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Editorial

Urgent need to address infectious diseases due to immunosuppressive therapies

Daniel B. Chastain and Kayla R. Stover

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Correspondence to:
Daniel B. Chastain
Clinical Associate Professor, University of Georgia College of Pharmacy, 1000 Jefferson Street, Albany, GA 31701, USA.
daniel.chastain@uga.edu

Kayla R. Stover
Department of Pharmacy Practice, University of Mississippi School of Pharmacy, Jackson, MS, USA

Immunosuppression due to deficiencies in one or more components of host defense (physical barriers, innate immunity, or adaptive immunity) is a major risk factor for a number of infectious diseases.[1] In the context of infectious diseases clinical practice, we often associate immunosuppression with disease effects, including HIV, asplenia, cancer, uncontrolled diabetes, and so on. But outside of disease-induced immunosuppression, a large proportion of the population experiences immunosuppression induced by therapeutic drug exposures. Although there are many medical causes of immunosuppression, the use of conventional, biological, and targeted immunosuppressive therapies for a growing number of indications has led to an increase in the number of patients at risk of infectious diseases.[1,2] However, the prevalence, as well as evidence guiding the management, of these infections remains limited.

Some of the most common offenders of therapeutic immunosuppression include systemic glucocorticoids, antimetabolites, calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, and biologic agents such as tumor necrosis factor (TNF) alpha antagonists, interleukins, and immunoglobulins (Table 1).[2–8]

With chemotherapy, antimetabolites, alkylating agents, and related agents, therapeutic immunosuppression occurs as a byproduct of the mechanism of the drugs.[4,9] The administration of these agents results in cytotoxic effects to rapidly dividing bone marrow cells, leading to disruptions in DNA synthesis and cell reproduction. Glucocorticoids affect immune cell survival and activity, specifically depleting CD4+ T cells while concomitantly inhibiting the production of all inflammatory cytokines.[3] Biologic agents directly target components of the immune pathway (TNF alpha, interleukins, etc.), leading to immunologic dysfunction and, in many cases, resultant increased risk of infection.[5–8]

Administration of these agents is in and of itself a risk for immunosuppression, although there are populations who are at higher risk of these immunosuppressive effects.[10] The degree of immunosuppression depends on a multitude of factors: the underlying disease process being treated, host functional status, and immunosuppressive medication(s), all of which contribute to the development of infections in this population. Chronic comorbidities influence the baseline immune response, which is then further impacted by immunosuppressive medications. When evaluating patients who fit this category, clinicians should do a full work-up, including a thorough medical history, social history, and medication history of current and prior treatments, including drug, dose, route, frequency, indication, duration of therapy, and therapeutic monitoring, if applicable.

Although treatment of specific infections in patients with therapeutic immunosuppression does not differ from disease-induced immunosuppression in most cases, it is important for clinicians to consider the effects of the immunosuppressive therapy on the host immune response. Often, in addition to treating the infection, the intensity of immunosuppression must be reduced or lowered, at least during the acute treatment phase. Alternatively, resolution of opportunistic

Table 1. Effect of select immunosuppressive therapies on the host immune system.[2–8]

Medication class	Innate immune system	Adaptive immune system		Effects[a]
		Cell-mediated immunity	Humoral immunity	
Systemic glucocorticoids	Impaired	Impaired	Impaired	Increased risk of common bacterial, viral, and fungal infections, including opportunistic infections (tuberculosis, *Pneumocystis jirovecii*, *Strongyloides* hyperinfection syndrome)
Antimetabolites (e.g. methotrexate)	Impaired	Impaired	Possibly impaired	Increased risk of common infections, including some reports of opportunistic infections (tuberculosis, *P. jirovecii*)
Calcineurin inhibitors (e.g. tacrolimus)	Impaired	Impaired	Impaired	Increased risk of tuberculosis and common viral infections (HZ and HBV)
mTOR inhibitors (e.g. sirolimus, everolimus)	Impaired	Impaired	Impaired	Increased risk of tuberculosis and common viral infections (HZ and HBV)
TNF alpha antagonists (e.g. adalimumab, infliximab, etanercept, etc.)	Not impaired	Impaired	Impaired	Increased risk of tuberculosis, common bacterial infections, viral infections (HZ and HBV), and invasive fungal infections (cryptococcosis, histoplasmosis, coccidioidomycosis, *P. jirovecii*)
IL-6 pathway inhibitors (e.g. tocilizumab, sarilumab, siltuximab)	Impaired	Minimally impaired	Impaired	Increased risk of common bacterial (*Staphylococcus aureus*, *Escherichia coli*) and viral infections Minimally higher risk of opportunistic infections
Complement pathway inhibitors (e.g. eculizumab)	Impaired	Minimally impaired	Impaired	Increased risk of infections caused by *Neisseria* species, but minimal to no increased risk of other infections
BTK inhibitors (e.g. ibrutinib)	Not impaired	Impaired	Impaired	Increased risk of opportunistic infections (aspergillosis, cryptococcosis, histoplasmosis, coccidioidomycosis, *P. jirovecii*)
Anti-CD20 agents (e.g. rituximab)	Minimally impaired	Impaired	Impaired	Increased risk of common bacterial and viral infections (HZ and HBV) and opportunistic infections (*P. jirovecii*)
Anti-CD52 agents (e.g. alemtuzumab)	Minimally impaired	Impaired	Impaired	Increased risk of common bacterial infections and opportunistic infections (tuberculosis, *P. jirovecii*)

BTK, Bruton tyrosine kinase; HBV, hepatitis B virus; HZ, herpes zoster; IL, interleukin; mTOR, mammalian target of rapamycin; TNF, tumor necrosis factor.
[a]The anticipated effects and risk of infection associated with immunosuppressive medications may be compounded by the underlying disease process being treated, host functional status, and concomitant immunosuppressive medication(s).

infections (e.g. tuberculosis, invasive fungal infections) is frequently dependent on immunologic response. During treatment, it is also crucial to monitor for relevant adverse effects that develop as a result of infections or adjustments to therapeutic immunosuppression, including organ rejection, disease flares or reactivations, worse control of other medical problems (diabetes, Crohn's disease, ulcerative colitis, etc.), or immune reconstitution syndrome.

Predictive tools are needed to evaluate the overall risk of infection in patients requiring treatment with immunosuppressive therapies. Therapeutic drug monitoring for immunosuppressive therapies and assays to estimate the functionality of the host immune response to determine the 'net state of immunosuppression' may lead to improvements in prevention and management of infections associated with drug-induced immunosuppression. Due to limited descriptions in randomized clinical trials, post-marketing data and observational studies are critical to provide a greater understanding of these infectious complications associated with conventional, biological, and targeted immunosuppressive therapies in this patient population.[9]

In this Special Collection of *Therapeutic Advances in Infectious Disease*, considerations for treatment and evaluation of infectious diseases due to therapeutic

immunosuppression will be presented. The aim of this Special Collection is to bring together high-quality, innovative, and cutting-edge articles related to infectious diseases due to therapeutic immunosuppression.

Declarations

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Not applicable.

Consent for publication
Not applicable.

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Daniel B. Chastain: Conceptualization; Writing – original draft; Writing – review & editing.

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ORCID iDs
Daniel B. Chastain https://orcid.org/0000-0002-4018-0195

Kayla R. Stover https://orcid.org/0000-0002-8635-0137

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