lymph node biopsy is the gold standard in establishing the diagnosis of suspected lesions in PTLD. These specimens are histologically graded (based on cell morphology and nodal architecture) and assessed for clonality (polyclonal or monoclonal) and for the presence of an EBV genome and copy number. Specific

cell marker studies are required to establish the clonality, but most lesions are EBV positive and of B-cell lineage. Experienced Pathologists with working knowledge of PTLD as well as with graft rejection and opportunistic infections should review the biopsy. Consensus conference standards for the grading and classification of PTLD are used [93]. Histologic classification currently uses the Harris standard formulation [94,95]. EBV serology does not typically add to the diagnostic workup of PTLD, with many false negatives in patients with established primary EBV infections. Similarly, peripheral cytology is not helpful in making the diagnosis and molecular techniques need to be employed [94]. If PTLD is suspected, patients should undergo imaging of the head, thorax, and abdomen. Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT scanning has high specificity as a diagnostic and/or staging tool and in follow-up studies of PTLD patients [94].

Currently, there is little information to provide direction regarding optimal prophylaxis against PTLD. Clearly, it is important to identify, and closely monitor, high-risk patients (e.g., children, liver and small-bowel transplant recipients; EBV-negative transplant recipients, particularly those with an EBV-positive donor; and transplant recipients on intense antilymphocyte therapy for rejection). Both antiviral agents and passive immune transfer with CMV-IVIG immune globulin have been used as prophylaxis against PTLD, with no proven efficacy. Several trials are ongoing to establish the best prophylactic approach. Reduction of immunosuppressive regimen with evidence of rising EBV titer has shown to be helpful when compared to historical controls [94].

Treatment of established PTLD depends on each patient's clinical situation and histologic diagnosis. With few trials to guide therapy, a gradual, individualized approach is taken. Ordinarily, immunosuppression is reduced to the barest minimum, and specific therapy is directed at the neoplasm. In 25% to 50% of patients, PTLD regresses after their immunosuppression is reduced [94].

Surgical intervention is clearly indicated for patients with GI PTLD that manifests as aggressive disease (e.g., viscus obstruction or perforation). Surgical debulking of the tumor burden has also been used in amenable cases, as has radiotherapy. Isolated CNS disease initially should be treated with external beam irradiation [94].

Medical approaches to treating PTLD include (a) antiviral medications (e.g., acyclovir, ganciclovir); (b) interferon-α2b; (c) immunoglobulins (d) standard, low-dose, and high-dose chemotherapy protocols; and (e) most recently, monoclonal antibodies directed against B-cell surface markers, such as CD19 and CD20 (rituximab). In unusual cases, immunomodulatory therapy with adoptive transfer of cytotoxic T cells sensitized to EBV has been attempted with some success [94].

Late-onset PTLD, occurring more than 1 to 2 years posttransplant, often does not respond to the reduction in immunosuppression and to the medical therapy typically used in patients with early-onset disease. Often EBV-negative, late-onset PTLD is difficult to treat because of side effects, including infectious complications of the aggressive chemotherapy that is often required. Similarly, CNS involvement may be a marker for PTLD that is potentially refractory to therapy, possibly because of the relatively privileged immune site. Therapeutic options include intrathecal administration of interferon-α and anti–B-cell antibody therapy in addition to local radiotherapy, but the prognosis remains guarded [94].

Skin cancer

Non-melanotic skin cancers are the most common neoplasms associated with transplants and immunosuppression. Increased incidence is found with increasing time posttransplant and sun-exposure. Often-quoted studies show a prevalence of 66% in transplant recipients in Australia after 24 years of surveillance [96] and 40% after 20 years in the Netherlands [97]. Those figures correlate to a 4-to 21-fold increase in prevalence in transplant recipients, as compared with the immunocompetent population, with synergistic increases seen in the areas of highest sunlight exposure in countries such as Australia [91].

Squamous cell carcinoma is the most common skin cancer in transplant recipients. Many recipients develop multiple lesions; the transplant patients are generally younger when compared to members of general population. The incidence of melanomas is also 2.4 times higher than the general population representing [98]. Even nonmelanotic squamous cell carcinomas behave more aggressively in transplant recipients, with lymph node metastasis and a 6% mortality rate due to disseminated disease [99]. On identification of skin lesions, prompt surgical excision should be undertaken. Solid-organ transplant recipients are instructed to avoid direct exposure to sunlight for any prolonged period and to liberally use sunblock. Clearly, close dermatologic counselling, education and follow-up are warranted in this patient population [100].

Kaposi sarcoma

Kaposi's sarcoma (KS) is a nodular vascular neoplasm commonly seen cutaneously but may be multicentric involving visceral tissues (such as the lungs and GI tract). Endemic in the Mediterranean region and Middle East, it is strongly associated with either endogenous or exogenous immunosuppression, as a result both of AIDS and of immunosuppressive therapy. The incidence of this disease in U.S. transplant recipients is 0.4%, which represents a 20-fold increase over the basal rate in the population at large [101]. Recently, human herpes virus (HHV)-8 has been implicated as a causal agent in KS.

Cutaneous KS is easily identified by clinical appearance and biopsy. But patients with only visceral KS often present with more advanced disease, usually GI bleeding or viscus perforation, sometimes dyspnea related to pulmonary disease. Immunosuppression should be reduced to the greatest extent possible, after which about 30% to 55% of patients will experience remission. Chemotherapy is reserved for patients with visceral KS and for those who do not experience remission after their immunosuppression is reduced. However, of patients with visceral KS, 45% to 50% die of it [102]. Anecdotal evidence indicates that certain patients may respond to antiviral agents (e.g., ganciclovir).

Cervical cancer

Pretransplant it is important to screen and rule out cervical intraepithelial neoplasia with Papanicolaou smear. With an estimated 50% incidence in solid organ transplant recipients and elevated levels of the disease by 10-to 14-fold [103]. Cervical carcinoma was seen in 10% of all women with posttransplant cancer in the Transplant Tumor Registry [90]. In 2016 triennial screening was recommended by the American College of Gynecologist for women. However, studies to evaluate solid organ recipients as being suitable candidates for such prolonged screening tine has been inconclusive [104]. Annual screening appears to be supported by longitudinal studies on the subject [105]. Close surveillance by pelvic examination and Papanicolaou smear is essential in this population, given the increased incidence of disease. In the post-transplant patient with potentially advanced cervical cancer, there is no standardized approach. A functional graft will make the treatment options a logistically tricky.

Transmitted and recurrent malignancy

Transmissions of malignancy from grafts to recipients are feared complications of transplantation because of the potentially devastating outcomes. Thankfully, the incidences are not widespread. Case reports have described patients who have received grafts that harbored malignant cells, leading to the development of malignancy. Transmission to transplant recipients of renal cell carcinoma, metastatic cancer of the breast or lung, and melanoma has been reported. Currently, cancer or recent history of cancer is a contraindication to organ donation, except for some low-grade skin cancers, noninvasive CNS neoplasms, and small, limited cancers that has been excised and is not likely to recur or spread. Nonetheless, some grafts are found to contain foci of neoplasia, which develop

into a clinically significant cancer in recipients. This finding emphasizes the need for a thorough examination of donors during organ procurement, particularly considering the present trend toward the use of older donors [106].

Patients with a history of malignancy clearly are at risk for recurrent disease posttransplant, presumably due to the use of immunosuppression. Data from the Transplant Tumor Registry show a 21% recurrence rate, with the highest rates seen in patients with multiple myeloma (67%), nonmelanotic skin cancer (53%), bladder cancer (29%), soft-tissue sarcoma (29%), renal cell cancer (27%), and breast cancer (23%) [107] and there is a tendency to using organs with small, incidental renal cell carcinoma may be reasonable [108]. Tumors were least likely to recur if more than 5 years had passed between cancer treatment and the transplant.

Liver transplants to treat patients with primary, well-circumscribed liver tumors represent a special case. In this population, liver tumor size and the number of liver tumors are considered indicative of the likelihood of disease recurrence and patient survival posttransplant. Adjuvant techniques, such as cryoablation and radiofrequency ablation, to reduce the tumor burden pretransplant have been used, but currently the data are insufficient to clearly define the ability of adjuvant techniques to reduce posttransplant morbidity and mortality secondary to disease recurrence. Risk factors for recurrence include tumor size >6 cm, number of nodules >5, and vascular invasion per the final pathology report [109]. Clearly, tumor biology dictates the risk of disease recurrence [110]. Milan criteria and USCF criteria for determining candidacy for liver transplant in patients with existing hepatocellular carcinoma are used as standards by large number of transplant programs. However, the increasing role of biology is being investigated as an important criteria for the judicious use of organs in transplanting patients with HCC [111].

Rejection

The human immune system is an evolutionarily more advanced, adaptive, efficient, "specific," and versatile host defense mechanism against the invasion of pathogens as compared to the nonspecific innate immune system of invertebrates. However, a side effect of the ability of the host immune system to recognize and attack "nonself" tissues is rejection of grafted tissues posttransplant. This phenomenon was observed clinically for centuries before Medawar demonstrated that it was an intrinsic property of the host immune system in response to foreign tissue [112]. The exogenous modulation of the host immune system to allow sustained graft function has proceeded along with—and often preceded—our understanding of the physiologic mechanism of rejection and tolerance.

Understanding the immune system is integral to our understanding of rejection. The immunologic disparity among members of the same species of mammals that leads to lack of recognition of "self" tissue and to rejection of nonself tissue is based on the differences in cell surface molecules that are expressed. In humans, these major histocompatibility antigens were first identified in leukocytes, and hence are termed *human leukocyte antigens* (HLAs). HLAs are subdivided into two classes: class I (HLA-A, -B, and -C), expressed on the surface of all nucleated cells, and class II (HLA-DR, -DQ, and -DP), expressed on the surface of *antigen-presenting cells* (APCs). The recognition of nonself tissue occurs via two distinct immunologic pathways: *direct* and *indirect allorecognition*. Direct allorecognition consists of recipient T-helper cells recognizing donor HLA disparity expressed on the donor cell surface. Indirect allorecognition consists of recipient APCs (for example activated macrophages, dendritic cells, and B lymphocytes) phagocytosing donor cellular debris, including HLAs, which are then processed and re-presented on the APC surface to be recognized by recipient T-helper cells (CD4+ lymphocytes).

In either pathway, costimulation signals between CD4+ T-helper lymphocytes and CD8+ cytotoxic T lymphocytes trigger a cascade of immunologic events. Interleukin (IL-2), an important and early signal in immune activation, is secreted by activated CD4+ T-helper lymphocytes, stimulating increased T-cell responsiveness, clonal expansion of alloreactive T lymphocytes, and acquisition of the cytolytic phenotype by host T lymphocytes. Direct allorecognition leads to a more immediate and vigorous immune response against foreign tissue, but, in both pathways, additional helper T lymphocytes are recruited and secrete a wide array of cytokines (e.g., IL-1, interferon-γ, tumor necrosis factor-α), facilitating the further recruitment of cytotoxic T lymphocytes, natural killer cells, and B lymphocytes. Then, B lymphocytes begin to secrete antibody directed against the allogeneic tissue in ever-increasing quantities. Rejection mechanistically occurs by infiltration of the graft by effector cells, the binding of antibody, and the activation of complement. Unchecked, the phenomenon inexorably leads in graft loss (Table 1).

Donor-recipient mismatches between HLAs may produce an immune response by either the direct or indirect pathways; however, minor non-HLA mismatches typically produce an immune response by the indirect pathway only.

Rejection is classified according to the temporal relation between the implantation of the graft and its dysfunction supported by the histologic features seen in allograft. The three main types of rejection are *hyperacute (HAR)*, *acute (AR)*, and *chronic (CR)*. Each type is mediated by a different host immune mechanism. Consequently, each type poses different problems for the patient, clinicians and pathologists.

Hyperacute rejection

HAR occurs within a few minutes to a few hours after the reperfusion of the graft. Preformed antibodies directed against antigens presented by the graft mediate activation of complement [113], activation of endothelial cells, and formation of microvascular thrombi, leading to graft thrombosis and loss [113]. The process is irreversible; currently, no treatment is available. Because HAR is mediated by circulating preformed antibodies normally directed against ABO system (comprising the four main blood types, i.e., A, B, AB, and O) antigens or against major HLA antigens, thorough screening of potential transplant recipients and strict adherence to ABO verification policies should prevent nearly all HAR.

The panel-reactive antibody (PRA) assay is a screening test that examines the ability of serum from potential transplant recipients to lyse lymphocytes from a panel of HLA-typed donors. A numerical value, expressed as a percentage, indicates the likelihood of a sensitization status and this should be used judiciously. Therefore, patients lacking preformed antibodies to random donor lymphocytes are defined as having a PRA of 0% and have a very low probability of eliciting a positive lymphocyte crossmatch to any donor. The finding of a higher PRA identifies patients at higher immunologic risk for a positive crossmatch and thus for HAR and for subsequent graft loss. Most often, such patients were previously sensitized by childbirth, blood transfusions, or a prior transplant.

Pretransplant, crossmatch testing is performed to identify preformed antibodies against class I HLAs (T-lymphocyte crossmatch testing) and class II HLAs (B-lymphocyte crossmatch testing). In renal and pancreas transplantation, a strong positive class I-HLA crossmatch immediately pretransplant is ordinarily an absolute contraindication. At most centers, heart and liver transplants are performed without a crossmatch, unless the recipient is highly sensitized or has previously received a graft possessing major antigens in common with the current donor (i.e., donor-specific antibody [DSA]). A positive B-lymphocyte crossmatch indicates preformed antibodies directed against class II HLAs and is a relative, but not absolute, contraindication to a transplant. Recent studies confirmed the efficacy of plasmapheresis followed by administration of immune globulin to reduce PRA levels and to convert strongly positive crossmatch results to weakly positive or negative results, thereby allowing organs to be transplanted across what were previously considered as strong immunologic barriers [114]. The use of antibody

lysing agents has also revolutionized thereby have a negative cross match prior to transplant. This is currently in clinical trials but is showing promising results [115,116].

Crossmatch testing helps clinicians to identify the presence of antibodies against potential donor antigens and to assess the risks of posttransplant rejection and subsequent graft loss. However, these cross-matching assays are not standardized. Since the mid-1960s, crossmatch testing was based on the complement-dependent cytotoxicity (CDC) assay. The CDC assay was further refined by adding a wash step and an antihuman globulin (AHG) step, to increase its sensitivity and specificity. Then, with the introduction of technology based on flow cytometry (FC), the presence of recipient antibody on the surface of donor lymphocytes could be detected independent of complement binding.

One of the latest developments in anti-HLA antibody screening was the introduction of Luminex® technology, using HLA-coated fluorescent microbeads and FC. This method in theory pinpoints the DSAs in sera of recipients with high PRA levels. Since all transplant donors are HLA typed nowadays, a negative cross-match for recipients with high PRA levels can be ensured by avoiding the selection of donors carrying unacceptable HLA antigens (virtual cross-match) [117].

The main concerns with these new developments in antibody typing and crossmatch testing are between-center test variability and the thresholds of defining false-negative results (results that could deny recipients with high PRA levels a chance for a potential lifesaving transplant). Currently, it is up to an individual transplant center to implement its own HLA typing and crossmatch policy, depending on the center's experience, clinical outcomes and risk tolerance.

Although screening has all but eliminated HAR as a clinical problem, active investigation is nonetheless directed at dissecting the underlying pathophysiologic mechanisms of HAR. Another research focus is on the similar rapid rejection of xenoreactive antigens that serve as a barrier to the development of xenotransplantation.

Acute rejection

AR is the most common form of graft rejection in modern clinical transplantation. It may develop at any time, but is most frequent during the first several months posttransplant. Rarely, it occurs within the first several days posttransplant, a process termed *accelerated acute rejection* (AAR), most likely a combination of amnestic immune response driven by sensitized memory B lymphocytes and activation of the direct allorecognition pathway. Under such circumstances, the donor antigen exposure often occurred in the distant past, so the level of circulating DSAs would have been too low to be detected by conventional crossmatch techniques. Once challenged by the same donor antigens introduced by the organ transplant, dormant memory lymphocytes reactivate, replicate, and differentiate. Within several days, large numbers of antibodies are directed against the donor allograft resulting in graft rejection.

Acute rejection may be cell mediated, antibody-mediated (AMR) or very occasionally mixed. However, they are not mutually exclusive. Histologically, AR generates an infiltration of activated T lymphocytes into the graft, resulting in gradually progressive endothelial damage, microvascular thrombosis, and parenchymal necrosis. Pathologic grading schemes have been developed regarding the extent to which AR involves vascular damage, cellular infiltration, or a combination of both. Vascular AR is thought to be mediated by the presence of DSAs, albeit not in sufficient numbers to cause HAR. C4d, a complement split product detected immunohistochemically in the capillaries of biopsied graft specimens, is highly correlated with AMR [118]. Without intervention, AR inevitably progresses to graft loss. The clinical presentation of AR varies markedly, depending on the specific organ, on the level of immunosuppression, and on the attendant level of inflammation in the affected tissues.

Unless the host immune system is adequately suppressed pharmacologically, a transplant inevitably leads to AR. A combination of immunosuppressive agents is typically used chronically to prevent AR, including a lymphocyte antagonist (usually a calcineurin inhibitor [CNI] such as cyclosporine or tacrolimus) and an antiproliferative agent (such as azathioprine or mycophenolate mofetil), with or without corticosteroids. Antilymphocyte antibody therapy is often added during induction of immunosuppression or for treatment of "steroid-resistant" AR.

In the last decade, immunosuppression for transplant recipients has been undergoing a paradigm shift. Since the mid-1990s, the use of antibody induction in solid-organ transplant recipients has increased from 25% to more than 90% [119]. Monoclonal antibodies such as basiliximab and daclizumab (both anti-CD25 [IL-2 receptor]) use has declined in the face of increasing use of T-cell depleting agents. Daclizumab is no longer on the market. Furthermore, strategies such as corticosteroid avoidance and CNI-reduced or CNI-free maintenance immunosuppression were shown to be equivalent to traditional triple-drug maintenance [120]. Nonetheless, all immunosuppressive agents carry some risk of toxicity and adverse reactions that may complicate therapy (Table 3).

Chronic rejection

CR is a largely frustrating and poorly understood clinical phenomenon, with slightly different manifestations in each type of graft. Over time, the accumulation of microvascular injury in a graft degrades graft function, with eventual graft loss. This process appears to be mediated by multiple mechanisms, likely including both immune and nonimmune factors. Evidence for the contribution to CR of immune factors includes the observation that AR episodes significantly increase the likelihood of CR as well as the correlation, observed in renal transplant recipients, between a poor response to AR treatment and the subsequent development of CR [121]. A similar association between a poor response to AR treatment and the subsequent development of CR has been observed in liver transplant recipients, although reversible AR has little impact. Nonimmune factors likely also contribute to the development and progression of CR, including the toxic effects of immunosuppressive medication and cumulative injury from infection such as that caused by cytomegalovirus (CMV) [122]. CR nearly always eventuates in graft loss, although the rapidity of the process varies considerably.

Table 3: Immunosuppressive medications, mechanisms of action, and common side effects

Medications	Mechanisms of action	Side effects
Corticosteroids	Upregulate IκB	Cushing syndrome, Cataracts
	Decrease IL-1, TNF-α, IFN-γ	Bone demineralization
	Exert anti-inflammatory effect	
Azathioprine	Acts as an antimetabolite	Marrow suppression
		GI, liver toxicity
Mycophenolate mofetil	Acts as an antimetabolite And specifically affect lymphocytes	Marrow suppression
		GI intolerance
Cyclosporine	Acts as a calcineurin inhibitor	Nephrotoxicity
	Downregulates IL-2	Neurologic symptoms
Tacrolimus (FK506)	Acts as a Calcineurin inhibitor	Nephrotoxicity
	Downregulates IL-2, IFN-γ	Neurotoxicity
		Diabetogenic
Sirolimus (rapamycin)	Blocks IL-2R, IL-4, IL-6, platelet-derived growth factor signaling	Impaired wound healing
		Hypertriglyceridemia
Antilymphocyte globulins	Act as a cytolytic antibody	Leukopenia
	Block and deplete T cells	Thrombocytopenia
		"Serum sickness"
IL-2 receptor blocker (or basiliximab)	Blocks IL-2R	Minimal impact
	Inhibit T-cell activation	

GI: Gastrointestinal, IFN: Interferon, IL: Interleukin

Renal grafts

Acute rejection occurs in 10% to 25% of renal transplant recipients. Because most episodes are clinically silent, the diagnosis of AR must be considered in recipients whose serum creatinine, blood urea nitrogen, and urinary output values have normalized and whose graft function has been stable in the outpatient setting, but whose serum creatinine and blood urea nitrogen values subsequently rise while their urinary output decreases. The presence of hypovolemia, drug nephrotoxicity (e.g., high calcineurin levels), ureteral obstruction or leak, lymphocele, or vascular anastomotic complications should be excluded, and the diagnosis of AR should be established via histologic examination of a percutaneous graft biopsy specimen. Rarely, tenderness and swelling in the area of the graft occur, and occasionally fever or other signs of systemic inflammation, although such findings used to be common.

A high degree of clinical suspicion should be held in recipients who experience delayed graft function, as up to 30% exhibit evidence of AR on biopsy; 20% of recipients who require dialysis posttransplant have AR [123]. Intriguingly, up to 30% of recipients with well-functioning grafts also have AR, per early posttransplant protocol biopsies, but whether such findings are clinically important and whether mild episodes should invariably be treated remain controversial [124]. Recent studies have provided data that may allow prediction of individual risk of AR, with the potential for individualizing immunomodulatory therapy. For example, donor IL-6 genetic polymorphism is strongly associated with an increased incidence of AR posttransplant [125].

The diagnostic workup for AR includes studies that may identify alternative causes of recipient graft dysfunction (Table 4). It is vital to consider alternative diagnoses, particularly in the early postoperative period, including vascular problems with the arterial or venous anastomoses, ureteral obstruction, or urinary leak. Other common causes of apparent graft dysfunction include the acute tubular necrosis associated with delayed graft function, hypovolemia and attendant prerenal azotemia, and the nephrotoxic effects of cyclosporine and tacrolimus. To rule out the vascular and ureteral problems discussed previously, a duplex ultrasound study of the renal graft is commonly obtained. Several ultrasound findings may suggest the diagnosis of AR: increased size of the graft, increased cortical thickness, enlargement of the renal pyramids, and decreased graft renal artery blood flow [126]. The resistive index has not been shown to be significant in helping with the diagnosis [127]. The diagnosis of AR is clearly established by percutaneous allograft biopsy and histologic examination. Biopsy is generally safe when performed by experienced practitioners; however, complications include bleeding, hematoma and arteriovenous fistula formation, and ureteral or major vascular injury.

Rejection is graded according to the modified Banff Criteria, which may be used to guide therapy which has been expanded to include c4d negative antibody mediated rejection [128]. Fine-needle aspiration biopsy has been used by some centers to establish the diagnosis of AR; however, some consider the loss of microstructural data, as compared with traditional core biopsy, to be a weakness of the technique. In particular, the diagnoses of acute vascular rejection and CR are difficult to make using fine-needle aspiration biopsy.

Table 4: Basic workup of recipients with graft dysfunction or acute rejection

History and physical examination	Establish and order differential diagnosis
Doppler ultrasound	Rule out vascular surgical complication
	Rule out leak (e.g., biliary, ureteral)
Serum chemistry	Evaluate relative blood urea nitrogen and creatinine, amylase, bilirubin, etc
	Detect and treat electrolyte abnormalities
Drug levels	Evaluate for potential drug toxicity
	Detect inadequate drug levels
Blood cell count, cultures	Evaluate for potential infection
Graft biopsy	Firmly establish and grade graft rejection

The treatment of AR in renal transplant recipients is not standardized and varies between centers. High-dose methylprednisolone (500 to 1,000 mg per day or every other day [2 to 3 doses] is common) is often the initial approach. Corticosteroid-resistant AR, or AR that is histologically graded as severe or vascular, is often treated with potent depleting antilymphocyte antibodies such as polyclonal antithymocyte globulin (antithymocyte gamma globulin, Thymoglobulin). Since some AR episodes occurred while the recipients were on stable immunosuppression, their maintenance therapy was switched from cyclosporine to tacrolimus or from azathioprine to mycophenolate mofetil. Most AR episodes are reversible with current therapies; however, as noted previously, the long-term outlook for preservation of graft function is lessened with each episode, especially when the posttreatment serum creatinine level does not return to the pre-AR baseline.

CR in renal transplant recipients is a frustrating clinical problem and appears to be multifactorial, with immunologic and nonimmunologic factors driving the gradual loss of graft function. As described earlier, minimizing the frequency and severity of AR episodes is important in decreasing the likelihood of eventual CR. Nonimmunologic factors thought to contribute to CR include (a) episodes of infection, particularly due to CMV and BK virus (*vide infra*); (b) the nephrotoxicity of CNI therapy; (c) ischemia-reperfusion injury and delayed graft function in the peritransplant period; and (d) innate cell senescence within the graft from donor derieved factors [129]. Attention is being directed toward identifying inflammatory activity within the graft, in response to both immune and nonimmune insults that may contribute to the development of CR. One of the leading causes of kidney retransplants is CR. It remains a formidable problem that is still poorly understood.

Hepatic grafts

The transplanted liver is immunologically "privileged" in that evidence of some degree of immune tolerance occurs in a substantial number of liver transplant recipients over time. Despite that observation, all forms of rejection can occur posttransplant. At one time, it was thought that HAR did not occur in the hepatic graft; this idea is now known to be incorrect, as anti-HLA antibody-mediated HAR has been described in liver transplant recipients [130]. Unlike the renal graft, the hepatic graft undergoes HAR over a few days, not minutes to hours, probably secondary to its ability to absorb a large amount of antibody and its functional reserve before the onset of the significant microthrombosis and vascular damage seen in HAR. A more delayed form of antibody-mediated rejection is seen in up to 33% of patients who undergo liver transplants across ABO-incompatible blood groups, but even this barrier appears surmountable with the use of plasmapheresis along with aggressive immunosuppression.

AR remains an important clinical problem in liver transplantation; even with the use of standard multiagent immunosuppression, the incidence of AR ranges from 30% to 80%. In two large, multicenter trials, double therapy with a CNI and steroids resulted in a 60% to 80% incidence of AR [131]. The most common liver transplant regimen consists of two doses of a monoclonal anti-IL2 receptor (basiliximab) as induction therapy and dual maintenance therapy with the CNI (tacrolimus) and the anti-metabolite mycophenolate mofetil which lessens the incidence and severity of rejection without increase the infection rate [132].

The diagnosis of AR in liver transplant recipients is normally suggested by elevated levels of transaminases, bilirubin, or alkaline phosphatase. Among patients with T-tube drainage (which is increasingly uncommon), the biliary drainage may be seen to thicken, darken, and decrease in amount. The suspicion of AR mandates graft biopsy and studies to eliminate other possible causes of early hepatic graft failure. Duplex ultrasonography and, in some cases, cholangiography are increasingly being replaced by magnetic resonance imaging. Biopsy findings are classified, according to a standardized set of criteria, as *mild*, *moderate*, and *severe*, with clear

implications for prognosis [133]. AR is normally treated with high-dose corticosteroids, but 5% to 10% of cases are steroid-resistant; such recipients are then treated with an antilymphocyte antibody or tacrolimus at higher levels.

CR in liver transplant recipients is characterized by vascular obliteration and bile duct loss ("the vanishing duct syndrome"). This is seen in 5% to 10% of recipients, it is more common in those with vasculitic findings during AR episodes; if larger vessels are not seen on biopsy, the diagnosis of CR may be misread as AR. Tacrolimus has been used to salvage grafts in recipients with CR on cyclosporine-based immunosuppression, with a 73% success rate [134].

Pancreas grafts

Diabetic patients undergo pancreas alone (PTA), pancreas after kidney (PAK) or simultaneous pancreas–kidney (SPK) transplants and receive more potent immunosuppression than do renal transplant recipients, supported by initial studies demonstrating a higher rate of AR after pancreas transplants. Overall success rates continue to improve: the risk of AR has been reduced by standardized induction therapy with antilymphocyte antibody preparations, and it may be further reduced with mammalian target of rapamycin (mTOR) inhibitors and/or with IL-2 receptor monoclonal antibodies [135].

Establishing the diagnosis of AR in pancreas transplant recipients can be difficult. Hyperglycemia is a late finding that only occurs with substantial loss of functional islet-cell mass. By the time hyperglycemia is seen, it may be too late to salvage a functional graft. Clinical findings may include fever and graft tenderness; however, pancreas graft rejection is often clinically silent.

For pancreas grafts transplanted along with a renal graft, a rising creatinine level is often used as a surrogate marker of rejection, with antirejection therapy aimed at both the pancreas and the renal allograft. However, isolated pancreas graft rejection is observed in up to 20% of simultaneous pancreas–kidney transplant recipients who have AR [136,137].

Advantages of a bladder drained pancreas is the use of a decreasing urinary amylase level as a marker of graft rejection [138]. Other possible markers of rejection (serum anodal trypsinogen, serum amylase, soluble HLA, and analysis of glucose-disappearance kinetics during a brief glucose tolerance test) have been examined but have failed to gain widespread acceptance [137].

The diagnosis of pancreas graft rejection is confirmed by biopsy, which may be performed percutaneously or, in bladder-drained recipients, through a cystoscopic, transduodenal approach. Complications (bleeding, arteriovenous fistula formation, graft pancreatitis) have been described, but most biopsies do not lead to complications. Pancreas transplant recipients with early evidence of graft dysfunction should undergo Doppler ultrasonography to rule out graft thrombosis, which occurs in up to 10% to 20% of grafts [139].

Treatment of AR for pancreas transplant recipients is similar to that for renal or liver transplant recipients. High-dose corticosteroids are given initially, with a low threshold maintained for possibly switching to antibody-based therapy, given the relatively common steroid resistance. Most AR episodes are reversed with treatment.

Intestinal graft

There is no serum test for intestinal transplant. As a result, biopsy of the intestinal allograf is the gold standard for diagnosis (via ostomy initially). It has the highest rates of acute rejection and graft vs host disease amongst all solid organ transplants. The results have markedly improved over the past 2 decades: at 1 year, patient survival rates of intestinal transplants alone are > 80% of multivisceral transplants > 70%; the respective graft survival rates are > 60% and > 50%. Although treatment protocols for acute rejection have significantly improved, chronic rejection remains a major issue because of its poorly understood nature in intestinal transplantation.

Cardiac grafts

Rejection in heart transplant recipients is a significant cause of morbidity and mortality among these patients and accounts for up to a third of the deaths. All forms of rejection are seen in heart transplant recipients. Albeit rare, HAR due to preformed antigraft antibodies occurs within minutes to days; it manifests with rapid deterioration of cardiac function, with prolonged need for inotropic support. In recipients whose grafts fail to recover rapidly, an attempt to reverse HAR by plasmapheresis may be made, but success is uncommon, and an immediate retransplant is usually required.

AR in heart transplant recipients is common and usually occurs in the first 3 to 4 months posttransplant. At one time, the diagnosis was made based on the development of congestive heart failure or the elaboration of electrocardiographic abnormalities. However, the present-day routine of protocol endomyocardial biopsies has eliminated such late findings of AR, except in noncompliant recipients. Most centers use frequent percutaneous transjugular right ventricular endomyocardial biopsies as part of a standardized surveillance protocol. Biopsies are evaluated histologically, according to an international grading system [140], and therapy is directed accordingly.

Several investigators have developed noninvasive approaches to establishing the diagnosis of AR, including electrocardiographic frequency analysis, nuclear scintigraphic techniques, and echocardiography; however, no approach has attained sufficient sensitivity to eliminate the need for protocol biopsies. The need for continued endomyocardial biopsies later than 1-year posttransplant is controversial, and center specific with most choosing to discontinue its performance of biopsies at 1 year unless indicated on clinical grounds.

The treatment of AR is based on histologic findings. High dose steroid bolus therapy is used in lower-grade rejection without hemodynamic compromise; oral prednisone therapy for mild AR also has been used with success [141]. Salvage therapy with an antilymphocyte antibody agent is most common in recipients with histologic findings of more severe rejection, in recipients with steroid-resistant rejection, and in recipients with signs of hemodynamic compromise.

Other approaches include switching from cyclosporine-based to tacrolimus-based immunosuppression in recipients with refractory AR in an effort to rescue to the graft, a strategy that was proved to be safe and efficacious [141]. Photopheresis has been used in the treatment of recipients with T-cell lymphoma and autoimmune disease. Studies of photopheresis and triple-drug immunosuppression have provided evidence of a decrease in the total number of AR episodes, as compared with triple-drug immunosuppression alone [141].

CR manifests in heart transplant recipients as cardiac allograft vasculopathy (CAV), an entity that is the major cause of late-term morbidity and mortality. The pathologic findings of CAV include progressive intimal thickening in a concentric manner, which begins distally within the cardiac vasculature. It is associated with the loss of response to endogenous (and pharmacologic) vasodilators [141]. CAV is thought to be immunologically mediated, because HLA donor-related matching is clearly associated with reduced rates of CAV but it could be ameliorated with the use of sirolimus [142]. In addition, nonimmunologic mechanisms are thought to be involved; identifiable risk factors for CAV include hyperlipidemia, donor age older than 25 years, recipient weight gain, CMV disease, preexisting donor or recipient coronary artery disease, and increasing time posttransplant [141]. Another nonimmunologic risk factor for CAV is ischemic time during the peritransplant period.

Lung grafts

The lung graft is highly immunologic organ and as a result prone to rejection—nearly all lung transplant recipients experience at least 1 AR episode. The clinical difficulty posed by rejection is in distinguishing it from other causes of decreased graft function, most commonly infection.

HAR of the lung graft [143] is mediated by recipient preformed antibodies to the donor graft, in a fashion similar to other organs. The

clinical manifestation is like the more common ischemia-reperfusion injury, which, unlike HAR, usually resolves. HAR of the lung graft is rare and only described in case reports. HAR is uniformly fatal in lung transplant recipients. It must be prevented via initial crossmatch testing and exclusion of immunologically unsuitable donor organs and strict adherence to ABO verification policies.

Most AR episodes occur during the first 3 to 6 months posttransplant. Some recipients experience symptoms, including fever, cough, and dyspnea. Early diagnosis of AR in lung transplant recipients is essential: untreated AR can lead to respiratory insufficiency or failure, and repeated AR episodes are associated with an increased risk of bronchiolitis obliterans and eventual graft failure [143].

Transbronchial biopsy is the gold standard for establishing the diagnosis of AR, although less invasive techniques continue to be assessed [143]. Bronchoalveolar lavage (BAL) is also performed to rule out infection before increasing immunosuppression; infection and rejection may occur simultaneously in up to 25% of lung transplant recipients with AR [143]. Early diagnosis of AR may be aided by spirometry; decreases in timed forced expiratory volume, in pulmonary capillary blood volume, and in the diffusing capacity of the lungs for carbon monoxide are associated with AR and should prompt investigation. Radiography is not very sensitive. The histologic findings of AR include lymphocytic infiltrates into the perivascular and interstitial spaces; AR is graded according to histologic findings [144].

The initial treatment of AR in lung transplant recipients is like other organs with the use of high-dose corticosteroids; if they are not successful, anti–T-cell antibody therapy are the second line for steroid resistant cases. Many recipients initially respond to the steroid pulse therapy, yet it may not completely clear their AR, and secondary episodes are common, so additional therapy may be required. For that reason, surveillance bronchoscopy with transbronchial biopsies and BAL are common after initial treatment [143].

CR in lung transplant recipients is extremely common, affecting up to 40% of recipients at 2 years posttransplant and up to 70% of recipients after 5 years [145]. The mean time to diagnosis of graft dysfunction posttransplant is 16 to 20 months. A definitive histologic diagnosis of early bronchiolitis obliterans may be difficult to obtain, so a high degree of clinical suspicion must be maintained. Radiography, again, is not specific. Typical presenting symptoms are cough, progressive dyspnea, and loss of exercise tolerance. There is myriad of therapeutic modalities which have been attempted for recipients with bronchiolitis obliterans, but with little success. Increases in immunosuppression, antilymphocyte antibody therapy, and inhaled cyclosporine have all been tried. Ultimately, the progress of bronchiolitis obliterans is inexorable, with continued loss of graft function and subsequent death. A lung retransplant is the only viable option [143].

Summary

For more than half century, substantial advances in the field of solid-organ transplantation have propelled the clinical practice from an experimental to a standardized and routine stage. Dramatic improvements in surgical techniques, immunosuppressive therapy and medical/critical care have made it possible to increase the pool of potential recipients and now include those who would have been considered too sick or with too many comorbidities even a few years ago. However, despite all progress, until medical science can develop immunosuppressive drugs and regimens without side effects, or achieve routine tolerance induction, the predominant challenges in transplantation will remain the prevention, diagnosis and treatment of Graft versus Host Disease, infection, malignancy and rejection. These clinical problems have, however, improved in the nearly six decades since the first successful kidney transplant was performed, but they may become more complex throughout the twenty-first century as we now transplant many more complicated patients.

References

1. Starzl T, Marchioro TL, Waddell WR. The Reversal of rejection in human renal homografts with subsequent development of homograft tolerance. *Surg Gynecol Obstet.* 1963; 117: 385-395.
2. Hill RB, Rowlands DT, Rifkind D. Infectious Pulmonary Disease in Patients Receiving Immunosuppressive Therapy for Organ Transplantation. *New Eng J Med*. 1964; 271: 1021-1027.
3. Starzl TE, Penn I, Putnam CW, Groth CG, Halgrimson CG. Iatrogenic Alterations of Immunologic Surveillance in Man and Their Influence on Malignancy. *Immunol Rev*. 1971; 7(1): 112-145.
4. Schoemans HM, Lee SJ, Ferrara JL, Wolff D, Levine JE, et al. EBMT−NIH− CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. *Bone Marrow Transplant*. 2018; 53: 1401-1415.
5. Akbulut S, Yilmaz M, Yilmaz S. Graft-versus-host disease after liver transplantation: a comprehensive literature review. *World J Gastroenterol.* 2012; 18: 5240-5248.
6. DePaoli AM, Bitran J. Graft-versus-host disease and liver transplantation. Case Reports Comment Letter. *Ann Intern Med*. 1992; 117: 170-171.
7. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015; 21: 389-401.e1.
8. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005; 11: 945-956.
9. Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016; 22: 4-10.
10. Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol*. 1997; 97: 855-864.
11. Sun B, Zhao C, Xia Y, Li G, Cheng F, et al. Late onset of severe graft-versus-host disease following liver transplantation. Case Reports. *Transpl Immunol*. 2006; 16: 250-253.
12. Alfred A, Taylor PC, Dignan F, El-Ghariani K, Griffin J, et al. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. *Br J Haematol*. 2017; 177: 287-310.
13. Weitz M, Strahm B, Meerpohl JJ, Bassler D. Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients. Review. *Cochrane Database Syst Rev*. 2014; 6: CD009898.
14. Sakellari I, Gavriilaki E, Batsis I, Mallouri D, Panteliadou AK, et al. Favorable impact of extracorporeal photopheresis in acute and chronic graft versus host disease: Prospective single-center study. *J Clin Apher*. 2018; 33: 654-660.
15. Amat P, López-Corral L, Goterris R, Pérez A, López O, et al. Biomarker profile predicts clinical efficacy of extracorporeal photopheresis in steroid-resistant acute and chronic graft-vs-host disease after allogenic hematopoietic stem cell transplant. *J Clin Apher*. 2021; 36: 697-710.
16. Vidal E, Cervera C, Cordero E, Armiñanzas C, Carratalá J, et al. Executive summary. Management of urinary tract infection in solid organ transplant recipients: Consensus statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI). *Enferm Infecc Microbiol Clin*. 2015; 33: 680-687.

17. van Delden C, Stampf S, Hirsch HH, Manuel O, Meylan P, et al. Burden and timeline of infectious diseases in the first year after solid organ transplantation in the Swiss transplant cohort study. *Clin Infect Dis*. 2020; 71: e159-e169.

18. Levitsky J, Formica R, Bloom R, Charlton M, Curry M, et al. The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation. *Am J Transplant*. 2017; 17: 2790-2802 .

19. Shaffer AA, Durand CM. Solid organ transplantation for HIV-infected individuals. *Curr HIV/AIDS Rep*. 2018; 10: 107-120.

20. Botha J, Fabian J, Etheredge H, Conradie F, Tiemessen CT. HIV and solid organ transplantation: Where are we now. *Curr HIV/AIDS Rep*. 2019; 16: 404-413.

21. Blumberg EA, Rogers CC, Practice ASoTIDCo. Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019; 33: e13499.

22. Craig-Schapiro R, Salinas T, Lubetzky M, Abel BT, Sultan S, et al. COVID-19 outcomes in patients waitlisted for kidney transplantation and kidney transplant recipients. *Am J Transplant*. 2021; 21: 1576-1585.

23. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, et al. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*. 2011; 306: 1891-1901.

24. Florescu DF, Qiu F, Schmidt CM, Kalil AC. A Direct and Indirect Comparison Meta-Analysis on the Efficacy of Cytomegalovirus Preventive Strategies in Solid Organ Transplant. *Clin Infect Dis*. 2014; 58: 785-803.

25. Park UJ, Hyun SK, Kim HT, Cho WH, Han SY. Successful Treatment of Disseminated Adenovirus Infection With Ribavirin and Intravenous Immunoglobulin in an Adult Renal Transplant Recipient: A Case Report. *Transplant Proc*. 2015; 47: 791-793.

26. Khedmat H, Karbasi-Afshar R, Agah S, Ghamar-Chehreh ME, Amini M. A meta-analysis of potential relationship between Epstein-Barr-Encoded-RNA (EBER) and onset time of post-transplant lymphoproliferative disorders. *Saudi J Kidney Dis Transpl*. 2015; 26: 232-237.

27. Kauffman CA, Miceli MH. Histoplasmosis and Blastomycosis in Solid Organ Transplant Recipients. *Journal of Fungi*. 2015; 1: 94-106.

28. Kaminski MM, Alcantar MA, Lape IT, Greensmith R, Huske AC, et al. A CRISPR-based assay for the detection of opportunistic infections post-transplantation and for the monitoring of transplant rejection. *Nat Biomed Eng*. 2020; 4: 601-609.

29. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, et al. Weak anti–SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. *Kidney Int*. 2021; 99: 1487-1489.

30. Parapiboon W, Ingsathit A, Jirasiritham S, Sumethkul V. High incidence of bacteriuria in early post-kidney transplantation; results from a randomized controlled study. *Transplant Proc*. 2012; 44: 734-736.

31. Gurusamy KS, Nagendran M, Davidson BR. Methods of preventing bacterial sepsis and wound complications after liver transplantation. *Cochrane Database Syst Rev*. 2014; 3: CD006660.

32. Orlando G, Manzia TM, Sorge R, Iaria G, Angelico R, et al. One-shot versus multidose perioperative antibiotic prophylaxis after kidney transplantation: a randomized, controlled clinical trial. *Surgery*. 2015; 157: 104-110.

33. de la Torre M, Fernández R, Fieira E, González D, Delgado M, et al. Postoperative surgical complications after lung transplantation. *Rev Port Pneumol (2006)*. 2015; 21: 36-40.

34. Tevar A, Humar A, Zureikat A, et al. Pancreas Transplantation. In: Humar A, Sturdevant ML, eds. *Atlas of Organ Transplantation*. Springer London; 2015: 155-222:chap 6.

35. Santos C, Brennan DC, Yusen RD, Olsen MA. Incidence, Risk Factors and Outcomes of Delayed-Onset Cytomegalovirus Disease in a Large Retrospective Cohort of Lung Transplant Recipients. *Transplantation*. 2015; 99: 1658-1666.

36. Ulubay G, Kupeli E, Duvenci BO, Seyfettin EP, Dogrul MI, et al. A 10-year experience of tuberculosis in solid-organ transplant recipients. *Exp Clin Transplant*. 2015; 13: 214-218.

37. Gallagher C, Smith JA. CNS infections in solid organ transplant recipients. *Neurology*. 2016; 9: 1.

38. Saliba F, Pascher A, Cointault O, Laterre PF, Cervera C, et al. Randomized trial of micafungin for the prevention of invasive fungal infection in high-risk liver transplant recipients. *Clin Infect Dis*. 2015; 60: 997-1006.

39. Lamoth F, Alexander BD. Antifungal Activity of SCY-078 (MK-3118) and Standard Antifungal Agents against Clinical non-Aspergillus Mold Isolates. *Antimicrob Agents Chemother*. 2015; 59: 4308-4311.

40. Raad II, El Zakhem A, El Helou G, Jiang Y, Kontoyiannis DP, et al. Clinical experience of the use of voriconazole, caspofungin or the combination in primary and salvage therapy of invasive aspergillosis in haematological malignancies. *Int J Antimicrob Agents*. 2015; 45: 283-288.

41. Heylen L, Maertens J, Naesens M, Van Wijngaerden E, Lagrou K, et al. Invasive Aspergillosis After Kidney Transplant: Case-Control Study. *Clin Infect Dis*. 2015; 60: 1505-1511.

42. Bodilsen J, Brouwer MC, Nielsen H, Van De Beek D. Anti-infective treatment of brain abscess. *Expert Rev Anti Infect Ther*. 2018; 16: 565-578.

43. Cornely OA, Meems L, Herbrecht R, Viscoli C, Amsterdam RG, et al. Randomised, multicentre trial of micafungin vs. an institutional standard regimen for salvage treatment of invasive aspergillosis. *Mycoses*. 2015; 58: 58-64.

44. Chen Y-C, Chang T-Y, Liu J-W, Chen FJ, Chien CC, et al. Increasing trend of fluconazole-non-susceptible Cryptococcus neoformans in patients with invasive cryptococcosis: a 12-year longitudinal study. *BMC Infect Dis*. 2015; 15: 277.

45. Johnson RH, Heidari A. Coccidioidomycosis. *Diagnosis and Treatment of Fungal Infections*. Springer; 2015: 205-216.

46. Miceli MH, Kauffman CA. Treatment Options for Mucormycosis. *Current Treatment Options in Infectious Diseases*. 2015: 1-13.

47. Marion O, Del Bello A, Abravanel F, Couat C, Faguer S, et al. Safety and Immunogenicity of Anti–SARS-CoV-2 Messenger RNA Vaccines in Recipients of Solid Organ Transplants. *Ann Intern Med*. 2021; 174: 1336-1338.

48. Machingaidze S, Wiysonge CS. Understanding COVID-19 vaccine hesitancy. *Nat Med*. 2021; 27: 1338-1339.

49. Aslam S, Goldstein DR, Vos R, Gelman AE, Kittleson MM, et al. COVID-19 vaccination in our transplant recipients: The time is now. *J Heart Lung Transplant*. 2021; 40: 169-171.

50. Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. *JAMA*. 2021; 325: 1784-1786.

51. Connolly CM, Boyarsky BJ, Ruddy JA, Werbel WA, Christopher-Stine L, et al. Absence of humoral response after two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases: a case series. *Ann Intern Med*. 2021; 174: 1332-1334.

52. Marinaki S, Adamopoulos S, Degiannis D, Roussos S, Pavlopoulou ID, et al. Immunogenicity of SARS-CoV-2 BNT162b2 vaccine in solid organ transplant recipients. *Am J Transplant*. 2021; 21: 2913-2915.

53. Negrea L, Rovin BH. Gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 in 2 patients with IgA nephropathy. *Kidney International*. 2021;99: 1487.

54. Stephanie GY, Knight RJ, Graviss EA, Moore LW, Nguyen DT, et al. Kidney transplant recipients rarely show an early antibody response following the first COVID-19 vaccine administration. *Transplantation*. 2021; 105: e72-e73.

55. Del Bello A, Abravanel F, Marion O, Couat C, Esposito L, et al. Efficiency of a boost with a third dose of anti-SARS-CoV-2 messenger RNA-based vaccines in solid organ transplant recipients. *Am J Transplant*. 2021; 22: 322-323.

56. Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. *JAMA*. 2021; 326: 1063-1065.

57. Kute V, Meshram HS, Sharma A, et al. Update on COVID-19 vaccine guidelines for transplant recipients. Elsevier; 2021:

58. Nelson CS, Jenks JA, Pardi N, Goodwin M, Roark H, et al. Human cytomegalovirus glycoprotein B nucleoside-modified mRNA vaccine elicits antibody responses with greater durability and breadth than MF59-adjuvanted gB protein immunization. *J Virol*. 2020; 94: e00186-20.

59. Tan BH. Cytomegalovirus treatment. *Current treatment options in infectious diseases*. 2014; 6: 256-270.

60. Mumtaz K, Faisal N, Husain S, Morillo A, Renner EL, et al. Universal prophylaxis or preemptive strategy for cytomegalovirus disease after liver transplantation: a systematic review and meta-analysis. *Am J Transplant*. 2015; 15: 472-481.

61. Ghassemieh B, Ahya VN, Baz MA, Valentine VG, Arcasoy SM, et al. Decreased incidence of cytomegalovirus infection with sirolimus in a post hoc randomized, multicenter study in lung transplantation. *J Heart Lung Transplant*. 2013; 32: 701-706.

62. Potena L, Bianchi G, Chiereghin A, et al. Reconstitution of CMV-Specific Immunity After Heart Transplantation May Guide Customization of Immunosuppressive and Antiviral Strategies: A Prospective Randomized Study. *The Journal of Heart and Lung Transplantation*. 2014; 33: S154-S155.

63. Ahlenstiel-Grunow T, Koch A, Grosshennig A, Frömke C, Sester M, et al. A multicenter, randomized, open-labeled study to steer immunosuppressive and antiviral therapy by measurement of virus (CMV, ADV, HSV)-specific T cells in addition to determination of trough levels of immunosuppressants in pediatric kidney allograft recipients (IVIST01-trial): study protocol for a randomized controlled trial. *Trials*. 2014; 15: 324.

64. Peters AC, Akinwumi MS, Cervera C, Mabilangan C, Ghosh S, et al. The changing epidemiology of posttransplant lymphoproliferative disorder in adult solid organ transplant recipients over 30 years: a single-center experience. *Transplantation*. 2018; 102: 1553-1562.

65. Allen UD, Preiksaitis JK, Practice AIDCo. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019; 33: e13652.

66. Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev*. 2014; 2014: CD010699.

67. Tan H-H, Goh C-L. Viral Infections Affecting the Skin in Organ??Transplant Recipients. *Am J Clin Dermatol*. 2006; 7: 13-29.

68. Yamada N, Sanada Y, Okada N, Wakiya T, Ihara Y, et al. Successful rescue of disseminated varicella infection with multiple organ failure in a pediatric living donor liver transplant recipient: a case report and literature review. *Virol J*. 2015; 12: 91.

69. Delbue S, Bella R, Ferraresso M. Reactivation of the Human Herpes Virus 6 in Kidney Transplant Recipients: An Unsolved Question. *J Transplant Technol Res*. 2015; 5: e134.

70. Saberi B, Hamilton JP, Durand CM, Li Z, Philosophe B, et al. Utilization of hepatitis C virus RNA–positive donor liver for transplant to hepatitis C virus RNA–negative recipient. *Liver Transpl*. 2018; 24: 140-143.

71. Bohorquez H, Bugeaud E, Bzowej N, Scheuermann J, Hand J, et al. Liver transplantation using hepatitis C virus–viremic donors into hepatitis C virus–aviremic recipients as standard of care. *Liver Transpl*. 2021; 27: 548-557.

72. Chevaliez S, Pawlotsky J-M. Virology of hepatitis C virus infection. *Best Practice & Research Clinical Gastroenterology*. 2012; 26: 381-389.

73. Mahboobi N, Tabatabaei SV, Blum HE, Alavian SM. Renal grafts from anti-hepatitis B core-positive donors: a quantitative review of the literature. *Transpl Infect Dis*. 2012; 14: 445-451.

74. Buti M, Tabernero D, Mas A, Homs M, Prieto M, et al. Hepatitis B virus quasispecies evolution after liver transplantation in patients under long-term lamivudine prophylaxis with or without hepatitis B immune globulin. *Transpl Infect Dis*. 2015; 17: 208-220.

75. Duvoux C, Villamil F, Renner EL, Grazi GL, Firpi RJ, et al. Sustained Virological Response to Antiviral Therapy in a Randomized Trial of Cyclosporine versus Tacrolimus in Liver Transplant Patients with Recurrent Hepatitis C Infection. *Ann Transplant*. 2014; 20: 25-35.

76. Burton Jr JR, Terrault NA, Goldberg DS, Bloom RD, Gilroy R, et al. Liver and kidney recipient selection of hepatitis C virus viremic donors: Meeting Consensus Report from the 2019 Controversies in Transplantation. *Transplantation*. 2020; 104: 476-481.

77. Bethea E, Arvind A, Gustafson J, Andersson K, Pratt D, et al. Immediate administration of antiviral therapy after transplantation of hepatitis C-infected livers into uninfected recipients: Implications for therapeutic planning. *Am J Transplant*. 2020; 20: 1619-1628.

78. Biggins S, Gralla J, Dodge J, Bambha KM, Tong S, et al. Survival Benefit of Repeat Liver Transplantation in the United States: A Serial MELD Analysis by Hepatitis C Status and Donor Risk Index. *Am J Transplant*. 2014; 14: 2588-2594.

79. Stewart ZA, Shah SA, Rolls JA, Guarrera JV, Kandaswamy R, et al. Best Practice Recommendations for the Use of Hepatitis C Viremic Donor Organs for Hepatitis C Virus Naïve Recipients. *Clin Transplant*. 2021; 35: e14381.

80. Naggie S, Cooper C, Saag M, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. *New England Journal of Medicine*. 2015;

81. Simonds RJ. HIV transmission by organ and tissue transplantation. *AIDS*. 1993; 7: S35-S38.

82. Miro J, Agüero F, Duclos-Vallée JC, Mueller N, Grossi P, et al. Infections in solid organ transplant HIV-infected patients. *Clin Microbiol Infect*. 2014; 20: 119-130.

83. Sawinski D, Goldberg D, Blumberg E, Abt PL, Bloom RD, et al. Beyond the NIH Multicenter HIV Transplant Trial Experience: Outcomes of HIV+ liver transplant recipients compared to HCV+ or HIV+/HCV+ co-infected recipients in the United States. *Clin Infect Dis*. 2015; 61: 1054-1062.

84. Nambiar PH, Doby B, Tobian AA, Segev DL, Durand CM. Increasing the Donor Pool: Organ Transplantation from Donors with HIV to Recipients with HIV. *Annu Rev Med*. 2021; 72: 107-118.

85. Gavaldà J, Aguado J, Manuel O, Grossi P, Hirsch H. A special issue on infections in solid organ transplant recipients. *Clin Microbiol Infect*. 2014; 20: 1-3.

86. Lee BT, Gabardi S, Grafals M, Hofmann RM, Akalin E, et al. Efficacy of levofloxacin in the treatment of BK viremia: a multicenter, double-blinded, randomized, placebo-controlled trial. *Clin J Am Soc Nephrol*. 2014; 9: 583-589.

87. Baliu C, Sanclemente G, Cardona M, Castel MA, Perez-Villa F, et al. Toxoplasmic encephalitis associated with meningitis in a heart transplant recipient. *Transpl Infect Dis*. 2014; 16: 631-633.

88. Avila JD, Živković S. The Neurology of Solid Organ Transplantation. *Curr Neurol Neurosci Rep*. 2015; 15: 38.

89. Al-Adra DP, Hammel L, Roberts J, Woodle ES, Levine D, et al. Pretransplant solid organ malignancy and organ transplant candidacy: A consensus expert opinion statement. *Am J Transplant*. 2021; 21: 460-474.

90. Penn I. Cancers in renal transplant recipients. *Adv Ren Replace Ther*. 2000; 7: 147-156.

91. Sherston SN, Carroll RP, Harden PN, Wood KJ. Predictors of cancer risk in the long-term solid-organ transplant recipient. *Transplantation*. 2014; 97: 605-611.

92. Gifford G, Fay K, Jabbour A, Ma DD. Primary central nervous system posttransplantation lymphoproliferative disorder after heart and lung transplantation. *Intern Med J*. 2015; 45: 583-586.

93. Paya CV, Fung JJ, Nalesnik MA, Kieff E, Green M, et al. EPSTEIN-BARR VIRUS-INDUCED POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS. *Transplantation*. 1999; 68: 1517-1525.

94. Lauro A, Arpinati M, Pinna AD. Managing the challenge of PTLD in liver and bowel transplant recipients. *Br J Haematol*. 2015; 169: 157-172.

95. Harris NL, Ferry JA, Swerdlow SH. Posttransplant lymphoproliferative disorders: summary of society for hematopathology workshop. *Semin Diagn Pathol*. 1997; 14: 8-14.

96. Sheil AG, Disney AP, Mathew TH, Amiss N. De novo malignancy emerges as a major cause of morbidity and late failure in renal transplantation. *Transplant Proc.* 1993; 25: 1383-1384.

97. Bavinck JNB, Vermeer BJ, van der Woude FJ, van der Woude FJ, Vandenbroucke JP, et al. Relation between Skin Cancer and HLA Antigens in Renal-Transplant Recipients. *N Engl J Med*. 1991; 325: 843-848.

98. Dahlke E, Murray CA, Kitchen J, Chan AW. Systematic review of melanoma incidence and prognosis in solid organ transplant recipients. *Transplant Res*. 2014; 3: 10.

99. McKnight J, Cen H, Riddler S, Breinig MC, Williams PA, et al. EBV Gene Expression, EBNA Antibody Responses and EBV+ Peripheral Blood Lymphocytes in Post-Transplant Lymphoproliferative Disease. *Leuk Lymphoma*. 1994; 15: 9-16.

100. Robinson JK, Guevara Y, Gaber R, Clayman ML, Kwasny MJ, et al. Efficacy of a sun protection workbook for kidney transplant recipients: a randomized controlled trial of a culturally sensitive educational intervention. *Am J Transplant*. 2014; 14: 2821-2829.

101. D'Amico F, Fuxman C, Nachman F, Bitetti L, Fauda M, et al. Visceral Kaposi's sarcoma remission after intestinal transplant. First case report and systematic literature review. *Transplantation*. 2010; 90: 547-554.

102. Gutierrez JCL. Classification of Vascular Tumors. *Hemangiomas and Vascular Malformations*. Springer; 2015: 59-65.

103. Alberu J, Pascoe MD, Campistol JM, Schena FP, Rial Mdel C, et al. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation*. 2011; 92: 303-310.

104. Long ME, Chantigian PD, Weaver AL. Would Women With Solid Organ Transplant Qualify for Triennial Cervical Cancer Screening as Recommended by the American College of Obstetricians and Gynecologists in 2016 and American Society for Colposcopy and Cervical Pathology in 2019? *J Low Genit Tract Dis*. 2021; 25: 92-97.

105. Long ME, Chantigian PD, Weaver AL. Cervical cytology and histology after solid organ transplant: a longitudinal cohort study. *J Low Genit Tract Dis*. 2018; 22: 362-366.

106. Eccher A, Girolami I, Motter JD, Marletta S, Gambaro G, et al. Donor-transmitted cancer in kidney transplant recipients: a systematic review. *J Nephrol*. 2020; 33: 1321-1332.

107. Penn I. Evaluation of transplant candidates with pre-existing malignancies. *Ann Transplant*. 1997; 2: 14-17.

108. Xiao D, Craig JC, Chapman JR, Dominguez-Gil B, Tong A, et al. Donor cancer transmission in kidney transplantation: a systematic review. *Am J Transplant*. 2013; 13: 2645-2652.

109. Onaca N, Klintmalm GB. Liver transplantation for hepatocellular carcinoma: the baylor experience. *J Hepatobiliary Pancreat Sci*. 2009; 17: 559-566.

110. Halazun KJ, Patzer RE, Rana AA, Verna EC, Griesemer AD, et al. Standing the test of time: Outcomes of a decade of prioritizing patients with hepatocellular carcinoma, results of the UNOS natural geographic experiment. *Hepatology*. 2014; 60: 1957-1962.

111. Halazun K, Sapisochin G, von Ahrens D, Agopian V, Tabrizian P. Predictors of outcome after liver transplantation for hepatocellular carcinoma (HCC) beyond Milan criteria. *Int J Surg*. 2020; 82S: 61-69.

112. Medawar PB. EXPERIMENTAL WORK. *Plastic and Reconstructive Surgery*. 1947; 2: 387.

113. Squifflet JP, De Meyer M, Malaise J, Latinne D, Pirson Y, et al. Lessons learned from ABO-incompatible living donor kidney transplantation: 20 years later. *Exp Clin Transplant*. 2004; 2: 208-213.

114. Magee CC. Transplantation across previously incompatible immunological barriers. *Transpl Int*. 2006; 19: 87-97.

115. Jordan SC, Lorant T, Choi J, et al. IgG endopeptidase in highly sensitized patients undergoing transplantation. *N Engl J Med*. 2017; 377: 442-453.

116. Lonze BE, Tatapudi VS, Weldon EP, Min ES, Ali NM, et al. IdeS (Imlifidase): a novel agent that cleaves human IgG and permits successful kidney transplantation across high-strength donor-specific antibody. *Ann Surg*. 2018; 268: 488-496.

117. Taylor CJ, Kosmoliaptsis V, Summers DM, Bradley JA. Back to the future: application of contemporary technology to long-standing questions about the clinical relevance of human leukocyte antigen-specific alloantibodies in renal transplantation. *Hum Immunol*. 2009; 70: 563-568.

118. Haas M, Rahman MH, Racusen LC, Kraus ES, Bagnasco SM, et al. C4d and C3d Staining in Biopsies of ABO- and HLA-Incompatible Renal Allografts: Correlation with Histologic Findings. *Am J Transplant*. 2006; 6: 1829-1840.

119. National Institutes of Health NIoDaDaKD. United States Renal Data System, 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. . Accessed 07/12/2015, 2015.

120. Vincenti F, Schena FP, Paraskevas S, Hauser IA, Walker RG, et al. A Randomized, Multicenter Study of Steroid Avoidance, Early Steroid Withdrawal or Standard Steroid Therapy in Kidney Transplant Recipients. *Am J Transplant*. 2008; 8: 307-316.

121. Matas AJ. Impact of acute rejection on development of chronic rejection in pediatric renal transplant recipients. *Pediatr Transplant*. 2000; 4: 92-99.

122. Sayegh MH. Chronic renal allograft dysfunction (CAD): new frontiers. *Kidney Int Suppl*. 2010; 78: S1-S1.

123. Jain S, Curwood V, White SA, Williams ST, Doughman T, et al. Weekly protocol renal transplant biopsies allow detection of sub-clinical acute rejection episodes in patients with delayed graft function. *Transplant Proc*. 2000; 32: 191.

124. Dalpiaz T, Nogare ADL, Carpio V, Veronese FV, Manfro RC, et al. Noninvasive Molecular Biomarkers of Acute Antibody Mediated Rejection in Renal Transplant Patients. *Transplantation Journal*. 2012; 94: 263.

125. Marshall SE, McLaren AJ, McKinney EF, Bird TG, Haldar NA, et al. DONOR CYTOKINE GENOTYPE INFLUENCES THE DEVELOPMENT OF ACUTE REJECTION AFTER RENAL TRANSPLANTATION. *Transplantation*. 2001; 71: 469-476.

126. Kirkpantur A, Yilmaz R, Baydar DE, Aki T, Cil B, et al. Utility of the Doppler Ultrasound Parameter, Resistive Index, in Renal Transplant Histopathology. *Transplant Proc*. 2008; 40: 104-106.

127. Naesens M, Heylen L, Lerut E, Claes K, De Wever L, et al. Intrarenal resistive index after renal transplantation. Research Support, Non-U.S. Gov't. *N Engl J Med*. 2013; 369: 1797-806.

128. Mubarak M. Evolution of the Banff Working Classification of Renal Allograft Pathology: Updates and Future Directions. *J Transplant Technol Res*. 2013; 03(02).

129. Waaga AM, Gasser M, Laskowski I, Tilney NL. Mechanisms of chronic rejection. *Current Opinion in Immunology*. 2000; 12: 517-521.

130. Demetris AJ, Zeevi A, O'Leary JG. ABO-compatible liver allograft antibody-mediated rejection. *Curr Opin Organ Transplant*. 2015; 20: 314-324.

131. A Comparison of Tacrolimus (FK 506) and Cyclosporine for Immunosuppression in Liver Transplantation. *N Engl J Med*. 1994; 331: 1110-1115.

132. Neuhaus P. Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: Results from a double-blind randomized placebo-controlled trial. *Liver Transpl*. 2002; 8: 132-142.

133. Banff Working Group on Liver Allograft P. Importance of liver biopsy findings in immunosuppression management: biopsy monitoring and working criteria for patients with operational tolerance. *Liver Transpl*. 2012; 18: 1154-1170.

134. Wong P, Devlin J, Gane E, Ramage J, Portmann B, et al. FK 506 rescue therapy for intractable liver allograft rejection. *Transpl Int*. 1994; 7: 0934-0874.

135. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. *Nat Rev Endocrinol*. 2013; 9: 555-562.

136. Norman SP, Kommareddi M, Samaniego M, Ojo AO, Luan FL. EARLY PANCREAS GRAFT LOSS IS ASSOCIATED WITH INCREASED MORTALITY IN SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANT RECIPIENTS. *Transplantation Journal*. 2010; 90.

137. GRUESSNER RWG, SUTHERLAND DER. In: Solez K, Racusen LC, Billingham ME, eds. *Solid Organ Transplant Rejection: Mechanisms, Pathology and Diagnosis*. Marcel Dekker Inc., New York; 1996: 455-499:chap Clinical diagnosis in pancreas allograft rejection.

138. Nghiem DD, Gonwa TA, Corry RJ. Metabolic Effects Of Urinary Diversion Of Exocrine Secretions In Pancreatic Transplantation. *Transplantation*. 1987; 43: 70-72.

139. Gruessner AC. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud*. 2011; 8: 6-16.

140. Everitt MD, Hammond MEH, Snow GL, Stehlik J, Revelo MP, et al. Biopsy-diagnosed antibody-mediated rejection based on the proposed International Society for Heart and Lung Transplantation working formulation is associated with adverse cardiovascular outcomes after pediatric heart transplant. *J Heart Lung Transplant*. 2012; 31: 686-693.

141. Hunt SA, Haddad F. The Changing Face of Heart Transplantation. *J Am Coll Cardiol*. 2008; 52: 587-598.

142. Matsuo Y, Cassar A, Yoshino S, Flammer AJ, Gulati R, et al. Attenuation of cardiac allograft vasculopathy by sirolimus: Relationship to time interval after heart transplantation. Research Support, N.I.H., Extramural. *J Heart Lung Transplant*. 2013; 32: 784-791.

143. Martinu T, Howell DN, Palmer SM. Acute cellular rejection and humoral sensitization in lung transplant recipients. Research Support, N.I.H., Extramural Review. *Semin Respir Crit Care Med*. 2010;31:179-188.

[*] ***Correspondence:*** Rainer W.G. Gruessner, MD, FACS, Professor, Department of Surgery, State University of New York, SUNY Downstate Health Sciences University, Brooklyn, NY, USA, E-mail: Gruessner46@lsus.edu / Rainer.Gruessner@downstate.edu

Received: February 10, 2023; **Accepted:** April 30, 2023; **Published:** May 04, 2023

Citation: Whittaker VE, Gruessner RWG. Diagnosis and management of graft versus host disease, infection, malignancy and rejection in transplant recipients. *Front Transplant*. 2023; 2: 102.