Opportunistic Infection-Associated Immune Reconstitution Syndrome in Transplant Recipients

Hsin-Yun Sun1,3 and Nina Singh1,2

1Infectious Diseases Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; and 2University of Pittsburgh, Pittsburgh, Pennsylvania; and 3Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

Reversal of pathogen-induced immunosuppression upon employment of effective antimicrobial therapy and withdrawal of iatrogenic immunosuppression has the potential to shift the host immune repertoire towards pathologic inflammatory responses conducive to immune reconstitution syndrome (IRS). Posttransplant IRS has been observed with fungi, M. tuberculosis, cytomegalovirus, and polyoma virus nephropathy. This review discusses the existing state of knowledge regarding IRS and the immune mechanisms that underlie its pathogenesis, with significant implications for developing reliable diagnostic biomarkers and optimal management strategies for post-transplant opportunistic infection-associated IRS.

Outcomes in infectious diseases have long been regarded as damage inflicted by the pathogen. However, immunologic sequelae of host-pathogen interaction are now considered to play a key role in disease expression [1]. Although inflammation is a beneficial host response, restoration of immunity during treatment of infections, particularly if restoration is abrupt and rapid, has the potential to promote excessive inflammatory pathology and tissue damage. The ensuing clinical entity, termed immune reconstitution syndrome (IRS), poses previously unappreciated challenges in the management of opportunistic infections in transplant recipients. Although our knowledge base of IRS is still sparse, significant strides have been made in elucidating its biologic basis and associated risk factors, which has implications for optimal management of this syndrome. The present review aims to summarize the current understanding of the scope of the problem and the clinical characteristics of post-transplant IRS, its pathophysiologic basis, potential biomarkers, and management strategies.

PROPOSED PATHOGENESIS OF IRS

Upon activation by pathogens-induced specific cytokines, naive CD4+ cells (Th0) differentiate into subsets with distinct functions. Traditionally, Th1 and Th2 cells have been recognized as the main Th0 subsets [2]. Th1 primarily produce interferon IFN-γ, activate macrophages, promote natural killer (NK) cell-induced cytoxicity, and elicit proinflammatory responses [3]. Th2 cells secrete mainly interleukin (IL)-4 and IL-10, leading to anti-inflammatory and immunosuppressive responses [4, 5]. This paradigm has been updated by 2 additional divergent lineages of Th: Th17 and regulatory T cells (Tregs) [5–9]. Th17 cells, characterized by the production of IL-17 and IL-22, promote potent proinflammatory responses and induce chemokines and metalloproteinases for recruitment of neutrophils for pathogen eradication [10]. Tregs, on the other hand, play a critical role in limiting inflammation and subsequent tissue damage caused by vigorous immune response [11].
Several lines of evidence suggest that IRS represents an exaggerated pathogen-driven effector response or the failure of regulatory responses to restrain effector responses [12–15]. That IRS is an antigenic-driven Th1 cell response was suggested by the fact that *Mycobacterium avium*-infected, T cell–deficient mice succumbed to IRS within 12 days after inoculation with CD4+ T cells [16]. Furthermore, IFN-γ-/- T cells induced less disease than did wild-type T cells, and neutralization of tumor necrosis factor TNF-α delayed the onset of the illness [16]. These data suggest that rapid replenishment of the T cell population in the setting of profound immunodeficiency triggered IRS. Defects in the number or function of Tregs have also been proposed to characterize IRS in human immunodeficiency virus (HIV)–infected individuals [17, 18]. The ability of Tregs to induce suppression was compromised, despite their expansion during mycobacterial IRS [19]. On the other hand, no decrease in Tregs was documented in cytomegalovirus (CMV) immune recovery uveitis [20]. Specific mechanistic studies are lacking in transplant recipients; however, the conceptual principles of immune dysregulation in other hosts have implications that are relevant for post-transplant IRS.

Growing evidence suggest that immunomodulatory characteristics of antimicrobial agents (eg, antifungal drugs) may contribute to microbial pathogenesis [21]. Amphotericin B deoxycholate upregulates Th1 cells by Toll-like receptor (TLR) 2–mediated transcription of inflammatory cytokines [22]. On the other hand, the lipid formulations of the polyenes either downregulate or have no effect on inflammatory cytokine expression [23]. Echinocandins unmask β-glucan and have the ability to illicit inflammatory cytokine release from macrophages [24]. Voriconazole enhanced phagocytic proinflammatory activity by upregulation of TLR2 mediated by nuclear factor-κB [25, 26]. Although intriguing, the clinical relevance of antifungal agent-associated immune modulation in the context of IRS remains to be fully defined.

Although the prevailing wisdom is that IRS is a cell-mediated phenomenon, antibody immunity could also contribute to inflammatory imbalance. A phenomenon similar to prozone-like effect, in which excessive antibody enhances disease expression, has been described [27]. Finally, in addition to adaptive immunity, signaling pathways that modulate innate inflammatory responses may also underlie IRS [28].

### Unifying Scenario for the Development of IRS in Transplant Recipients

Th1 and Th17 cells are also the primary mediators of allograft rejection and targets of immunosuppressive agents in transplant recipients, whereas Tregs and Th2 cells promote graft tolerance [5, 29–31]. Calcineurin inhibitors preferentially suppress Th1 cells and promote Th2 cells, and tacrolimus inhibits Th1 cells to a greater extent than does cyclosporine A [32–34]. Additionally, calcineurin inhibitors inhibit Th17 cell generation and Treg function [35]. Rapamycin, on the other hand, promotes Tregs and suppresses Th17 cells [36, 37] (Table 1). Corticosteroids inhibit Th1 cells and marginally expand Th2 cells and Tregs [38, 39]. The cumulative effect of an immunosuppressive regimen in stable transplant recipients reflects induction of tolerance by suppression of Th1 and Th17 cells and upregulation of Th2 cells, with or without Tregs expansion [43]. The basis of post-transplant IRS is believed to be the reversal of anti-inflammatory to proinflammatory responses as a result of withdrawal of iatrogenic immunosuppressive agents and the employment of antimicrobial therapy, which reverses pathogen-induced immunosuppression [44] (Figure 1).

### SPECIFIC PATHOGEN-ASSOCIATED IRS

#### Fungi

**Cryptococcosis**

Cryptococcosis is the most frequently described infection associated with IRS in solid-organ transplant (SOT) recipients [45–50]. Certain characteristics of this yeast, such as its ability to elicit mitogenic responses that are highly inflammatory, may partly account for the high rate of IRS observed with cryptococcosis [51]. Preferential inhibition of Th1 cells with the induction of Th2 cells that compromises host resistance is another unique attribute of *Candida* [52–54]. Reversal of Th2 cells with appropriate antifungal therapy and concurrent reduction of immunosuppression is proposed to be the basis of IRS after cryptococcosis [55].

An estimated 5%–11% of the SOT recipients with cryptococcal disease may develop IRS, typically 4–6 weeks after initiation of antifungal therapy [50], although onset as late as 9 months has been reported [45, 46, 50]. IRS was more prevalent among patients who received potent immunosuppressive treatment comprising tacrolimus, mycophenolate mofetil (MMF), and prednisone and among those with disseminated disease [49, 50]. IRS may present as lymphadenitis, cellulitis, aseptic meningitis, cerebral mass lesions, spinal arachnoiditis, hydrocephalus or pulmonary nodules [50]. Nonviable yeast forms may be visualized histopathologically [47], and antigen

<table>
<thead>
<tr>
<th>Table 1. Effect of Iatrogenic Immunosuppressive Agents in Transplant Recipients on T-helper Cell Phenotype</th>
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<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>CALCINEURIN INHIBITORS</td>
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<tr>
<td>MYCOPHENOLATE MOFETIL</td>
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<tr>
<td>INHIBITORS OF mTOR</td>
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<tr>
<td>corticosteroids</td>
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<tr>
<td>CD-52 antibody</td>
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</table>

*NOTE: Data adapted from [32–42]. mTOR, mammalian target of rapamycin; Tregs, T regulatory cells.*

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titers either decreased or remained unchanged [45, 47]. Neuroimaging findings of IRS include new parenchymal lesions with brain edema, leptomeningeal enhancement, and hydrocephalus [45, 46, 56] (Table 2). Cryptococcus-associated IRS appears to preferentially manifest with central nervous system (CNS) disease; CNS involvement and neuroimaging abnormalities were more common at the time of diagnosis of IRS than at initial presentation [61].

Of 8 patients with detailed descriptions about immunosuppressant changes and management of IRS, immunosuppressants were reduced in all patients after the diagnosis of cryptococcosis [45–49]. Symptoms of IRS improved after employment of corticosteroids in 3 patients, resolved with supportive care in 4 patients, and required surgery in 1 patient. Among renal transplant recipients with cryptococcosis, the allograft was lost to rejection in 66% of those with IRS and in 5.9% of those without IRS ($P = .012$) [62]. In SOT recipients with cryptococcosis, 90-day mortality was 9% in patients with IRS and 16% in those without IRS [50].

**Aspergillosis**

Aspergillosis-associated IRS has only been reported in the setting of neutropenia and hematopoietic stem cell transplantation (HSCT) [63, 64]. In 19 neutropenic patients with invasive pulmonary aspergillosis, including 7 HSCT recipients (4 with autologous and 3 with allogeneic transplants), the mean time to clinical and radiologic findings of IRS after an absolute neutrophil count >100 cells/µL and >500 cells/µL was 3.5 days and 2 days, respectively [64]. Clinical presentations consisted of worsening or new onset of hypoxia, cough, chest pain, dyspnea, and hemoptysis [64]. Radiologic findings included increasing and/or new pulmonary infiltrates, pleural effusion, nodular lesions, intrathoracic lymphadenopathy and cavitation [64]. Decreasing titers of sequential serum galactomannan were observed in all patients. Three patients died, and autopsies failed to identify invasive aspergillosis as the cause of death. The remaining 16 patients improved; however, 2 required treatment with methylprednisone for impending respiratory failure [64].

**Other Fungi**

Other types of mycoses-related IRS in transplant recipients include histoplasmosis [59], candidiasis [57], and spondylodiscitis caused by *Dipodascus capitatus* [58]. A renal transplant recipient received 60 mg of prednisone daily for suspicion of thrombocytopenic thrombotic purpura that was rapidly tapered to 5 mg daily upon diagnosis of disseminated histoplasmosis [59].
Table 2. Published Reports of Transplant Recipients With Infection-Associated Immune Reconstitution Syndrome (IRS)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Type of transplant (no. of patients)</th>
<th>Time to onset of IRS</th>
<th>Manifestations of IRS</th>
<th>Imaging at IRS</th>
<th>Status of original infection at diagnosis of IRS</th>
<th>Management for IRS (no. of patients)</th>
<th>Graft loss (no. of patients)</th>
<th>Death (no. of patients)</th>
<th>Ref</th>
</tr>
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<tbody>
<tr>
<td><strong>Fungi</strong></td>
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<tr>
<td>Cryptococcus</td>
<td>Renal (7), liver (1)</td>
<td>4–6 wk after antifungal agents</td>
<td>Lymphadenitis, cellulitis, aseptic meningitis, cerebral mass lesions, spinal arachnoiditis, hydrocephalus, or pulmonary nodules</td>
<td>Newly emerged enhanced nodules with brain edema, leptomeningeal enhancement, and hydrocephalus</td>
<td>Negative in CSF, decreasing CSF and serum Crypto Ag levels</td>
<td>Steroid (3), none (4), amputation (1)</td>
<td>Yes (2), No (1), NA (5)</td>
<td>25% (2/8) [45–49]</td>
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<tr>
<td>Aspergillosis</td>
<td>HSCT (8)</td>
<td>3.5 and 2 d after an ANC 100 and 500/L, respective</td>
<td>Worsening or new onset of hypoxia, cough, chest pain, dyspnea, and hemoptysis</td>
<td>Increasing and/or new pulmonary infiltrates, pleural effusion, nodular lesions, lymphadenopathy, and cavitation</td>
<td>Decreasing serum galactomannan titers</td>
<td>Steroid (1) or none (7)</td>
<td>NA</td>
<td>12.5% (1/8) [63, 64]</td>
<td></td>
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<tr>
<td>Candidiasis</td>
<td>Renal (1)</td>
<td>3–4 wk after antifungal agents</td>
<td>Comatose, requiring mechanical ventilation</td>
<td>Fluctuation in the size and location of the brain lesions, new laminar necrosis</td>
<td>NA</td>
<td>Steroid (1)</td>
<td>NA (1)</td>
<td>No (1)</td>
<td>[57]</td>
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<tr>
<td>D. capitatus</td>
<td>HSCT (1)</td>
<td>3 mo after voriconazole</td>
<td>Back pain and bilateral L5 radiculitis</td>
<td>New lesions on L4–5 and L2–3 with epididymitis</td>
<td>Negative in bone biopsy</td>
<td>None</td>
<td>NA</td>
<td>No (1)</td>
<td>[58]</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Renal (1)</td>
<td>24 d after antifungal therapy</td>
<td>Hemoptysis and dyspnea</td>
<td>Worsening pulmonary infiltrates, opacities and nodules</td>
<td>Negative in lung biopsy</td>
<td>None</td>
<td>Yes (1)</td>
<td>No (1)</td>
<td>[59]</td>
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<tr>
<td><strong>Bacteria</strong></td>
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<tr>
<td>Tuberculosis</td>
<td>Renal (1), heart-lung (1)</td>
<td>30 and 131 d after anti-TB agents</td>
<td>Fever recurrence</td>
<td>Worsening pulmonary infiltrates</td>
<td>Negative</td>
<td>None (1), steroid (1)</td>
<td>No (2)</td>
<td>No (2)</td>
<td>[72, 73]</td>
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<tr>
<td><strong>Viruses</strong></td>
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<tr>
<td>CMV</td>
<td>Liver (1), heart (1), renal (1), HSCT (2)</td>
<td>11 wk after antiviral agents</td>
<td>Chorioretinitis-vitritis, posterior uveitis however, vitritis, episcleritis and macular edema</td>
<td>NA</td>
<td>Clearance of CMV viremia</td>
<td>Vitrectomy</td>
<td>No (1)</td>
<td>No (1)</td>
<td>[74, 77, 100]</td>
</tr>
<tr>
<td>BK virus</td>
<td>Renal (1)</td>
<td>3 mo after the diagnosis of PVAN</td>
<td>Worsening serum creatinine</td>
<td>NA</td>
<td>Decreasing BK viremia and less virus-infected cells</td>
<td>None</td>
<td>No (1)</td>
<td>No (1)</td>
<td>[60]</td>
</tr>
</tbody>
</table>

**NOTE.** ANC, absolute neutrophil count; anti-TB, antituberculous; Crypto Ag, cryptococcal antigen; CMV, cytomegalovirus; CSF, cerebrospinal fluid; HSCT, hematopoietic stem cell transplantation; NA, not available; PVAN, polyoma virus associated nephropathy; Ref, reference.
Bacteria

**Tuberculosis**  Antigen-specific IFN-γ–producing T cells and Th1 cells are responsible for resistance, whereas Th2 cells inhibit the immune responses to *Mycobacterium tuberculosis* [65–68]. Like *Cryptococcus*, *M. tuberculosis* has the ability to modulate immune response by inducing Th2 cells and naturally occurring Tregs [65–68]. Antituberculous therapy can reverse Th2 cell–mediated immunosuppression and may lead to potentially life-threatening inflammatory reactions [69–71]. Tuberculosis-associated IRS has been reported in 2 organ transplant recipients [72, 73]. The first case was in a woman who received a renal transplant with pleural tuberculosis who developed new persistent high fever with worsening chest radiograph findings 1 month after antituberculous therapy [72], and the second case was in a woman who underwent heart-lung transplantation with pulmonary tuberculosis who had recurrent fever and worsening pulmonary infiltrates on day 131 after initiation of therapy [73]. The fever and pulmonary lesions improved spontaneously without change in infiltrates on day 131 after initiation of therapy [73]. Another allogeneic HSCT recipient with *D. capitatus* spondylodiscitis developed new vertebral lesions with epidural inflammation that was deemed to be consistent with IRS, because the patient’s immunosuppression was decreased, results of culture and panfungal polymerase chain reaction were unrevealing, and histological analysis showed nonspecific osteitis with inflammatory cells [58].

**Histoplasmosis**-related IRS developed ~24 days after antifungal therapy was initiated, and it presented with hemoptysis, respiratory distress, worsening pulmonary infiltrates, and nodules visible on imaging studies. Histopathological analysis of the lung tissue demonstrated granulomatous pneumonitis containing numerous yeast forms consistent with *Histoplasma capsulatum*, whereas culture results were negative. An allogeneic HSCT recipient developed *Candida parapsilosis*–related CNS IRS that improved dramatically after treatment with dexamethasone [57]. Another allogeneic HSCT recipient with *D. capitatus* spondylodiscitis developed new vertebral lesions with epidural inflammation that was deemed to be consistent with IRS, because the patient’s immunosuppression was decreased, results of culture and panfungal polymerase chain reaction were unrevealing, and histological analysis showed nonspecific osteitis with inflammatory cells [58].

**Polymavirus**  A renal transplant recipient with polyoma virus–associated nephropathy developed worsening renal function upon aggressive reduction of immunosuppression, with allograft biopsy findings that showed dense focal to massive diffuse lymphohistiocytic infiltrates; this patient also experienced the emergence of BK virus–specific immunoglobulin (Ig) G and IgM antibodies and T cells, which was presumptively considered to be due to BK virus–related IRS [60].

**DIAGNOSTIC MARKERS**

Because of the lack of reliable means to diagnose IRS, efforts remain ongoing to search for useful biomarkers that can serve as indicators of worsening disease versus of IRS. Compared with HIV-positive patients with cryptococcal meningitis who did not develop IRS, those with IRS after ART initiation had significantly less inflammation in their cerebrospinal fluid (CSF) at the diagnosis of cryptococcal meningitis, and they presented with lower white blood cell (WBC) counts, lower protein levels, and lower levels of proinflammatory cytokines, such as IL-6, IL-8, IFN-γ, and TNF-α [79]. The combination of initial CSF WBC count ≤25 cells/μL and CSF protein levels ≤50 mg/dL was associated with development of IRS (odds ratio [OR], 7.2; 95% CI, 2.7–18.7) with a diagnostic sensitivity of 69% and a specificity of 76% [79]. D-dimer and C-reactive protein (CRP) levels, although they were nonspecific, were higher at baseline and during IRS. In a cohort of HIV-positive, ART-naïve patients who began ART, pre-ART D-dimer and CRP levels were significantly elevated in those with IRS, compared with levels in control subjects without IRS [80]. Furthermore, compared with control subjects who did not have IRS, patients with IRS had higher plasma D-dimer concentrations at 1 month after ART
initiation, which approximated the onset of IRS [80]. It should be noted that specific studies assessing the diagnostic usefulness of the aforementioned tests in the transplant setting are lacking.

Hypercalcemia can be a helpful clue indicating the presence of IRS. Initiation of granuloma formation relies on Th1 cells (eg, IFN-γ and 1-hydroxylase of activated macrophages increases the synthesis of 1,25 (OH)2D3, which results in hypercalcemia [81–83]. Polymorphisms in cytokine genes may play a role in host susceptibility to IRS [80, 84]. Compared with HIV-positive patients without IRS, patients with herpesvirus infection–associated IRS were more likely to harbor TNFA-308*2 (52% vs 24%; P < .05), which is associated with lower TNF production in monocytes, and were homozygous for IL-12B-3’UTR*1 (92% vs 58%; P < .05), which encodes IL-12p40, a component of the Th1 cytokine, IL-12 [84]. Likewise, patients with CMV retinitis or encephalitis-associated IRS had similar findings [84]. Another study demonstrated that individuals who develop IRS have an underrepresentation of the HLA-A02 allele and an overrepresentation of HLA-A03 and HLA-A29 alleles [80].

MANAGEMENT

The optimal management of IRS in immunocompromised individuals without HIV infection remains unknown. Reported treatment modalities in these populations include corticosteroids, intravenous Ig, nonsteroidal anti-inflammatory drugs, and surgical excision (eg, vitrectomy for IRU) [46, 47, 64, 73, 74, 85–87]. Based on case reports and series, corticosteroids have been used as the therapeutic agent for IRS [88, 89]. In a randomized trial of tuberculosis-related IRS in HIV-infected patients, prednisone (1.5 mg/kg/d for 2 wk followed by 0.75 mg/kg/d for 2 wk) significantly reduced the duration of hospitalization and led to more-rapid improvement in symptoms and markers of inflammation [90]. However, given the potential for adverse sequelae and nonspecific immunosuppressive effects, routine use of corticosteroids for IRS remains a concern. Furthermore, there is a mechanistic basis by which corticosteroids may, in fact, worsen inflammation rather than suppress it [91]. Studies in murine models have shown that corticosteroids lead to over expression of inflammatory cytokines in response to lipopolysaccharide by altering signaling pathways that regulate these responses and that this effect was independent of lineage-committed cells [91]. The permissive effects of corticosteroids in enhancing immune responsiveness are potentially troubling in the setting of IRS, and there remains a need for optimizing pharmacologic therapies for IRS.

Although known primarily for their cholesterol lowering effects, statins have immunomodulatory and anti-inflammatory attributes. They promote the development of Th2 cells and Tregs, inhibit Th1 cells, and block Th17 cell development [92]. Additionally, statins intervene with the functions of antigen-presenting cells and disturb the interaction between lymphocytes and endothelia [92]. A beneficial effect of these drugs has been shown for other inflammatory disorders. For example, in experimental autoimmune arthritis and myocarditis, statins inhibited proinflammatory cytokines and promoted a shift from Th1 to Th2 cells [93]. In patients undergoing T cell–replete allogeneic HSCT, a lower rate of grade II–IV graft-versus-host disease was observed in statin recipients than in those not receiving statins [94]. Paradoxically, the capacity to mount protective immune responses to pathogens and cognate antigens is not diminished with statins [95]. Indeed, statins have demonstrated a beneficial effect for the treatment and prevention of infections and have led to a lower incidence of and have halted the progression of certain cancers [95, 96]. Thus, it is plausible that, in patients who are at risk for IRS once the infection is microbiologically controlled, statins may mitigate unfettered inflammation. Future studies are warranted to investigate the effects of statins alone or in combination with other agents for IRS.

Given a role of TNF-α in recruiting inflammatory cells and in granuloma formation, TNF-α inhibitors have been anecdotally used for treatment of IRS. Infliximab was successfully employed for IRS refractory to high-dose corticosteroid therapy and to cyclophosphamide in CNS tuberculosis [97]. Anti-inflammatory effects of this agent ameliorated acute rejection after intestinal transplantation [98]. Finally, an important consideration in the treatment of opportunistic infection is the management of immunosuppression. Because rapid reduction or withdrawal of immunosuppressive agents might predispose SOT recipients to IRS, it is prudent to space or separate initiation of treatment with antimicrobial agents and reduction in immunosuppression to reduce the risk of IRS and of allograft loss. The aim should be gradual tapering, as opposed to abrupt cessation, with consideration first given to reduction of corticosteroids. Existing literature suggests that calcineurin agents have antifungal activity and offer synergistic interactions with antifungal agents [99]. Furthermore, abrupt cessation of calcineurin agents has been associated not only with the risk of IRS but also with the risk of allograft rejection [62].

SUMMARY AND FUTURE DIRECTIONS

Existing evidence suggests that IRS is an imbalance between protective immunity and inflammatory pathology that is likely mediated by anti-inflammatory responses (Tregs and Th2 cells) and proinflammatory responses (Th17 and Th1 cells). Given the lack of reliable diagnostic tools, the prevalence of IRS in the transplant population is likely to be underestimated. IRS has been reported in post-transplant cryptococcosis (in 5%–11% of cases), aspergillosis, candidiasis, histoplasmosis, tuberculosis, and polyoma virus nephropathy.
Post-transplant IRS remains a poorly studied entity, and our knowledge of its biological basis is rudimentary at best. Because of its rarity, research focusing on IRS in transplant recipients will require a concerted and collaborative multicenter effort to advance the field. Specific studies on predictive and diagnostic biomarkers in the transplant setting warrant assessment. Foremost among these needs is the determination of the precise nature of the inflammatory milieu and of markers that may be diagnostically useful for IRS and useful in recognizing that a state of beneficial immune reconstitution has been achieved during evolution of opportunistic infection. To be clinically useful, these biomarkers should ideally be amenable to testing in real-time. Optimal management of iatrogenic immunosuppression and approaches that exploit antifungal agent–associated immunomodulation warrant assessment. Finally, candidate agents that may be beneficial for the treatment of IRS, such as statins, anti-TNF antibodies, and immune-based approaches that target regulatory pathways for IRS warrant future investigations.

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