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Immunosuppressive Agents and Infectious Risk in Transplantation: Managing the "Net State of Immunosuppression"

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Successful solid organ transplantation reflects meticulous attention to the details of immunosuppression, balancing risks for graft rejection against risks for infection. The "net state of immune suppression" is a conceptual framework of all factors contributing to infectious risk. Assays that measure immune function in the immunosuppressed transplant recipient relative to infectious risk and allograft function are lacking. The best measures of integrated immune function may be quantitative viral loads to assess the individual's ability to control latent viral infections. Few studies address adjustment of immunosuppression during active infections; thus, confronted with infection in solid organ recipients, the management of immunosuppression is based largely on clinical experience. This review examines known measures of immune function and the immunologic effects of common immunosuppressive drugs and available studies reporting modification of drug regimens for specific infections. These data provide a conceptual framework for the management of immunosuppression during infection in organ recipients.

Keywords. transplant immunosuppression; allograft rejection; viral infection; opportunistic infection; immune function assays.

Optimal management of immunosuppression coupled with antimicrobial prophylaxis and meticulous clinical care are foundations for successful human solid organ transplantation (SOT) [1, 2]. The risk for infection in these immunocompromised hosts reflects the relationship between epidemiologic exposures to potential pathogens and the nature and intensity of immunosuppression required to prevent graft rejection. The immunological impact of immunosuppressive drugs varies based on factors including the genetics of the individual's innate and adaptive immune responses and drug metabolism [3]. Using multiple simultaneous or sequential agents creates additional complexity. Some measures of an individual's immune deficits are required to assess infectious risk to design preventive strategies and manage infections [3–6]. Individual infectious risk is captured by a conceptual framework, the "net state of immune deficiency," which includes the immunosuppressive regimen and individual predisposing factors such as diabetes, renal dysfunction, surgery, or nutritional deficits [7, 8]. In SOT, a key challenge is the absence of standardized assays to assess simultaneously an individual's risk for graft rejection and infection. Clinical judgment remains essential.

This review describes the effects of common immunosuppressive agents and summarizes data on management of immunosuppression during infection in transplant recipients.

MEASURING THE NET STATE OF IMMUNE SUPPRESSION

Drug Levels

Objective measurements of the net state of immune suppression are needed to minimize infectious risk and optimize immunosuppression. Measurement of immunosuppressive drug levels is used to avoid drug toxicities, graft rejection, and infection. Trials examining infectious outcomes relative to drug level targets are scarce. Infection was more common with higher overall calcineurin-inhibitor (CNI) trough concentrations after kidney transplantation; multiple shifts in immunosuppression obscures interpretation [9]. Correlations exist between rates of herpesvirus infections and mycophenolate levels [10]. Several trials reported infection-related outcomes for various immunosuppressive combinations but lack simultaneous drug levels [11, 12]. For many drugs, treatment is based on weight-based dosing or end effect (eg, reversal of rejection, T-cell depletion) without measurable levels (eg, corticosteroids, antibody-based therapies, costimulatory blockade). Similarly, mycophenolate dosing in the absence of therapeutic drug metabolism studies may be predicated on racial differences in drug metabolism or end effect [13–15].

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Immune Function Assays

Immune function assays are used to supplement drug levels. Some basic methods are useful, including white blood cell counts, cell differentials, and T-lymphocyte subsets. Reduced CD4+ and CD8+ T-lymphocyte counts risk opportunistic infection and cytomegalovirus (CMV) posttransplant [16–19]. Similarly, low total lymphocyte counts pretransplant identify individuals at increased infectious risk [20, 21]. Low total lymphocyte counts after CMV treatment predicts increased risk for relapse [22]. In vitro assays associate reduced natural killer cell function with more severe infections [23]. Markers of T-cell exhaustion in response to chronic antigenic stimulation (eg, PD-1) and cytokine levels (eg, interleukin-10) correlate with immune responses to specific antigens [24]. Similarly, the degree of T-cell commitment and antibody levels against specific pathogens are markers of immune responsiveness [25]. Hypogammaglobulinemia, reduced serum complement component 3 and mannose binding lectin (MBL) deficiency are associated with increased infectious risk after SOT [26–39]. Immunoglobulin replacement is common with immunoglobulin deficiency despite the absence of data demonstrating benefit [40].

Given the complexity of immune responses required to resolve infection, functional assays reflecting integration of innate and adaptive immune components are desirable. The only assays that measure all limbs of coordinated immune responses are measurements of circulating viral loads (eg, intrinsic antiherpesvirus immunity). Lifetime viral infections are normally suppressed by an integrated immune response. Quantitative molecular viral loads in blood measure the effectiveness of immune responses [41–43]. Host immunity during viral infection may be reestablished in SOT by reduction in immunosuppression. Rejection may occur, but does so less often than expected, possibly because of immunosuppressive indirect effects of virus [3, 44]. This is best described for Epstein-Barr virus (EBV) as well as for CMV, varicella zoster, and herpes simplex virus [41–43, 45, 46]. The presence of viremia (quantitative viral loads for CMV, EBV, or human herpesvirus 6 or 7 or BK and JC polyomaviruses) suggests overimmunosuppression relative to specific viral strains, the intensity of infection, and coordination of host immune responses [3]. Although viremia reflects the intensity of immunosuppression, this has not been simultaneously correlated with the adequacy of immunosuppression for graft maintenance. The presence of viremia may suggest a need for reductions in immunosuppression or antiviral prophylaxis. Viremia is common in transplant recipients; up to 30% of individuals with viremia have 2 or more viruses circulating at any one time. In 1 study in pediatric renal recipients, viremia occurred in 73% (EBV, 34%; CMV, 23%; BK, 23%; and JC, 21%) [47]. Torque teno virus (TTV, an anellovirus) is ubiquitous but of unknown pathogenic significance. TTV viremia is related to the degree of immunosuppression; higher TTV levels are associated with reduced allograft rejection but heightened risk for infection [48–52]. Experience is limited and TTV levels have not been examined in interventional trials of immunosuppression. Related pathogen-specific quantitative measures of immune function, primarily focused on CMV-specific immunity, allow stratification of risk for CMV disease after completion of antiviral prophylaxis [53–57].

Soluble CD30 (sCD30) has been investigated as a marker of T-cell function. Mouse models and human studies demonstrate association of low levels of sCD30 with risk for graft rejection [58]. In 100 cardiac recipients, lower pretransplant sCD30 levels were associated with increased posttransplant infections and higher levels with reduced infection up to 2 years' posttransplant; there was no relationship with rejection [59, 60]. Similarly, in 586 patients, higher sCD30 levels before kidney transplant predicted lower rates of rejection, and lower levels with higher risk of pneumonia [61]. Results vary. One study of 652 patients before kidney transplant found no correlation between pretransplant sCD30 and allograft rejection [62]. A meta-analysis found poor correlation between sCD30 and acute rejection [63]. Thus, available data do not yet support sCD30 as a tool for immunosuppressive management.

Stimulated intracellular adenosine triphosphate levels (iATP) are used as indicators of global T-cell function. Prospective studies are limited with discordant results obtained regarding infectious risk in SOT. In 248 liver recipients, low iATP was associated with invasive fungal infection, but not bacterial infection [64]. In 100 kidney recipients, lower iATP was associated with CMV disease, but not bacterial infections [65]. Meta-analyses of iATP studies found discordant results [66–68]. The clinical utility of this tool remains uncertain.

An assay combining adaptive and innate immune functions used plasma interferon-gamma (IFN-γ) release after whole blood stimulation with various antigens [69, 70]. In 137 patients, IFN-γ levels were significantly lower in those with infection episodes up to 6 months posttransplant; rejection episodes did not correlate with IFN-γ level [70]. Assay-based interventional trials are needed.

Without assays predictive of infectious risk, composite scores of natural killer cell number, immunoglobulin levels, complement levels, T-cell subsets or function, neutrophil function, and CMV status have been proposed [71–77]. The composite "immune risk profile" (IRP) includes a positive CMV serology with at least 1 of CD4/CD8 ratio <1 and/or CD8 T-cell count >90th percentile. IRP-positive patients demonstrated more pronounced immune senescence with greater frequencies of both opportunistic infections (hazard ratio, 2.97 [95% confidence interval, 1.53–5.76], $P = .001$) and severe bacterial infection (hazard ratio, 2.33 [95% confidence interval, 1.34–3.92], $P = .008$). Acute rejection rates were less frequent in IRP+ patients. The assay has not been reported in management of immunosuppression [75, 77].

Immunoregulatory Genes, Comorbid Conditions, and Dysbiosis

The association of allelic variants of immunoregulatory genes for innate and adaptive immune function, or for colonization or invasion of specific pathogens (eg, *Aspergillus* species) may allow refinement of individual immune assessments. The liver-derived lectin pathway of complement activation is an effector of innate immunity; genetic polymorphisms determine functional activity. Single-nucleotide polymorphisms in genes for MBL2, ficolin-2, and MBL-associated serine protease 2 of recipients and donors were each associated with 2-fold increased risks for infection. Liver recipients with donor polymorphisms in all 3 components had a 75% risk for infection compared with 18% for wild-type livers. Cumulative increases in infectious risk were observed with multiple allelic variants and were associated with up to 6-fold higher mortality ($P = .9 \times 10^{-8}$); 80% were infection-related [31, 33, 38]. Other innate immune genetic polymorphisms are associated with specific infections (eg, Toll-like receptor-4 is associated with increased risk of CMV disease) [36, 37]. Polymorphisms of nucleotide binding oligomerization domain containing 2 (NOD2) was associated with increased infectious risk after liver-intestinal transplant [34, 35]. Increased risk of viral infections was found with certain cytotoxic T-lymphocyte associated protein 4 polymorphisms [39]. Pentraxin 3 (PTX3) is a soluble pattern recognition receptor produced by neutrophils, dendritic cells, macrophages, and epithelial cells. Genetic polymorphisms in PTX3 are associated with increased invasive mold infections in SOT [78]. Risk for colonization and invasive mold infection is cumulatively affected by genes encoding PTX3, interleukin 1β, interleukin 1 receptor antagonist, and β-defensin 1 [78].

Underlying medical comorbidities play a significant role as "immune background." Contributions to infectious risk of common comorbidities such as diabetes are difficult to quantify [79, 80]. Diabetes is a risk factor for perioperative infection [81–83]. Other contributors include nutritional status, pretransplant dialysis, and obesity [84–87]. Individuals with systemic lupus erythematosus, polymyalgia rheumatica, and giant cell arteritis have infectious risks that increase with disease activity independent of immunosuppressive therapy [88–90]. The risk of infection in systemic lupus erythematosus is assessed by composite scores that require validation in SOT [91–93]. The heightened risk of infection in autoimmune disease is compounded by immunosuppressive therapies with prolonged durations of effect (eg, rituximab, tocilizumab). The contribution of underlying autoimmune conditions to immunodeficiency in SOT must be considered, but cannot be quantified [7].

The microbiome has emerged as an important determinant of immune function. Dysbiosis is common because of immunosuppression, antibiotics, and surgery [94–97]. Reduced gastrointestinal butyrate-producing bacteria in kidney recipients was associated with increased viral respiratory infections [98]. Transplantation of skin between mice demonstrated prolonged graft survival in germ free and antibiotic pretreated mice compared with mice with normal flora. This effect was associated with alloreactive T-cell priming in untreated mice, suggesting a role of the microbiome in allograft rejection [99]. Similarly, obese mice demonstrated enhanced allograft rejection [100]. Modification or normalization of allograft recipients' microbial patterns may reduce graft rejection and modify the immunosuppression required for graft maintenance [101–104].

Although there are many tools that measure various aspects of immunity, none, individually or in aggregate, have been shown to guide clinical decisions regarding infectious risk versus graft rejection. Hence, management of immunosuppression during infection has largely been based on clinical experience.

IMMUNE EFFECTS OF COMMON IMMUNOSUPPRESSIVE AGENTS IN TRANSPLANTATION

Management of immunosuppression during infection requires a basic understanding of the effects of individual agents. These are outlined (Tables 1–3) as a foundation for clinical decision-making.

STUDIES ON REDUCTION OF IMMUNOSUPPRESSION IN INFECTION

It is instinctive for clinicians to reduce immunosuppression in the face of infection (Table 4). Sepsis, graft infection (eg, pyelonephritis, hepatitis, pneumonia), or systemic inflammation (eg, coronavirus disease 2019 [COVID-19]) may coexist with, or be indistinguishable from, graft rejection. Clinical data on management of immunosuppression are limited (Table 4). Immunosuppressive strategies vary widely; judgments for specific patients are based largely on infectious patterns under specific regimens. With infection in SOT, considerations include:

1. The role of immunosuppression in the pathogenesis of infection.
2. Likelihood that infection can be resolved without reduced immunosuppression.
3. Risk for graft rejection with reduced immunosuppression.
4. Risk of immune reconstitution syndromes.

Several common infectious syndromes merit consideration:

1. Management of chronic viral infections normally controlled by the immune system for which antiviral therapies exist (eg, CMV, EBV, varicella zoster, herpes simplex virus, hepatitis B [HBV], hepatitis C)
2. Opportunistic infections requiring immune responses for resolution (eg, tuberculosis, nontuberculous mycobacteria, *Nocardia* spp., *Pneumocystis jirovecii*, invasive fungal infections)

Table 1. Mechanisms of Action of Common Immunosuppressive Therapies

	Mechanism	Immune Target
Calcineurin inhibitors (cyclosporine and tacrolimus)	Cyclosporine binds cyclophilins and tacrolimus binds FKBP12 (FK-506 binding protein 12) with a resultant molecular complex that competitively inhibits calcineurin [105, 106]	Calcineurin inhibition results in inhibition of gene transcription in nuclear factor activated T-cells region in a broad range of cells including T cells, B cells, and all myeloid lineage cells [107].
MMF	Mycophenolate inhibits IMPDH in purine synthesis [108].	IMPDH inhibition with resultant impaired purine synthesis has broad effects in T cells, B cells, dendritic cells, monocytes, and macrophages [108].
Azathioprine	Azathioprine is metabolized to 6MP with resultant compounds (6-methyl-MP and 6-thioguanine) being incorporated into DNA of replicating cells as well as inhibiting purine synthesis [109].	Inhibits DNA synthesis, impairing B- and T-cell proliferation [109, 110].
mTOR inhibitors	Binds FKBP-12 to create sirolimus-FKBP12 complex, which binds and inhibits mTOR [111].	Inhibition of regulatory kinase, mTOR, with resultant impairment of cell cycle at G1-S phase [111]. Impairs IL-2–dependent and CCD-28–dependent pathways to T-cell progression through cell cycle [112, 113].
Glucocorticoids	Bind intracellular glucocorticoid receptor [114].	Alteration of gene regulation with resultant alteration in cell function, indirect effects via alterations in cytokine release and cell signalling [114].
Belatacept	Fusion protein of cytotoxic T-lymphocyte associated protein-4-immunoglobulin, preventing T-cell co-stimulation [115].	Blocks CD28 binding to CD80/CD86 thereby preventing co-stimulation required for T-cell activation [115].
ATG	Polyclonal immunoglobulin G that has been immunized with human thymocyte and T-cell lines [116].	Broad antigen target depletes T cells through complement-mediated or activation-associated destruction [116].
Basiliximab	IL-2 receptor antibody.	Binds to IL-2 receptor antibodies (anti-CD-25) on T cells, competitively inhibiting IL-2 binding to IL-2 receptor and thus inhibiting IL-2 dependent T-cell proliferation [117].
Alemtuzumab	Anti-CD52 monoclonal antibody.	Binds to CD-52 producing antibody dependent lysis in T-cells and B-cells [118]
Anti-CD20 (rituximab)	Anti-CD20 monoclonal antibody.	Binds to CD-20 producing B-cell depletion via a variety of mechanisms including antibody dependent cytotoxicity and antibody-dependent cellular cytotoxicity [119].
Eculizumab	Anti-complement (C5) monoclonal antibody.	Prevents cleavage of C5 into C5a and C5b and thus prevents formation of membrane attack complex [120].
Anti-IL6 inhibitors (eg, tocilizumab)	IL-6 receptor antagonist	Bind soluble and membrane bound IL-6 receptors, thus inhibiting the action of cytokine IL-6 [121].

Abbreviations: ATG, Anti-thymocyte globulin; IL, interleukin; IMPDH, inosine-5′-monophosphate dehydrogenase; MMF, mycophenolate mofetil; mTOR, mechanistic target of rapamycin.

3. Severe life-threatening infections (eg, bacterial sepsis, COVID-19)
4. Infections lacking specific therapies, cure relying on immune responses (eg, *Norovirus*, cryptosporidiosis, BK virus, JC virus (progressive multifocal leukoencephalopathy [PML]), COVID-19, hepatitis E virus)
5. Common bacterial and fungal (eg, *Candida* spp.) infections (ie, pneumonia, cholangitis, endocarditis) for which therapies exist.

Chronic Viral Infections

Optimal approaches to manipulation of immunosuppression with viral activation are based largely on anecdotal evidence. Most are largely controlled by T-cell–mediated immunity. Depending on the latency program for each virus, viral replication and viremia may emerge with waning immune surveillance. Donor-derived CMV infection emerges in more than one-half of immunologically naïve transplant recipients without prophylaxis, whereas CMV reactivation in immune recipients is less common with risk determined by the intensity of immunosuppression [229, 230]. The immunological or "indirect effects" of CMV (and other viral) activation are associated with increased rates of graft rejection and opportunistic infections [44, 230, 231]. For CMV, effective antiviral therapy permits maintained immunosuppression during treatment. Reduced immunosuppression may be required with refractory/resistant CMV disease or for recurrent infection; less intense immunosuppression is associated with more successful outcomes [232]. Reduction in CNI to reestablish T-cell function (or antiproliferative agents with neutropenia) might be considered. The intensity of corticosteroid therapy is also correlated with the risk for CMV disease [233]. CMV risk is amplified by T-cell–depleting agents and high-dose corticosteroids for graft rejection and may predispose to subsequent fungal infections [44, 234]. Mechanistic target of rapamycin (mTOR) inhibitors may reduce rates of CMV infection; this effect is not universally observed and a role in therapy merits further study [235]. More aggressive reductions may be required for resolution in thoracic transplant recipients than in renal recipients, but risks rejection. Belatacept has been associated with greater difficulty in treatment of CMV infections. The role of the humoral immune system in CMV infections is increasingly appreciated.

EBV infection is associated with posttransplant lymphoproliferative disorder (PTLD). Belatacept suppression

Table 2. Effects of Common Immunosuppressive Agents on Immune Function

	Innate	T-cell	B-cell/Humoral
CNIs	Impaired [107, 122] via - Impaired *Candida* killing [123] - Disrupted myeloid cell homeostasis, included impaired hematopoiesis and dendritic cell development [124] - Reduced neutrophil and macrophage bacterial phagocytosis and migration via nucleotide binding oligomerization domain containing 1 inhibition [125, 126] - Downregulation of Toll-like receptor function [126, 127] - Impaired LPS response [126, 128] - Impaired lateral transfer of fungi between macrophages [129]	Impaired via - Impaired T-cell activation and proliferation [105, 106, 130] - Impaired IL-2 production [106] - Impaired cytokine production from memory CD4 T cells [131] - Impair naïve CD4 T-cell differentiation [131] - Impaired mast cell degranulation [105, 130] - Reduced circulating Treg viability and proliferation [132, 133] - Reduced FOXP3 production [134] - Impaired Treg chemokine receptor expression [132] - Lymphocyte migration and distribution through reduction ion CD62L expression [135, 136]	Impaired via - Naïve B-cell activation [137] - B-cell antigen presentation - Immunoglobulin development [138, 139] Directly via - Impaired proliferation [137, 140] - Impaired T-cell–dependent responses in mice [140]; not reproduced in human [141] - IgA and IgE class switching [137] Indirectly via - Impaired T-cell stimulus to T-cell dependent responses [141] - Impaired T follicular helper cell differentiation [137] No change in B-cell tolerance [140]
MMF	Slightly impaired via - Increased monocyte apoptosis [142] - Reduced dendritic cell function and activation in response to LPS [143] - Reduced natural killer cell function and proliferation [144] Not impaired - Neutrophil chemotaxis or superoxide production [145] - Unchanged *Aspergillus* killing [146] - Monocyte function [147] - Improved natural killer cell number and function at 1 year after kidney transplant compared with azathioprine/cyclosporine A Potential adverse effect - Neutropenia	Impaired via - Impaired proliferation [148, 149] - Increased apoptosis and terminal proliferation [142, 150] - Impaired cell surface cytokine receptor expression [149] - Impaired cell adhesion and tissue infiltration [151]	Impaired via mechanism - Impaired immunoglobulin development and response [139, 148] - Impaired early B-cell activation and plasma cell differentiation [152] - Impaired naïve and memory B-cell expansion [152] - Impaired B-cell proliferation compared with non-MMF immunosuppressive therapies [153] - Impaired CD80 expression on B cells [154] - Lower immunoglobulin levels with MMF than azathioprine [155] - Impaired antibody response in MMF regimes after renal transplant [156] - Impaired antibody response to influenza vaccine [157] - Reduced antibody production after heart transplant compared with azathioprine [158] - Impaired humoral response to vaccine [159]
Azathioprine	Possibly impaired via - Reduced dendritic cell function in the setting of LPS [160] Not impaired [161–163]	Impaired via - Reduced T-cell proliferation [164, 165] - Reduced T-cell activation [166]	Impaired via - Reduced response to stimulus in vitro [167] - Impaired response to T-cell–dependent stimulation [168] - Impaired B-cell differentiation [169] - Impaired immunoglobulin synthesis [170]
mTOR inhibitors	Impaired via - Reduced oxidative burst of neutrophils [171] - Possibly impaired IL-10 production [172] - Reduced IL-8 and vascular endothelial growth factor release [173]	Impaired via - Smaller Th1 subset with reduced IL-12 and interferon-gamma production [174] - [133] - Lower adenosine triphosphate concentrations in CD4 cells correlating with impaired T-cell proliferation [175] Altered - Promotion of regulatory T-cell generation [176] - Increased development of CD8+ memory T cells in response to antigen [176]	Impaired via - B-cell proliferation and immunoglobulin production in vivo [177] Preserved - Humoral vaccine response [159]

Table 2. Continued

	Innate	T-cell	B-cell/Humoral
Prednisolone	Impaired via - Reduction in cellular response to PAMPS and DAMPS [114] - Inhibited cellular secretion of inflammatory mediators - Impaired cytokine release and response [114] - Impaired leukocyte extravasation and chemokine production - Impaired neutrophil adherence [178]	Impaired [114] via - Impaired T-cell development and survival - Impaired T-cell activation - Decreased lymphocyte migration [179]	Impaired [114] via - Immature B-cell apoptosis - Impaired B-cell proliferation - Impaired IgM and IgG production
ATG	Impaired via - Complement-mediated lysis of dendritic cells [116]	Impaired via - Dose-dependent T-cell depletion peripherally and within peripheral lymphoid tissue [180] - Alteration of adhesion and cell trafficking [116] - Impaired activation by dendritic cells [116]	Impaired via - B-cell depletion via antigen binding [116]
Basiliximab	Not described	Impaired via - Impaired T-cell proliferation [117] - CD3+/CD4+ T-cell suppression [117] - Reduced Treg and impaired activation of Treg subsets [181]	Not described
Belatacept	Not described	Impaired via - Impaired T-cell activation [182] - Impaired naïve T-cell response, relatively preserved mature T-cell response [183] - Reduced T-helper activation of B cells [184] - Impaired Treg production [185]	Impaired via - Reduced immunoglobulin secretion from plasma cells and reduce B-cell cytokine releases [184] - Impaired T-cell activation by B-cells [184] - Reduction in circulating effector B cell [184]
Alemtuzumab	Limited effect—innate cell function [186] Reduction in dendritic cell number [187]	Impaired via - Prolonged (y) lymphocyte depletion [188–191] - Reduce proportion of Tregs [188] - Preserved memory T-cell responses [192]	Impaired via - B-cell depletion, but repopulate within a 1 y [188, 189, 191] - Reduced repopulation with memory B cell, dominated by naïve B cells [191]
Rituximab	Not described Potential adverse effect - Delayed onset neutropenia	Mixed overall Impaired via - Impaired T-cell activation and proliferation [193, 194] Preserved via - Potential up regulation of Treg [195] - Some evidence of intact cellular immune response to vaccines [196] - Persevered T-cell response to varicella zoster but not staph aureus enterotoxin [197]	Impaired [198] via - B-cell depletion (prolonged) [198] - Impaired antibody production and hypogammaglobulinemia [198] - Impaired regulatory B cells and reduction of IL-10 production
Eculizumab	Impaired via - Impaired complement action with blocking of membrane attack complex formation [120]	Not described - Possible reduction in T-cell priming and activation [199]	Not described - Impaired antibody response resulting from complement inhibition [120, 199]
IL-6 antagonists	Impaired via - Impaired neutrophil survival, oxidative burst, and phagocytosis [200] - Reduced complement (component 3, component 4) levels [201] - Reduced neutrophil trafficking to bone marrow [202] - Reduction in neutrophil counts without increased clinical infections [203] Presumed effects based on known effects of IL-6 - Reduced responsiveness of C5 [204]	Mixed - No effect on Treg expansion [205] Presumed based on IL-6 functions - Reduced cytotoxic T-cell differentiation [206]	Impaired via - Reduction in B-memory cells and reduction in serum IgA and IgG [207]

Abbreviations: ATG, Anti-thymocyte globulin; CNI, calcineurin inhibitor; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharide; MMF, mycophenolate mofetil; mTOR, mechanistic target of rapamycin; Treg, T-regulatory cell; VEGF, vascular endothelial growth factor.

Table 3. Summary of Immunosuppressive Agents and Immune Function

	Innate Immune Function	Cell-mediated Immunity	Humoral Immunity
Calcineurin inhibitors	Impaired +	Impaired +++	Impaired ++
Mycophenylate	Slightly impaired +/-	Impaired +++	Impaired ++
Azathioprine	Possibly impaired +/-	Impaired +++	Impaired ++
Mechanistic target of rapamycin inhibitors	Impaired ++	Impaired +++	Impaired +
Corticosteroids	Impaired +++	Impaired +++	Impaired +++
Antithymocyte globulins	Impaired +	Impaired +++	Impaired ++
Basiliximab	Unknown	Impaired +++	Unknown
Alemtuzumab	Minimal -	Impaired +++	Impaired ++
Rituximab	Minimal	Possibly impaired +/-	Impaired +++
Eculizumab	Impaired +++	Possibly impaired +/-	Possibly impaired +/-
Interleukin-6 antagonists	Impaired ++	Possibly impaired +/-	Impaired +

of seronegative organ recipients has been associated with atypical EBV infections, including central nervous system PTLD [236]. Monitoring of quantitative EBV viral loads in seronegative recipients of seropositive organs, combined with early reduction of immunosuppression, are cornerstones of management of EBV viremia and PTLD [209, 210, 237, 238]. For PTLD, marked reductions in immunosuppression other than corticosteroids, especially with chemotherapy or anti-CD20 therapy, are well tolerated in terms of graft function; graft rejection may be observed as immune function returns with viral suppression. HBV immune control requires humoral and cell-mediated immunity; reactivation is associated with humoral dysfunction produced by rituximab [239]. HBV reactivation can generally be prevented with vaccination, prophylaxis, and antiviral agents.

Use of virus-specific immunotherapies has expanded to augment available antiviral agents and immune modulation. Passive immunization with human immunoglobulins may be of some use in prophylaxis for CMV and therapeutic monoclonal antibodies are under study [240, 241]. Adoptive T-cell therapies for 1 or more common viral pathogens have been used clinically, especially for refractory infections. The need for adjustment of immunosuppressive therapy during cellular therapies has not been demonstrated.

Opportunistic Infections

The contribution of specific agents to development of specific opportunistic infections is a good guide to modification of immunosuppression. The potential anatomic impact of immune reconstitution merits consideration [242]. Corticosteroids have greatest immediate impact on innate immunity and are permissive to invasive molds, *Pneumocystis*, and *Nocardia* spp. Corticosteroid reductions have immediate effects on inflammatory responses, but provoke immune reconstitution syndromes, notably in the central nervous system, mediastinum, and other restricted anatomic sites. Thus, in cryptococcal meningitis or pulmonary *Histoplasma* or *Pneumocystis* infections, initial reductions in CNIs may be preferred. Reductions of immunosuppression are required in invasive or refractory fungal infections [243] such as *Scedosporium* or *Mucorales* spp. with fungicidal antimicrobials. Surgical resection and treatment of coexisting CMV infection, reestablished innate immunity (initially reduced corticosteroids and mycophenolate mofetil [MMF]; subsequent CNI reductions to protect renal function) and monitoring for reconstitution effects and graft function are required [222].

Tuberculosis is common in endemic regions without empiric prophylaxis [244]. Despite the frequency of tuberculosis, few data exist to guide immunosuppressive management. Resolution of tuberculosis requires intact innate and adaptive immunity with minimization of immunosuppression and treatment of intercurrent CMV infections. Tuberculous meningitis may preclude rapid reductions in immunosuppression (notably corticosteroids) given risks of ventricular obstruction and hydrocephalus with immune reconstitution [245, 246].

Humoral and innate immune responses are required for resolution of recurrent bacterial infections. Repletion of antibody levels may be useful. The humanized anti-CD52–depleting monoclonal antibody alemtuzumab has a profound and often enduring effect on multiple limbs of the immune system including T and B lymphocytes, natural killer cells, monocytes, and dendritic cells and is most often associated with pneumocystis pneumonia and bacterial infections [247, 248]. Recurrent infections suggest contributing factors beyond immunosuppression including anatomic and circulatory defects, diabetes, anastomotic issues, or infected prosthetic materials.

Severe, Acute Life-threatening Infections

The management of acute infections such as sepsis in SOT requires innate immune reconstitution, avoiding adrenal insufficiency. For adrenal insufficiency, hydrocortisone is preferred and is less suppressive than prednisone [249]. Reduction in CNIs and antiproliferative agents may be beneficial (and reduce nephrotoxicity) acutely. In certain infections such as *Pneumocystis* or COVID-19 pneumonias *or Streptococcus pneumoniae* meningitis, adjunctive steroids may be useful [250, 251]. Acute graft rejection is uncommon with temporary

Table 4. Studies of Modulation of Immunosuppression for Infection

	Transplants With Infection (n)	Study Summary	IS Change	Infections	Rejection	Comments
Massarollo et al, 1998 [208]	Liver (18)	Retrospective single-center review: immunosuppression withdrawal for infection	Discontinuation of immunosuppression during infective episode (duration of interruption 5–102 days)	8 CMV 2 TB 3 Fungal 7 Bacterial	5/20 patients experienced rejection	
Manez et al [209]	Liver (31)	Retrospective single-center review of liver transplants: severe opportunistic infection and treated with at least 15 days of IS interruption	Discontinuation for at least 15 days	9 CMV 2 TB 8 Fungal 11 PTLD	4/31 required reinstitution of IS for rejection, CNI had been interrupted for longer in this group. 18/31 survived and had IS resumed with CNI reduction of >50%. With median follow-up of 942 days, only 2 surviving patients had chronic rejection.	13/31 died from infection, none with rejection on autopsy.
Reshef et al [210]	Heart (24) Lung (27) Kidney (59) Kidney/pancreas (9) Liver (27) Pancreas (1)	Retrospective single-center review (148 patients with PTLD): IS reduction alone vs. surgery and IS reduction or other therapy ± IS reduction	IS reduction for PTLD—not quantified	148 PTLD	32/101 managed with some form of IS reduction experienced rejection. Survival better in those with IS reduction compared with those without	
Hardinger et al [211]	Kidney (23)	Single-center review: IS reduction for BK viremia vs. no BK viremia (177)	MMF/Aza cessation for 3–4 weeks if BK viremia, then CNI minimization if no response	23 BK viremia	5/23 with acute rejection over 5 y, no different to 19/177 without viremia. Five-y graft survival and creatinine not different	
Schaub et al 2010 [212]	Kidney (38)	Prospective single-center study (203 kidney recipients): 18 months monitoring of BK viremia	Sequential reduction of tacrolimus dosing then reduction of MMF if no response	38 BK viremia	10/38 with BK viremia clearance developed rejection, 7/10 noted on surveillance biopsy only. No graft losses, allograft survival no different at 1 and 3 y when compared with those without BK viremia	
Brennan et al 2005 [213]	Kidney (23)	Prospective single center (n = 200): BK virus outcomes in cyclosporine A vs. tacrolimus	BK viremia triggered MMF/Aza cessation with subsequent tacrolimus reduction if no response at 4 weeks.	23 BK viremia 177 no infection	1/23 with rejection related to IS reduction, compared with 8/177 episodes of rejection.	
Azar et al 2017 [214]	Kidney (63)	Retrospective, single center (319 recipients): BK virus and graft loss	50%–100% mycophenolate reduction, tacrolimus trough target reduced to 5 ng/mL	27 BK viremia	2/27 developed rejection No difference in overall graft loss	
Kamar et al 2010 [215]	Kidney (17) Kidney/pancreas (2) Liver (8)	Retrospective review with chronic hepatitis E	Nonstandardized reduction in immunosuppression	27 Hepatitis E	Not reported	Immunosuppression was lower in those who spontaneously cleared the virus and clear chronic HEV infection
Kumar et al [216]	Kidney (87) Liver (47) Lung (33) Heart (45) Intestinal (5) Other combinations (20)	Retrospective multicenter review: pandemic influenza.	Immunosuppression reduced in 52 (22%)	237 H1N1 pandemic influenza	Not reported	

Table 4. Continued

	Transplants With Infection (n)	Study Summary	IS Change	Infections	Rejection	Comments
Sileri et al [217]	Kidney (40)	Observational single-center study: standardized protocol for management of severe pneumonia, including IS reduction	Reduction in CNI held for 2–3 days then adjusted to obtain trough of 75-100 ng/mL cyclosporine A and 5 for tacrolimus.	63 Severe pneumonia	No episode of rejection during episode of pneumonia	
Canet et al [218]	Kidney (74)	Retrospective multicenter: TB	Immunosuppression reduction in 22/74 not standardized or described	74 TB	No adverse consequences on graft, no comparator group. Graft survival at 1, 5, and 10 y was 97%, 85%, and 67%, respectively	
Bodro et al [219]	Kidney (10) Liver (7) Heart (1)	Retrospective outcomes of TB (Spain)	Not reported	18 TB	1 episode of rejection from low cyclosporine levels	
Hsu et al [220]	Kidney (6) Heart (7) Lung (2)	Retrospective outcomes of TB (Taiwan)	15 had immunosuppression reduced because of rifampicin, but increased doses used to supplement.	15 TB	1 episode of acute rejection with graft failure. 1 developed chronic rejection with graft failure	
Marques et al	Kidney (43)	Retrospective review (43 kidney recipients) with TB	15 (35%) had immunosuppression reduced, unspecified	43 TB	10-y death-censored graft loss no different with TB compared with 1506 recipients without TB	
El-Agroudy et al [221]	Kidney (45)	Retrospective: kidney transplants with TB (Egypt)	25 developed chronic rejection, associated with lower cyclosporine levels vs. 20 patients without rejection	45 TB		
Chen et al	Kidney (29)	Retrospective: kidney recipients (Taiwan)	3/29 acute rejection, 3/29 chronic rejection attributed to cyclosporine levels being lower	29 TB		
Almyroudis et al [222]	Kidney (73) Heart (16) Lung (4) Heart/lung (2) Liver (9) Kidney/pancreas (2)	Retrospective single center: Zygomycetes	18/84 had complete discontinuation of IS, 15/84 had >50% reduction in IS, 4/84 had <50% decrease 6/84 with Aza/MMF stopped 9/84 with unclear degree of reduction. No change in 32/84	84 with Zygomycetes infection	Rejection rates not provided	
Freifeld et al [223]	Liver (3) Kidney (5) Kidney/pancreas (1)	Retrospective single center: severe histoplasmosis	8 had immunosuppression reduction (5 MMF held and CNI reduced, 1 changed sirolimus to MMF and reduced CNI, 1 CNI reduced 1 CNI and prednisone reduced.	9 histoplasmosis	8/9 alive with good graft function. 1/9 had acute rejection. 1/9 who had no immunosuppression reduction died of disseminated histoplasmosis.	
Sun et al [224]	Kidney (63) Liver (11) Heart (7) Lung (6) Multivisceral (3)	Retrospective multicenter: rhino-orbital-cerebral Zygomycetes	25/48 had immunosuppression reduced, 16/48 had immunosuppression discontinued.	48 with rhino-orbital-cerebral zygomycosis	10/31 with data experienced rejection following infection. No increase in mortality from immunosuppression change.	

Table 4. Continued

	Transplants With Infection (n)	Study Summary	IS Change	Infections	Rejection	Comments
Lee at al [225]	Kidney (43) Kidney/pancreas (11) Liver (5) Heart (5) Others (3)	Retrospective review: chronic norovirus diarrhea	54/67 had immunosuppression change, 3 discontinued tacrolimus, 33 reduced dose tacrolimus, 30 had MMF dose reduced, 3, had MMF stopped, 7 had MMF changed (3 Aza, 2, sirolimus, 1 tacrolimus)	67 with chronic norovirus diarrhea	2/67 with graft failure at 1 month, 8 with graft failure at 1 year. 56 with functioning graft at 1 year, 18 with >20% increase in serum creatinine at 1 year. No difference in outcomes compared with 67 controls.	
van Beek et al [226]	Kidney (20) Heart (1) Lung (2)	Retrospective single-center review: chronic norovirus infections	18/23 had major changes in immunosuppression, not specified	23 chronic norovirus	Graft outcomes not reported	
Roos-Weil et al [227]	Kidney (15)	Retrospective single center: kidney recipients with chronic diarrhea	13/15 had mycophenolate dose reduction or conversion to Aza	15 with chronic norovirus diarrhea	10/15 had graft biopsies, 5 of which showed rejection	
Chou et al 2006 [228]	Heart (12)	Retrospective single-center review 1993–2004 of heart transplant recipients with severe sepsis and multiorgan failure	12 had temporary cessation of immunosuppression	12 with severe sepsis, 50% survival, 1/6 survivors with rejection		

Abbreviations: Aza, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; HEV, hepatitis E virus; IS, immunosuppression; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; TB, tuberculosis.

cessation of immunosuppression other than steroids in sepsis; survival may improve with immunosuppression withdrawal even in the early posttransplant period [228]. Resumption of immunosuppression as sepsis resolves can preempt rejection [208]. Specific modifications in immunosuppression in this setting are unstudied.

Common infections such as pneumonia, urinary tract infection, or cellulitis are generally managed without immunosuppression reductions; therapy may be prolonged in SOT. Restoration of immune function may aid clearance for pathogens lacking antimicrobial therapies (eg, multidrug-resistant organisms); optimal strategies are unclear.

Chronic Infections Without Specific Therapy

Chronic infections of SOT include norovirus and cryptosporidial and microsporidial infections, hepatitis E, BK virus, and PML. Optimal strategies for immune manipulation are unknown; reductions in immunosuppression have demonstrated some success [215, 225, 252]. For norovirus diarrhea, hypotension from volume loss may complicate renal function [227]. Given the frequency of diarrhea in mycophenolate toxicity, MMF is often reduced, switched to another formulation or to azathioprine, or discontinued [225, 227, 252]. Over time, CNI reduction and reconstitution of the microbiota may assist eradication [253]. Antiviral immunotherapy is under study. Hepatitis E and PML may respond to improvement in cellular immunity; optimal strategies are unknown.

BK polyomavirus (BKPyV) infection affects almost exclusively renal transplantation; antiviral therapy for BK virus nephropathy is ineffective. For sustained high or rising levels of plasma BKPyV-DNAemia or biopsy-proven BK nephropathy, stepwise reduction in immunosuppression is used to preempt disease progression [211–214]. Strategies for such reductions often include gradual reductions in mycophenolate and CNI (or mTOR switch) based on viral loads [254]. Unexplained rises in serum creatinine merit BKPyV studies before empiric treatment for graft rejection. Graft rejection may coexist with BK nephropathy or result from such reductions; judicious increases in immunosuppression may be attempted and lymphocyte depletion used if essential.

A recent challenge is management of acute COVID-19 infection resulting from severe acute respiratory syndrome coronavirus 2 in SOT. Features of this infection include lymphopenia, cytokine-driven inflammatory syndromes, and severe lung injury with multiorgan dysfunction. It remains unknown whether transplant immunosuppression is protective or is detrimental—and how to adjust immune suppression to augment viral clearance. Most published experience has modestly reduced immunosuppression. Use of additional anti-inflammatory agents such as dexamethasone in the immunosuppressed SOT population may risk hospital-acquired and ventilator-associated infections including those due to Aspergillus species [255–259].

CONCLUSION

The lack of quantitative measures of immune function relative to both allograft function and infectious risk poses a challenge for transplant clinicians. Conceptual measures of individual infectious risks cannot account for genetic predispositions to infection or the immune effects of immunosuppressive agents or infection. A useful approach includes understanding the effects of immunosuppressive agents in titrating drugs when confronted with infection in SOT. Modification of immunosuppression is most useful in augmenting T-cell functions during viral infections or of innate immune function in bacterial or fungal infections. In the absence of effective antimicrobial therapies, all limbs of the immune system may require reconstitution, risking graft rejection or acute inflammatory responses. Incorporation of immunotherapy in such cases may be beneficial. Studies are needed of management of immunosuppression with infection in transplant recipients.

Notes

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