Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

Unintended Consequences: Risk of Opportunistic Infections Associated With Long-term Glucocorticoid Therapies in Adults

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Glucocorticoids are widespread anti-inflammatory medications used in medical practice. The immunosuppressive effects of systemic glucocorticoids and increased susceptibility to infections are widely appreciated. However, the dose-dependent model frequently used may not accurately predict the risk of infection in all patients treated with long-term glucocorticoids. In this review, we examine the risks of opportunistic infections (OIs) in patients requiring glucocorticoid therapy by evaluating the influence of the glucocorticoid dose, duration, and potency, combined with biological and host clinical factors and concomitant immunosuppressive therapy. We propose strategies to prevent OIs, which involve screening, antimicrobial prophylaxis, and immunizations. While this review focuses on patients with autoimmune, inflammatory, or neoplastic diseases, the potential risks and preventative strategies are likely applicable to other populations. Clinicians should actively assess the benefit–harm ratios of systemic glucocorticoids and implement preventive efforts to decrease their associated infections complications.

Keywords. glucocorticoids; opportunistic infections; immune system diseases; infections; *Pneumocystis carinii*.

PRESENTATION OF A BRIEF CASE

A man in his early 70's with a 6-month history of peripheral ulcerative keratitis treated with adalimumab, methotrexate, and a 10-week prednisone taper starting at 80 mg once daily was hospitalized with acute hypoxic respiratory failure due to Pneumocystis jirovecii *pneumonia (PJP) and successfully treated with 21 days of trimethoprim/sulfamethoxazole (TMP/SMX).*

WHAT IS THE PURPOSE OF THIS CLINICAL REVIEW?

What factor(s) predisposed this patient to develop Pneumocystis jirovecii pneumonia?

Glucocorticoids provide potent anti-inflammatory effects to manage numerous inflammatory and immune-mediated diseases. The prevalence of systemic glucocorticoid use ranges from 0.5% to 17%, highest among older people, depending on the study location, time frame, and population [1, 2]. Despite their established efficacy, glucocorticoids pose significant risks, including osteoporosis, adrenal suppression, hyperglycemia, and various immunologic effects [3].

The immunosuppressive effects of glucocorticoids and increased susceptibility to infections are widely appreciated. While this association is frequently linked to the dose, duration, and intensity, the dose-dependent model often used may not accurately predict the risk of infection in all patients treated with long-term glucocorticoids. This review examines the quantitative and qualitative immunosuppressive effects of long-term glucocorticoids and other factors to elucidate the individualized risk of opportunistic infections (OIs). Additionally, recommendations are provided to prevent acute infections or reactivation of OIs in patients requiring long-term glucocorticoids.

WHAT ARE THE IMMUNOLOGIC EFFECTS OF GLUCOCORTICOIDS?

The immunologic effects of glucocorticoids, thought to be due to genomic regulation, are manifold, affecting immune cell survival, activity, and inflammatory cytokines (Table 1). Glucocorticoids bind to the glucocorticoid receptor and exert genomic effects by (1) direct binding to glucocorticoid response elements (GREs) to enhance gene expression or inhibit gene transcription, (2) interacting with transcription factors without binding to DNA (protein–protein interactions known as "tethering"), and (3) composite GRE binding to DNA sequences containing both GREs and a response element for a transcription factor [4].

Received 22 February 2023; editorial decision 05 July 2023; published online 4 September 2023

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Clinical Infectious Diseases® 2024;78(4):e37–e56

https://doi.org/10.1093/cid/ciad474

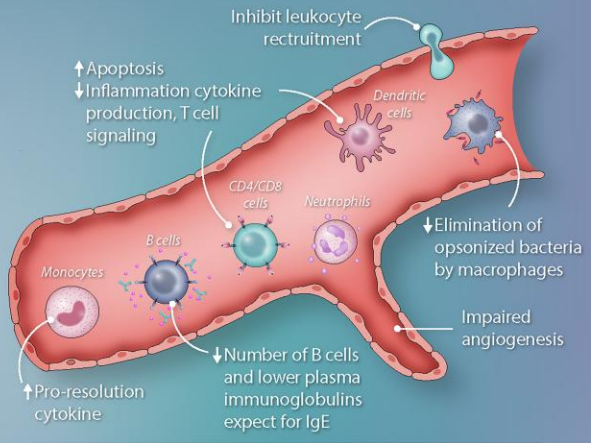
Navigating the risks of opportunistic infections in adults on long-term glucocorticoids

1 Understand the risks

- Long-term use of glucocorticoids increases the risk of opportunistic infections (OIs)
- Biological and host clinical factors and concomitant immunosuppressive therapy also contribute to the increased risk of OIs

2 Assess the risks of OIs

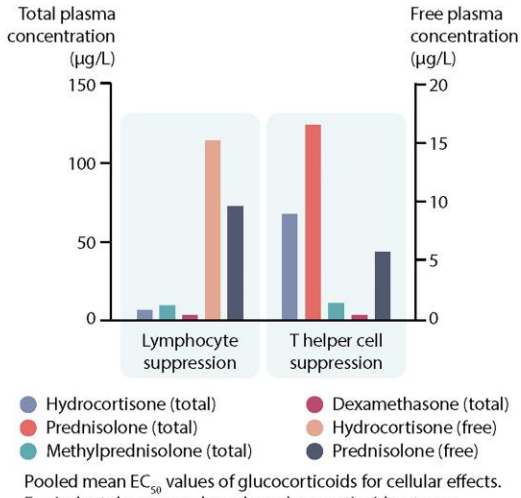
- Glucocorticoids suppress the immune response by impairing phagocytosis and opsonization, decreasing T cell proliferation and activity, and diminishing eosinophil activity
- Lymphodepletive effects are most profound on CD4 cells



3 Quantify the risks of OIs

- Dose-dependent model often used may not accurately predict the risk of infection in all patients treated with long-term glucocorticoids as the degree of immunosuppression differs between various glucocorticoids

Immunosuppressive potency of glucocorticoids



Pooled mean EC_{50} values of glucocorticoids for cellular effects. Equivalent doses were based on glucocorticoid potency.

4 Prevention strategies

- Multifactorial approach needed
- The heterogeneity of the risk for OIs in patients treated with glucocorticoids supports the need for shared decision-making and collaboration between clinicians and patients

Screen for asymptomatic OIs | Antimicrobial prophylaxis | Immunizations | Limit glucocorticoid use

5 Prioritize patient safety

- Conduct a thorough evaluation of personalized medical, social, and environmental risks associated with OIs
- Strategies to prevent acute infections or reactivation of OIs are critical

6 Future needs

- Determine the risk of OIs with refined precision

Detailed information about glucocorticoid treatments to better understand how different glucocorticoids affect immune function

Clinical calculators that consider additional glucocorticoid therapy features (dose, potency, exposure time) in addition to comorbidities, coexisting immunodeficiencies, and concomitant immunosuppressive therapies or advanced technology to measure cell-mediated immunity may provide a more accurate risk for OIs

Minimize the unintended consequences associated with long-term glucocorticoids

- Actively assess the risks of OIs
- Involve patients in decision-making
- Implement preventive measures and limit glucocorticoid use to decrease the risk of OIs

Table 1. Immunologic Effects of Glucocorticoids and Resultant Clinical Implications

Cell Type	Glucocorticoid Effects On Cellular Responses	Laboratory Finding(s)	Clinical Implications[a]
Neutrophils [11–15]	↑ Production ↓ Extravasation	Neutrophilia and impaired phagocytic activity	↑ Risk of common bacterial and viral infections [52, 53]
Eosinophils [16, 17]	↑ Apoptosis ↓ TLR signaling	Eosinopenia	↑ Risk of fungal infections
Basophils [18]	↑ Apoptosis	Basopenia and decreased histamine release	Limited clinical relevance
Mast cells [19–21]	↓ Cytokines, chemokine, and arachidonic acid derivative production, as well as FcεRI expression	Decreased histamine release and antiallergic actions	Limited clinical relevance
Macrophages and monocytes [11, 12, 22–26, 31, 32]	↑ Pro-resolution cytokine ↓ Inflammatory cytokine production, TLR signaling	Limited impact on macrophage function, although impaired opsonization and T_H-cell activation	↑ Risk of intracellular infections (eg, *Legionella* species, *Salmonella* species), MTB, and fungal infections
Natural killer cells [33, 34]	↑ Activation ↓ Inflammatory cytokine production	Reduced cytotoxicity	↑ Risk of viral infections or reactivation (eg, HSV, HZ, CMV) and fungal infections
Dendritic cells [39]	↑ Apoptosis ↓ Inflammatory cytokine production, antigen presentation, maturation	Decreased T-cell activity	Limited clinical relevance (although contributes significantly to T-cell response)
T_H cells (CD4 cells) [35, 36, 38, 42, 45]	↑ Apoptosis ↓ $T_H1 > T_H2$ and T_H17 cell response and inflammatory cytokine production, T-cell signaling	Decreased number of circulating T_H cells with shift from cell-mediated immunity to humoral-mediated immunity	↑ Risk of bacterial, viral, and fungal infections or reactivation, including intracellular (eg, *Legionella* species, *Salmonella* species) and opportunistic infections, (eg, MTB, *P. jirovecii*, candidiasis, cryptococcosis, aspergillosis, SHS)
Cytotoxic T cells (CD8+ T cells) [37]	↑ Apoptosis ↓ Inflammatory cytokine production, T-cell signaling	Reduced cytotoxicity	↑ Risk of viral infections or reactivation (eg, HSV, HZ, CMV)
B cells [4, 46–48]	↑ BAFF, IL-10, Blimp-10, apoptosis ↓ B-cell receptor signaling and TLR-7 signaling	Decreased number of circulating B cells and lower plasma immunoglobulins, except for IgE	↑ Risk of *Neisseria meningitides*, *Haemophilus influenzae*, *Streptococcus pneumoniae* [50, 51]

↑, indicates stimulatory effects; ↓, indicates inhibitory effects.

Abbreviations: BAFF, B-cell activating factor; Blimp1, B-lymphocyte–induced maturation protein 1; CMV, cytomegalovirus; FcεRI, Fcε receptor I; HSV, herpes virus; HZ, herpes zoster; IL, interleukin; MTB, *Mycobacterium tuberculosis*; SHS, *Strongyloides* hyperinfection syndrome; T_H, T helper; T_H1, type 1 T helper; T_H2, type 2 T helper; T_H17, type 17 T helper; TLR, Toll-like receptor.

[a]The increased risk of infection is influenced by a multitude factors including the dose, duration, and intensity of glucocorticoid treatment as well as the complex interactions with individual biological and host clinical factors, along with concurrent use of immunosuppressive therapies.

Pathogenic infections activate innate and adaptive immunity to elicit an inflammatory response. Activation of the hypothalamic-pituitary-adrenal axis following infection leads to the secretion of endogenous glucocorticoids to prevent an imbalanced or overwhelming immune response [5]. While these anti-inflammatory properties may benefit ongoing inflammation (pneumococcal meningitis), excessive endogenous or exogenous glucocorticoid exposure can lead to immunosuppression [6].

Glucocorticoids impair the expression of pattern recognition receptors (PRRs; eg, Toll-like receptors [TLRs]), which compromises the ability to detect specific pathogen-associated molecular patterns (PAMPs) and initiate an effective immunologic response [4]. The inflammatory signaling that follows pathogen detection is blunted by glucocorticoids, leading to decreased production of inflammatory mediators (Figure 1) [7–9]. Glucocorticoids can also reduce the production of antimicrobial polypeptides (eg, cathelicidins, defensins, lysozyme), an essential component of innate immunity [10]. As a result, glucocorticoids reduce the recruitment and activation of immune cells at the infection site and dampen the inflammatory response required for pathogen elimination. Alternatively, conflicting data suggest that glucocorticoids may enhance inflammation and immunity by upregulating innate immunity (stimulation of PRRs, cytokine receptors, and complement factors) while suppressing adaptive immunity (impaired T-cell activation) [4].

Glucocorticoids impair the inflammatory response by inhibiting leukocyte recruitment, particularly polymorphonuclear leukocytes (PMNs), and extravasation through the vascular endothelium [11, 12]. Reduced accumulation in tissues coupled with mobilization of immature neutrophils from the bone marrow into circulation and inhibition of apoptosis results in neutrophilia following glucocorticoid administration [11, 13, 14]. Phagocytic activity by PMNs is inhibited by prednisolone plasma concentrations from 0.005 to 1 μg/mL, noted to be consistent with long-term use, although specific doses or durations were not reported [15]. Glucocorticoids diminish the number

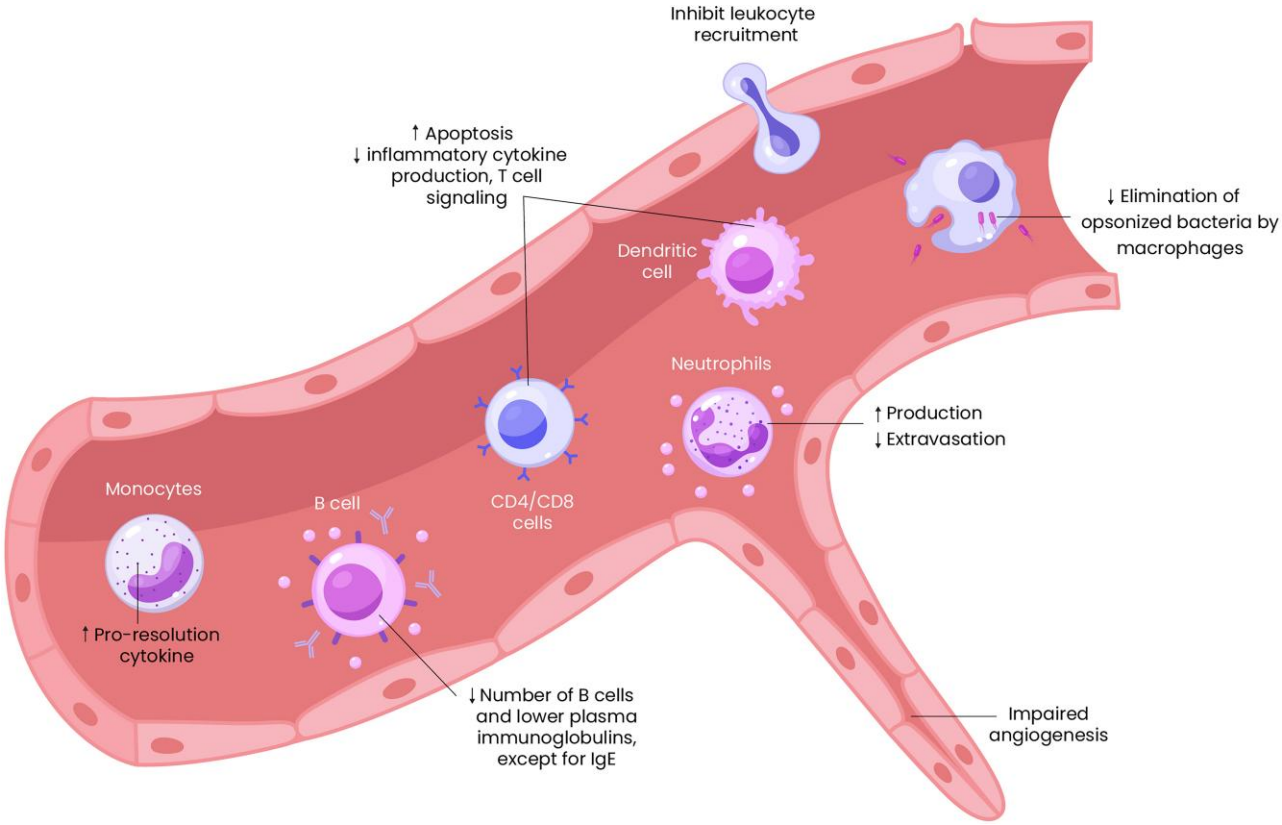


Figure 1. Immunologic effects of glucocorticoids. Glucocorticoids significantly impact both the innate and adaptive immune response [7–9]. Activated glucocorticoid receptors stimulate the production of anti-inflammatory products (including I-kappa-B-alpha [IκBα], interleukin [IL]-1 receptor II, lipocortin-1, IL-10, alpha-2-macroglobulin, and secretory leukocyte-protease inhibitor), induce expression of Toll-like receptor (TLR) signaling inhibitors, and simultaneously suppress proinflammatory transcription factors. As a result, glucocorticoids inhibit the production and secretion of numerous proinflammatory cytokines (including IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-12, IL-13, IL-16, IL-17, IL-18, interferon [IFN]-γ, tumor necrosis factor [TNF], and granulocyte–macrophage colony-stimulating factor [GM-CSF]), reducing recruitment and activation of immune cells at the site of infection, and inhibiting phagocytic activity of macrophages and neutrophils, hindering their ability to engulf and eliminate pathogens.

of eosinophils [16, 17] and basophils [18], while inhibiting mast cell maturation and cytokine, chemokine, and arachidonic acid derivative production, as well as the expression of Fcε receptor I [19–21].

Glucocorticoids increase the number of circulating macrophages and monocytes [22, 23]. However, the production of inflammatory mediators, including interleukin (IL)-1 and tumor necrosis factor (TNF), and the elimination of opsonized bacteria are decreased [11, 12, 24–31]. In addition, glucocorticoids may affect antigen presentation due to diminished expression of major histocompatibility complex (MHC) class II on circulating monocytes, leading to impaired activation of T-helper (T_H) cells [32]. Cytokine production (interferon [IFN]-γ) and cytotoxicity of natural killer (NK) cells are diminished by glucocorticoids, although "priming" or "preparative" effects for the increased capability of proinflammatory cytokine production upon stimulation have been described [33, 34].

Glucocorticoids are well recognized for their lympholytic activity, which varies by lymphocyte type. Glucocorticoids exert apoptogenic effects on both T_H and cytotoxic T cells while suppressing T-cell activation, proliferation, and cytokine production, reducing T-cell–mediated responses [35–39]. Glucocorticoids suppress inflammatory type 1 T_H (T_H1) cell responses to a greater degree than T_H2 cell responses but do not restrict, and may even promote, IL-17–producing T_H17 cell responses [40–44]. Similarly, glucocorticoids induce higher apoptosis rates in T_H1 cells than in T_H2 and T_H17 cells. Cytokine production by T_H1 and T_H2 cells is also inhibited. As a result, glucocorticoids promote a shift in the immunologic response from T_H1-cell–mediated immunity to T_H2 humoral-mediated immunity [45].

The effect of glucocorticoids on B cells and humoral immunity is limited compared with the impacts on T-cell activity [4, 46]. Glucocorticoids impair B-cell function, including decreased concentration of immunoglobulins (Ig), specifically IgG, but increased IgE production [47], affecting humoral immune responses. B-cell activating factor (BAFF), which is responsible for regulating B-cell maturation, antibody production, and stimulating T cells, is significantly diminished following glucocorticoid administration [48].

HOW DO THE EXPERIMENTAL GLUCOCORTICOID FINDINGS TRANSLATE TO CLINICAL PRACTICE?

Glucocorticoids produce a neutrophilic leukocytosis and concomitant monocytopenia, eosinopenia, and lymphopenia within 4 to 6 hours of administration, with higher doses resulting in more rapid effects [11, 49]. While T and B cells are affected, the lympho-depletive effects are most profound on CD4 cells. The resultant increase in susceptibility to bacterial, viral, fungal, and parasitic infections and reactivation of latent infections after treatment with glucocorticoids is immediate. It can be attributed to impaired phagocytosis and opsonization, decreased T-cell proliferation and activity, and diminished eosinophil activity, in addition to impaired wound healing (Table 1) [4, 11–17, 22–26, 31, 32, 35, 36, 38, 39, 42, 45–48, 50, 51]. The higher risk of infections is well recognized as a complication of glucocorticoids, although individual susceptibility is multifactorial.

WHAT ARE THE RISKS OF INFECTIONS AND OPPORTUNISTIC INFECTIONS IN PATIENTS REQUIRING GLUCOCORTICOIDS?

Shortly after glucocorticoids were introduced for treating inflammatory diseases, reports described associations between glucocorticoids and increased risks of infections [4, 52, 53]. However, these studies included heterogeneous populations, some of which had coexisting immunodeficiencies or received concomitant immunosuppressive therapies, and did not characterize the types of infections.

The increased susceptibility to infections, including OIs, is influenced by the glucocorticoid dose, duration, and intensity, in combination with biological and host clinical factors and concomitant immunosuppressive therapy. As in our case, glucocorticoids are often coupled with additional immunosuppressive medications. Due to its narrative nature, we have focused this review on clinical studies of patients receiving glucocorticoids for autoimmune inflammatory rheumatic diseases (AIIRDs) [54] or immune-related adverse events (irAEs) associated with checkpoint inhibitors (CPIs) that reported the incidence or risk of OIs stratified by glucocorticoid exposure. However, the associated risks and proposed prophylactic strategies extend to other populations.

Patients With Autoimmune Inflammatory Rheumatic Diseases

Patients with AIIRD are at increased risk of infections due to immunologic dysfunction and pharmacologic treatments, particularly glucocorticoids [55]. Most retrospective studies reported a dose-dependent increase in the risk of infections with doses greater than 10 mg of prednisone equivalents (PEQ) per day [56, 57]. In contrast, others, including a systematic review and meta-analysis of 21 randomized controlled trials and 42 observational studies, identified greater risks of serious bacterial infections in patients with rheumatoid arthritis (RA) treated with as little as 5 mg PEQ/day [58–60].

The risk of OIs is also increased in patients with RA treated with glucocorticoids based on findings from a prospective study (Table 2) [61]. Multiple case-control studies reported similar findings [62–64], with 1 study noting that the risk of any OI was dose-dependent, with higher risks in patients receiving 7.5 mg or more PEQ/day [62]. While the overall rates of PJP were low in a recent systematic review of 29 studies, 25 of which were case reports, 76% of cases were receiving glucocorticoids upon the diaagnosis of PJP [65]. The mean dose at diagnosis was 32 mg PEQ/day, but these data were not consistently reported and no analysis was performed to determine the relationship between PJP and glucocorticoid doses or duration. A case-control study comparing patients with and without AIIRD reported an increased risk of PJP in those with AIIRD treated with more than 10 mg PEQ/day [66]. In retrospective analyses to determine the risk of PJP based on glucocorticoid doses, one study that included patients receiving 30 mg or more PEQ/day for 4 weeks or more reported an increased risk with 60 mg or more PEQ/day in 1 study [67]. Conversely, a subsequent study by the same group noted a higher risk of PJP with doses between 15 and 29 mg PEQ/day for 4 or more weeks but only with baseline lymphopenia (<800 lymphocytes/mm^3) [68]. Alternatively, a territory-wide cohort study of patients with AIIRD from China identified most cases of PJP in those treated with 15 mg or more PEQ/day [69], whereas case series reported mean doses of 26.7 mg and 27.5 mg PEQ/day [70, 71]. The risk of PJP was also increased after treatment with glucocorticoid injection therapy [66] and pulse treatment [68], although no further details were provided.

The risk of herpes zoster (HZ) is increased among patients with AIIRD receiving glucocorticoids based on findings from large [72] and small [73] case-control, retrospective [74], and observational [75] studies. A dose-dependent relationship was observed, with higher risks noted in patients treated with doses up to 5 mg PEQ/day within 3 months [72] or 10 mg or more PEQ/day within 6 months [74] of HZ. *Mycobacterium tuberculosis* (TB) was significantly more common in patients with systemic lupus erythematosus (SLE) treated with glucocorticoids compared with those not treated with glucocorticoids [62]. Findings from a large case-control study reported higher rates of TB among patients with RA treated with glucocorticoids [76], whereas a smaller case-control study of patients aged 67 years or older with RA did not identify an association between glucocorticoid doses and TB [77]. A retrospective study identified an increased risk of TB in patients with SLE with a history of methylprednisolone pulse therapy, in which 98% were receiving glucocorticoids at baseline, although doses and durations were not reported [78]. An increased risk of nontuberculous mycobacteria (NTM) infection from any site was identified in patients 67 years or older with RA treated with 20 mg or more PEQ/day in a case-control study [77]. Still, an observational study of patients with primary Sjögren's syndrome failed to demonstrate a

Table 2. Analytical Studies Reporting Opportunistic Infections in Patients Receiving Glucocorticoids for Autoimmune Inflammatory Diseases

First Author [Ref]	Study Design	Study Population	Glucocorticoid Dose and Duration	Opportunistic Infection(s)	Comments
Opportunistic infections (nonspecific)					
Greenberg [61]	Prospective	7971 patients with RA treated with DMARDs	41% (n = 3286) of patients received concomitant prednisone (mean ± SD) of 5.5 ± 2.5 mg/d	IRR of overall infections (included OI and non-OI): • Any glucocorticoid dose: 1.05 (95% CI: .97–1.15), $P = .251$ • 10 mg PEQ/d: 1.30 (95% CI: 1.11–1.53), $P = .001$ Adjusted IRR of OIs: • Any glucocorticoid dose: 1.63 (95% CI: 1.20–2.21), $P = .002$	• Increased risk of infection in patients treated with >10 mg PEQ/d • Duration of glucocorticoid not reported • The risk of glucocorticoids might be confounded by concomitant use of MTX, TNF antagonists, or DMARDs
Yang [62]	Case-control	1850 patients with SLE treated with glucocorticoids versus 7400 patients with SLE not treated with glucocorticoids	Mean daily glucocorticoid dose: • <7.5 mg PEQ/d: 21% (n = 396) • 7.5–15 mg PEQ/d: 18% (n = 338) • 15–30 mg PEQ/d: 25% (n = 459) • 30–60 mg PEQ/d: 24% (n = 436) • >60 mg PEQ/d: 12% (n = 221)	Adjusted HR of OIs among patients treated with glucocorticoids: 39.73 (95% CI: 13.15–120.01) • 7.5–15 mg PEQ/d: 1.40 (95% CI: .78–2.51), $P = .2573$ • 15–30 mg PEQ/d: 1.72 (95% CI: 1.02–2.91), $P = .0419$ • 30–60 mg PEQ/d: 1.96 (95% CI: 1.17–3.28), $P = .0111$ • 60 mg PEQ/d: 2.24 (95% CI: 1.26–4.00), $P = .0078$ Adjusted HR of specific OIs: • TB, extrapulmonary TB, NTM: 11.00 (95% CI: 1.18–102.70), $P = .0355$ • HZ: 43.6 (95% CI: 10.67–178.06), $P < .0001$	• Cumulative incidence of OIs was higher among patients treated with glucocorticoids at 3 mo and 12 mo • Mean glucocorticoid doses calculated during first 3 mo after diagnosis of SLE, but total duration of glucocorticoid not reported • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Toruner [63]	Case-control	100 patients with IBD diagnosed with an OI versus 200 patients with IBD without an OI	Median glucocorticoid dose: 3600 mg	OR of OIs among patients treated with glucocorticoids: • Any glucocorticoid dose: 3.3 (95% CI: 1.8–6.1), $P < .001$ • Glucocorticoid doses <3600 mg: 2.5 (95% CI: 1.2–5.1) • Glucocorticoid doses >3600 mg: 5.0 (95% CI: 2.2–11.5) • Glucocorticoids plus thiopurines: 17.5 (95% CI: 4.5–68), $P < .001$ • Glucocorticoids plus thiopurines and infliximab: infinite, $P < .001$	• Doses and duration of glucocorticoid not reported • OIs ranged from mucosal HSV to disseminated IFI • OIs not differentiated by glucocorticoid use • The risk of glucocorticoids might be confounded by concomitant use of TNF antagonists or DMARDs

Table 2. Continued

First Author [Ref]	Study Design	Study Population	Glucocorticoid Dose and Duration	Opportunistic Infection(s)	Comments
Brassad [64]	Case-control	564 patients >65 y with IBD with serious infection versus 2646 patients >65 y with IBD without serious infection	Any glucocorticoid dose	Adjusted RR of serious infections among patients treated with glucocorticoids: • Exposure in past 45 d: 2.8 (95% CI: 2.1–3.7) • Exposure in 46–180 d: 1.6 (95% CI: 1.1–2.2) • Exposure in past 180 d: 2.3 (95% CI: 1.8–2.9) Adjusted RR of types of infections among patients treated with glucocorticoids: • Bacterial: 4.0 (95% CI: 2.5–6.6) • Viral: 0.8 (95% CI: .3–2.2) • Fungal, protozoal, helminthic, unspecified: 3.2 (95% CI: 2.2–4.6)	• Doses and duration of glucocorticoid not reported • Serious infections included bacterial, viral, fungal, protozoal, helminthic, and "unspecified" • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
PJP					
Hsu [66]	Case-control	103 117 patients with AIIRD versus 412 462 patients without AIIRD	Any glucocorticoid dose	Adjusted HR of PJP among patients with autoimmune rheumatic disease: • Oral glucocorticoid >10 mg PEQ/d: 9.15 (95% CI: 6.23–13.45) • Injection glucocorticoid therapy: 5.03 (95% CI: 1.23–3.34)	• Duration of glucocorticoids not reported • Definition for injection glucocorticoid therapy not provided • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Park [67]	Retrospective	30 cases of PJP among 1092 patients with AIIRD	≥30 mg PEQ/d for ≥4 wk; mean ± SD glucocorticoid dose 31.3 ± 20.1 mg PEQ/d at time of PJP diagnosis (n = 30) • <15 mg PEQ/d: 10% (n = 3) • 15–30 mg PEQ/d: 40% (n = 12) • ≥30 mg PEQ/d: 50% (n = 15)	IRR of PJP: • 40–60 mg PEQ/d: 2.26 (95% CI: .51–10.09), $P = .286$ • ≥60 mg PEQ/d: 3.35 (1.19–10.00), $P = .023$	• Only evaluated the risk of PJP with glucocorticoid doses ≥30 mg PEQ/d, but some cases of PJP occurred after glucocorticoids were taper d (3 cases when doses were <15 mg PEQ/d) • Glucocorticoid dose adjustments before PJP diagnosis not reported • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Park [68]	Retrospective	5 cases of PJP among 735 patients with AIIRD	≥15 mg and <30 mg PEQ/d for ≥4 wk	HR of PJP: • Initial glucocorticoid dose: 1.1 (95% CI: .9–1.4), $P = .377$ • Concomitant glucocorticoid-pulse treatment: 68.4 (95% CI: 5.3–876.0), $P = .001$ • Cumulative glucocorticoid dose ≥900 mg PEQ during previous 6 mo: 1.7 (95% CI: .1–4.8), $P = .610$	• Glucocorticoid dose adjustments before PJP diagnosis not reported • Definition for glucocorticoid-pulse treatment not reported • The risk of glucocorticoids might be confounded by concomitant use of use of MTX, TNF antagonists, or DMARDs

Table 2. Continued

First Author [Ref]	Study Design	Study Population	Glucocorticoid Dose and Duration	Opportunistic Infection(s)	Comments
Chan [69]	Observational	48 patients with AIIRD with PJP versus 21 538 patients with AIIRD without PJP	Any glucocorticoid dose	Most cases of PJP occurred in patients treated with ≥15 mg PEQ/d	• Doses and duration of glucocorticoid not reported • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Herpes zoster					
Hu [72]	Case-control	1555 patients with SLE with HZ versus 3049 patients with SLE without HZ	Any glucocorticoid dose, considered 10 mg PEQ/d as DDD and reported as DDD/d	Adjusted OR of HZ among patients treated with glucocorticoids: • Oral glucocorticoids: 3.68 (95% CI: 3.06–4.42), $P < .001$ • IV methylprednisolone: 2.18 (95% CI: 1.68–2.82), $P < .001$ • IV hydrocortisone: 1.36 (95% CI: .91–2.03), $P = .129$ Adjusted OR of HZ among patients treated with oral glucocorticoids: (DDD/d): • ≤0.5: 2.41 (95% CI: 1.90–3.04), $P < .001$ • 0.5–1: 2.7 (95% CI: 2.16–3.37), $P < .001$ • 1–1.5: 4.52 (95% CI: 3.51–5.83), $P < .001$ • 1.5–2: 5.57 (95% CI: 4.16–7.44), $P < .001$ • >2: 9.34 (95% CI: 7.1–12.28), $P < .001$	• Dose-dependent relationship in risk of HZ based on DDD/d • Glucocorticoid use determined within 3 mo prior to HZ • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Veetil [73]	Case-control	84 patients with RA with HZ versus 44 patients without RA with HZ	Any glucocorticoid dose	HR of HZ among patients treated with glucocorticoids: 1.72 (95% CI: 1.03–2.87)	• Doses and duration of glucocorticoid not reported • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Winthrop [74]	Retrospective	310 cases of HZ among 33 324 patients with RA, IBD, psoriasis, psoriatic arthritis, or ankylosing spondylitis	Any glucocorticoid dose	Adjusted HR of HZ among patients treated with glucocorticoid: • 0–4 mg PEQ/d: 1.37 (95% CI: 1.08–1.72) • 5–9 mg PEQ/d: 1.18 (95% CI: .89–1.56) • ≥10 mg PEQ/d: 2.13 (95% CI: 1.64–2.75)	• Glucocorticoid dose determined as mean daily dose of PEQs within 6 mo prior to HZ • The risk of glucocorticoids might be confounded by concomitant use of TNF antagonists or DMARDs
Pappas [75]	Observational	28 852 patients with RA contributed 95 287 patient-years accounting for 729 cases of HZ (crude incidence rate for HZ: 7.7 (95% CI: 7.1–8.2) per 1000 patient-years)	Any glucocorticoid dose	HR of HZ among patients treated with prednisone: • 1–7.5 mg/d: 1.12 (95% CI: .87–1.46) • ≥7.5 mg/d: 1.78 (95% CI: 1.20–2.63)	• Rate of HZ was 13 per 1000 person-years among patients treated with glucocorticoids • Duration of glucocorticoids not reported • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications

Table 2. Continued

First Author [Ref]	Study Design	Study Population	Glucocorticoid Dose and Duration	Opportunistic Infection(s)	Comments
Mycobacterium species					
Brassad [76]	Case-control	386 patients with RA with TB versus 38 600 patients with RA without TB	Any glucocorticoid dose	Adjusted RR of TB among patients treated with glucocorticoids: 1.7 (95% CI: 1.3–2.2)	• Doses and duration of glucocorticoid not reported • The risk of glucocorticoids might be confounded by concomitant use of DMARDs
Brode [77]	Case-control	37 patients ≥67 y with RA with TB versus 363 patients ≥67 y with RA without TB; 211 patients ≥67 y with RA with NTM versus 2071 patients ≥67 y with RA without NTM	Mean glucocorticoid dose based on most recent prescription: • ≤9 mg PEQ/d • 10–19 mg PEQ/d • ≥20 mg PEQ/d	Adjusted OR of TB among patients treated with glucocorticoids • ≤9 mg PEQ/d: 1.63 (95% CI: .60–4.44), $P = .34$ • 10–19 mg PEQ/d: 2.53 (95% CI: .55–11.6), $P = .23$ • ≥20 mg PEQ/d: 2.73 (95% CI: .81–9.20), $P = .11$ Adjusted OR of NTM among patients treated with glucocorticoids • ≤9 mg PEQ/d: 0.72 (95% CI: .45–1.14), $P = .16$ • 10–19 mg PEQ/d: 1.66 (95% CI: .99–2.78), $P = .05$ • ≥20 mg PEQ/d: 1.60 (95% CI: 1.02–2.52), $P = .04$	• Glucocorticoid dose determined as mean daily dose of PEQs based on most recent prescription, but time to diagnosis of TB not reported • NTM infection included all sites • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Hamijoyo [78]	Retrospective	131 patients with TB among 1278 patients with SLE	Glucocorticoids: 98% (n = 579); ever methylprednisolone pulse therapy: 19% (n = 239)	HR of TB among patients with a history of methylprednisolone pulse therapy: 1.64 (95% CI: 1.01–2.67), $P = .047$	• Doses and duration of glucocorticoid not reported • Definition for "ever" and methylprednisolone pulse therapy not reported • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications
Weingart [79]	Retrospective	51 patients with pSS with NTM versus 2127 patients with pSS without NTM	Any glucocorticoid dose	OR of NTM among patients treated with glucocorticoids: 0.6 (95% CI: .3–1.3)	• Doses and duration of glucocorticoid not reported • NTM infection restricted to pulmonary disease • The risk of glucocorticoids might be confounded by concomitant use of DMARDs
Cryptococcosis					
Chen [82]	Case-control	16 patients with LN with CM versus 32 patients with LN without CM	Any glucocorticoid dose	Prednisone dose at diagnosis (mean ± SD): 27.5 ± 10.2 versus 15.5 ± 7.8 mg/d, $P < .001$ Cumulative prednisone dose over last year (mean ± SD): 3850 ± 1420 versus 3250 ± 1810 mg, $P = .324$	• Duration of glucocorticoids not reported • Glucocorticoid dose adjustments before hospitalization not reported • The risk of glucocorticoids might be confounded by concomitant use of other immunosuppressive medications

Abbreviations: AIIRD, autoimmune inflammatory rheumatic disease(s); CI, confidence interval; CM, cryptococcal meningoencephalitis; DDD, defined daily dose; DMARD, disease modifying anti-rheumatic drug; HR, hazard ratio; HSV, herpes simplex virus; HZ, herpes zoster; IBD, irritable bowel disease; IFI, invasive fungal infection; IRR, incidence rate ratio; IV, intravenous; LN, lupus nephritis; MTX, methotrexate; NTM, nontuberculous mycobacteria; OI, opportunistic infection; OR, odds ratio; PEQ, prednisone equivalent; PJP, *Pneumocystis jirovecii* pneumonia; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; Ref, reference; RR, rate ratio; SD, standard deviation; SLE, systemic lupus erythematosus; TB, *Mycobacterium tuberculosis*; TNF, tumor necrosis factor.

similar relationship between glucocorticoids and NTM lung disease [79].

Fungal OIs are uncommon in patients with AIIRD treated with glucocorticoids [62, 63, 80, 81]. Coccidioidomycosis was identified in 16 of 854 patients with RA, of whom 11 were receiving glucocorticoids [81]. Most were receiving less than 10 mg PEQ/day, although the duration was not reported, and no analysis was performed to explore the relationship between glucocorticoids and coccidioidomycosis. Among 48 patients with lupus nephritis in a retrospective study, those with cryptococcal meningoencephalitis (CM) (n = 16) received similar cumulative glucocorticoid doses to those without CM in the prior year but significantly higher doses at diagnosis (27.5 ± 10.2 vs 15.5 ± 7.8 mg PEQ/d; $P < .001$) [82]. A single-center case series described 15 patients with SLE diagnosed with fungal OI over a 35-year period [80]. Cryptococcal meningoencephalitis was the most common and accounted for 9 cases, whereas there were 3 cases of invasive candidiasis, 1 case of scedosporiosis, and 2 cases with concomitant CM and invasive aspergillosis (IA). Within 3 months before the diagnosis, glucocorticoid use was reported in 87% with variable doses, which were highest in CM.

Strongyloides hyperinfection syndrome (SHS) has been reported in patients with AIIRD treated with glucocorticoids [83, 84]. In a systematic review of 244 cases of severe strongyloidiasis from 213 reports published between 1991 and 2011, 67% were receiving glucocorticoids [85]. While doses and durations were not reported in the systematic review [85], a case report described a patient with sarcoidosis who developed SHS after treatment with 40 mg PEQ/day for 6 weeks [86]. In addition, SHS was reported in patients with sarcoidosis and RA treated with glucocorticoids for 13 and 15 years, respectively [87, 88]. Reactivation of Chagas disease has been described in 13 cases with AIIRD, of whom 70% were receiving glucocorticoids (most often 5 mg PEQ/d) combined with other immunosuppressive therapies [89]. Numerous cases describing less common OIs in patients with AIIRD treated with varying glucocorticoid doses and durations have been reported elsewhere [90–93].

Patients With Immune-Related Adverse Events Associated With Checkpoint Inhibitor Therapies

Patients with neoplastic diseases are at higher risk of infections due to local tumor effects; disruption of physical barriers due to older age, poor functional status, disease progression, or interventions to treat the disease (eg, surgery or device implantation); comorbidities (eg, coexisting immunodeficiencies); and immune dysfunction caused by the ongoing malignancy or its treatment (eg, glucocorticoids, cytotoxic chemotherapy, CPI therapy, other immunomodulators). Glucocorticoids are widely used for premedication before chemotherapy, supportive care and refractory symptom management, and oncologic emergencies, and in many treatment protocols often combined with other immunosuppressive medications for hematologic and oncologic diseases [94].

Following the approval and increased utilization of CPI therapies, glucocorticoids have become the mainstay for managing irAEs. The use of CPIs has increased for many advanced malignancies due to substantial antitumor efficacy [95]. However, the benefits associated with CPIs are offset by the development of severe or life-threatening irAEs (grade 3–4 based on the Common Terminology Criteria for Adverse Events from the National Cancer Institute [96]), which affect 20–50% of patients and most often involve the respiratory or gastrointestinal tract [95, 97]. Glucocorticoids (1–2 mg PEQ/kg/d) are recommended and are tapered over 4 weeks or more as symptoms subside, although some patients require more than 6–8 weeks or additional immunosuppressive medications (eg, infliximab, vedolizumab, mycophenolate mofetil) [94].

The incidence of infections during or within 1 year after CPI therapy ranges from 18% to 27%, in which cutaneous, respiratory, genitourinary, and bloodstream infections were most common and frequently caused by *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* [98, 99]. In a retrospective study of patients treated with CPI therapy, age greater than 67 years was associated with an increased risk of infection (hazard ratio [HR]: 1.73; 95% confidence interval [CI]: 1.04–2.87; $P = .04$), whereas treatment with glucocorticoids did not influence the risk of infection (HR: 1.51; 95% CI: .91–2.49; $P = .11$), but doses and duration were not reported [99].

Opportunistic infections represented 2% of all infections in a retrospective study that included 740 patients with melanoma treated with CPIs (Table 3) [100]. Overall, 46% of patients received glucocorticoids, most often consisting of 40 mg PEQ/day for 60 days. Glucocorticoids were significantly associated with serious infections, although the association between glucocorticoids and OIs was not evaluated. A higher incidence of OIs (7% of all infections) was reported from a more recent retrospective analysis of 758 patients treated with CPIs and included oral candidiasis, HZ, PJP, and *Listeria monocytogenes* endophthalmitis [95]. The incidence of OIs was similar between patients treated with glucocorticoids for 28–59 days and those treated for 60 days or more (5% vs 11%; $P = .234$).

Additional cases of OIs have been reported in patients treated with CPIs who required glucocorticoids for irAEs and reviewed elsewhere, although doses, durations, and concomitant immunosuppressive medications varied [101].

CAN THE RISK OF OPPORTUNISTIC INFECTIONS IN PATIENTS REQUIRING GLUCOCORTICOIDS BE ESTIMATED?

A key question is how to best quantify the increased risk of OIs in patients treated with glucocorticoids, particularly when

Table 3. Analytical Studies Reporting Opportunistic Infections in Patients Receiving Glucocorticoids for Immune-Related Adverse Events Associated With Checkpoint Inhibitors

First Author [Ref]	Study Design	Study Population	Glucocorticoid Dose and Duration	Opportunistic Infection(s)	Comments
Del Castillo [100]	Retrospective	740 patients with melanoma treated with CPI therapy	46% (n = 339) of patients treated with glucocorticoids • Median dose: 40 mg PEQ/d • Median duration: 60 d	Serious infection occurred in 7% (n = 54/740) of patients an average of 135 d (range: 6–491 d) after starting CPI therapy • Candidemia: 2% (n = 1) • CMV enterocolitis: 2% (n = 1) • IPA: 4% (n = 2) • PJP: 6% (n = 3) • SHS: 2% (n = 1) • HZ: 6% (n = 3) OR of serious infection among patients treated with glucocorticoids: 7.71 (95% CI: 3.71–16.18), $P < .0001$	• Serious infection defined as infection requiring hospitalization or parenteral antimicrobials and included OIs • OIs not differentiated by glucocorticoid use • The risk of glucocorticoids might be confounded by concomitant use of TNF antagonists
Shah [95]	Retrospective	758 patients treated with CPI therapy • Melanoma: 61% (n = 68) • NSCLC: 19% (n = 21) • RCC: 7% (n = 8) • HCC: 4% (n = 4) • HNSCC: 3% (n = 3) • Other: 7% (n = 8)	15% (n = 112) of patients treated with ≥20 mg PEQ/d for ≥4 wk • Median starting dose: 100 mg PEQ/d • 42% required ≥60 d of glucocorticoids • 25% received additional immunosuppressive therapy (eg, infliximab, mycophenolate mofetil, etc)	OIs accounted for 7% (n = 8) of all infections: • Oral candidiasis: 50% (n = 4) • HZ: 25% (n = 2) • PJP: 13% (n = 1) • *Listeria monocytogenes* endophthalmitis: 13% (n = 1) OR of OIs among patients treated with <60 d of glucocorticoids: 0.41 (95% CI: .09–1.79), $P = .225$	• Of the patients who developed an OI, 38% (n = 3) were receiving TMP/SMX (HZ and oral candidiasis) • The risk of glucocorticoids might be confounded by concomitant use of TNF antagonists

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; CPI, checkpoint inhibitor; HCC, hepatocellular carcinoma; HNSCC, head and heck squamous cell cancer; HZ, herpes zoster; IPA, invasive pulmonary aspergillosis; NSCLC, non–small cell lung cancer; OI, opportunistic infection; OR, odds ratio; PEQ, prednisone equivalents; PJP, *Pneumocystis jirovecii* pneumonia; RCC, renal cell carcinoma; Ref, reference; SHS, Strongyloides hyperinfection syndrome; TMP/SMX, trimethoprim/sulfamethoxazole; TNF, tumor necrosis factor.

Table 4. Relative Potencies and Half-Maximum Effective Concentration (EC_{50}) Values of Glucocorticoids for Cellular Effects and Cortisol Suppression

Glucocorticoid	Equivalent Dose (Based on Glucocorticoid Potency)	Genomic Potency	Nongenomic Potency	Plasma Concentration Measured	Cellular Effects, µg/L					Cortisol Suppression, µg/L
					Lymphocyte Suppression	T-Helper Cell Suppression	Cytotoxic T-Cell Suppression	Basophil Suppression	Monocyte Suppression	Neutrophil Induction	
Hydrocortisone (cortisol)	20 mg	NR	NR	Total	6.7 ± 4.9	67.9 ± 20.7 (56.4–79.3)	103.0 ± 17.5	NR	NR	179.0 ± 66.2	4.6 ± 5.3
				Free	15.4 ± 3.4	NR	NR	NR	NR	NR	NR
Prednisolone[a]	5 mg	4	4	Total	NR	125.3 ± 65.2 (90.4–173.9)	NR	61.9 ± 40.6 (48.8–75.0)	NR	NR	9.7 ± 3.4 (9.0–10.3)
				Free	9.7 ± 7.8 (4.7–15.1)	5.8 ± 6.7 (3.2–15.1)	12.1 ± 8.1 (4.8–19.2)	5.7 ± 6.4	10.5 ± 6.1	29.2 ± 31.5 (15.0–57.7)	0.9 ± 1.3 (0.3–1.9)
Methylprednisolone	4 mg	5	13.3	Total	10.5 ± 13.9 (6.0–13.9)	11.8 ± 11.5 (1.4–22.8)	51.0 ± 43.3 (18.5–112.0)	7.2 ± 6.1 (2.1–14.3)	NR	22.4 ± 27.5 (8.4–36.0)	1.0 ± 1.1 (0.1–2.9)
Dexamethasone	0.75 mg	25	20	Total	2.9 ± 1.0 (0.9–6.0)	4.0 ± 4.7	18.0 ± 4.7	NR	NR	3.7 ± 5.3 (2.2–6.1)	0.1 ± 0.07

Data were adapted from Czock et al [104], Buttgereit et al [112], and Schmid et al [114] and are presented as the pooled mean ± pooled standard deviation for the half-maximum effective concentration (EC_{50}) values of glucocorticoids for cellular effects and cortisol suppression. In cases of more than 1 study, minimum and maximum values are provided in parenthesis. The potency of each glucocorticoid for various cellular effects increases as the EC_{50} value decreases.

Abbreviation: NR, not reported.

[a]Prednisolone is the active moiety, whereas prednisone requires activation to prednisolone.

combined with other immunosuppressive therapies. Most data suggest that the increased risk of infection is proportionate to the dose and duration [62, 63, 72]. For example, the initial thresholds for PJP based on case series from multiple populations ranged from 15 to 20 mg PEQ/day for 3 or more weeks [102, 103]. However, cases have been reported in patients receiving less than 15 mg PEQ/day, suggesting that the dose and duration thresholds are not universal [67]. The use of nonspecific terminology ("low dose," "high dose") and "prednisone equivalents" based on potency to report and compare glucocorticoid doses presents an added complexity in failing to recognize the differential effects on lymphocyte subpopulations between various glucocorticoids.

Traditionally, glucocorticoid potency was correlated with glucocorticoid receptor affinity and anti-inflammatory properties, although the degree of immunosuppression differs between various glucocorticoids [104]. The in vivo immunosuppressive potency of glucocorticoids is likely more complex due to the variable effects on cellular biomarkers compared with cortisol suppression (Table 4). Reductions in the number of circulating lymphocytes were similar, although dexamethasone significantly impaired lymphocyte-mediated cellular toxicity and inflammatory cytokine production compared with equivalent doses of hydrocortisone and prednisone [105]. Despite being less potent, methylprednisolone diminished lymphocyte proliferation to a greater extent compared with dexamethasone [106]. Alternatively, dexamethasone was 10 times more potent than prednisolone at inhibiting lymphocyte proliferation [107]. In a previous study comparing the dynamics of suppressing T_H-cell trafficking, the half maximal inhibitory concentration (IC_{50}) of cortisol (hydrocortisone) was 79.3 µg/L compared to 4.6 µg/L for methylprednisolone, which produced a potency ratio of 17.1 [108], despite dose equivalency being defined as 20 mg and 4 mg, respectively. While the anti-inflammatory potency of methylprednisolone is 25% greater than prednisolone, the antilymphocyte potency of methylprednisolone was more than 12 times higher than prednisolone [109]. The lympho-depletive effects of dexamethasone and methylprednisolone are likely greater than those observed with prednisolone. Indeed, a retrospective study detected prolonged graft survival time in renal transplant recipients treated with methylprednisolone compared with prednisolone for maintenance immunosuppression due to the greater lymphocyte-suppressive potency of methylprednisolone [109]. For example, an ongoing institutional quality-improvement effort identified dexamethasone pulses —primarily for patients with oncologic diseases—as a risk factor for PJP. Similar to our case, some glucocorticoid taper regimens may not be identified as treatment regimens in need of PJP prophylaxis. A higher risk of TB was also reported in patients with SLE treated with "methylprednisolone pulse therapy" [78]. Additionally, twice-daily dosing may result in

greater T_H-cell suppression than once-daily dosing despite the same daily dose [104]. When glucocorticosteroids are used as immunomodulators—even for such doses and duration—in the treatment of coronavirus disease 2019 (COVID-19), they can confer an increased risk for COVID-19–associated pulmonary aspergillosis [110] or SHS [111].

Clinical data comparing the immunologic effects of different glucocorticoids are lacking. Standardized nomenclature for glucocorticoid treatment to include the drug, dose, route of administration, and duration or cumulative dose based on "prednisone equivalents" was proposed by the European Alliance of Associations for Rheumatology in 2002 [112]. However, this guidance acknowledges the lack of experimental and clinical data to support the traditional glucocorticoid potencies and cautions extrapolating equivalent potencies to doses of more than 100 mg PEQ. At doses greater than 100 mg PEQ (used for acute diseases [113]), non–transcriptionally mediated (nongenomic) activity is observed, which differs in relative potency compared with genomic effects (Table 4) [114]. Nongenomic effects occur much faster (within minutes) than genomic action at the transcriptional level, with variable effects [115]. Indeed, experimental reports described rapid immunosuppressive effects of glucocorticoids through disruption of T-cell receptor signaling after 30 minutes of treatment with dexamethasone (equivalent human doses were not reported) [116, 117]. Additional experimental data observed differences in the mechanism of action of prednisone and dexamethasone, where both equally inhibited cytokine production by T cells. Still, dexamethasone inhibited nuclear factor-κB (NF-κB) signaling, involved in the activation and differentiation of T cells, less than prednisone [118]. The proposal to standardize glucocorticoid treatment nomenclature [112] improves consistency in reporting but fails to provide the nuanced details necessary to elucidate the complex mechanism of different glucocorticoids on host defense mechanisms. Future reports should give explicit details about glucocorticoid treatments (specific drug, dose, route of administration, duration or cumulative dose, additional intermittent or "pulse," and modifications prior to OI diagnosis) to better characterize the effect of differing glucocorticoids on immune function.

There are numerous additional risk factors for OIs in patients requiring glucocorticoids. In addition to the potential dose-dependent relationship, the primary comorbidity can intrinsically contribute to the overall host immunodeficiency. Other additive factors include advanced age, uncontrolled diabetes, transplant status, malignancy, chemotherapy, immune-mediated effects of AIIRD, end-organ injury or failure, and concomitant immunosuppressive medications. Developing calculators that consider additional factors beyond glucocorticoid potency, such as specific details about the glucocorticoid therapy in addition to comorbidities, coexisting immunodeficiencies, and concomitant immunosuppressive therapies or utilizing advanced technology to measure cell-mediated immunity, may provide a more accurate risk for OIs. For example, in a multicenter case-control study, the calculated annual risk of PJP for 20 mg PEQ/day was approximately 1.74% in a patient with AIIRD but 6.29% in a person with human immunodeficiency virus (HIV) [119]. Improved methods to determine the intensity or "net state" of immunosuppression, rather than traditional therapeutic drug monitoring for immunosuppressive therapies, have recently emerged in transplant recipients [120]. Assays to measure intracellular adenosine triphosphate synthesis to determine CD4 cell activity as a surrogate for cell-mediated immunity [121] and IFN-γ production to characterize both the adaptive (CD3 T-cell stimulant) and innate (TLR ligand) immune responses [122] are increasingly used, but data are lacking outside of transplant recipients.

Although the incidence of OIs ranged from 2% to 7% in observational studies of patients treated with glucocorticoids for irAEs associated with CPIs [95, 100], questions remain regarding the underlying mechanism for infections, including OIs, that occur post–CPI therapy. A recent review [123] noted that some infections after treatment with CPIs might be caused by other factors besides glucocorticoids or immunosuppression based on findings from recent studies that failed to identify an association between glucocorticoids and OIs [98, 99]. The authors argued that the diversity of infections observed in patients post–CPI therapy could be dichotomized into immunotherapy infections due to dysregulated immunity (ITI-DI) and immunotherapy infections due to immunosuppression (ITI-IS) [123]. ITI-DI likely represent the reactivation of latent diseases (eg, TB, cytomegalovirus [CMV], and hepatitis B virus), where immune checkpoint activity regulated the pathogen before treatment with CPIs. Alternatively, *Streptococcus pneumoniae*, IA, and PJP are most often characterized as ITI-IS in which the risk is directly associated with the degree of immunosuppression. However, a previous case of IA was reported in a patient treated with CPIs without concomitant immunosuppression [124]. Additional data are needed to distinguish ITI-DI from ITI-IS to better understand the pathogenesis and quantify the risks of OIs in patients treated with CPIs with or without concomitant glucocorticoids.

WHAT CAN BE DONE TO PREVENT ACUTE INFECTIONS OR REACTIVATION OF OPPORTUNISTIC INFECTIONS IN PATIENTS REQUIRING GLUCOCORTICOIDS?

Was PJP prophylaxis initially indicated in this patient? Could he benefit from secondary prophylaxis against PJP?

Interventions to prevent infections or disease progression caused by opportunistic pathogens in patients treated with glucocorticoids are critical, but identifying those who may benefit remains a clinical challenge. Until greater details about the immunologic effects of different glucocorticoid treatments or

methods to "calculate" or determine the "net state" of immunosuppression are validated in patients requiring glucocorticoids, we are forced to rely on the dose-dependent, prednisone-equivalent dogma to estimate the risk of OIs. The heterogeneity of the risk for OIs in patients treated with glucocorticoids supports the need for shared decision making and collaboration between clinicians and patients. Ongoing and open discussions about current disease activity, previous treatments, concurrent comorbidities, and individualized social and environmental risks allow the detection of those at greatest risk for OIs. Conveying the perceived risks of OIs improves patient understanding and may increase the use of preventive efforts, including screening for asymptomatic OIs, antimicrobial prophylaxis, and immunizations, which may aid in reducing health inequities.

Glucocorticoids, including "methylprednisolone pulse therapy," are associated with an increased risk of TB in patients with AIIRD [62, 76, 78], although the minimum dose or duration remains unknown. Guidelines recommend screening patients treated with 15 mg or more PEQ/day for 1 month or more for latent TB (Table 5) [54, 125]. However, the risk for TB reactivation was 2.8 and 7.7 times higher among patients treated with less than 15 mg and 15 mg or more PEQ/day, respectively [126]. Since recommendations based on PEQ may underestimate the risk of latent TB in those receiving glucocorticoids, a detailed history, including social and environmental risk factors along with shared decision making, may improve the identification of at-risk individuals. While glucocorticoids can blunt the response of the tuberculin skin test and IFN-γ release assays (IGRAs), data suggest that IGRAs are less affected by glucocorticoids and other immunosuppressants [54, 127, 128]. Therefore, IGRAs are preferred to screen for latent TB. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend patients undergo screening for latent TB before treatment with CPIs (Table 5) [94]. There are limited risk assessments, screening, and prophylactic recommendations for NTM or other atypical infections in patients receiving glucocorticoids.

Prophylaxis with TMP/SMX reduced the incidence of PJP in multiple studies enrolling patients with AIIRD receiving 15–30 mg PEQ/day for 2–4 weeks, but the duration was not provided in all studies [67, 68, 129–131]. The number needed to treat to prevent 1 case of PJP varied from 21 to 114, depending on the underlying AIIRD [69, 132]. A recent global health network analysis found an independently increased mortality related to PJP among patients without HIV with prior glucocorticoid exposure [133], potentially due to diagnostic delays. As such, PJP prophylaxis is indicated for patients receiving 15 mg or more PEQ/day for 14–28 days or more [54]. No cases of PJP were detected in patients with AIIRD treated with glucocorticoids who received TMP/SMX daily or 3 times weekly, although tolerability was improved with lower doses [134, 135]. Patients with a history of PJP or additional risk factors for PJP may require PJP prophylaxis with lower doses or even pulse doses of glucocorticoids (Table 5) [66, 68, 94]. While lymphopenia is common among patients with AIIRD with PJP, lymphocyte and CD4 counts were lower in patients with SLE 6–7 months before PJP diagnosis compared with age- and sex-matched patients with SLE but without PJP (520 ± 226 vs 1420 ± 382 lymphocytes/mm^3 and 156 ± 5 vs 276 ± 8 CD4 cells/mm^3, respectively) [103]. Before or during glucocorticoid treatment, multiple threshold values for lymphocyte or CD4 counts have been proposed [130, 136–139]. However, a defined value determining when prophylaxis should be initiated remains unknown, resulting in inconsistent clinical practice [140]. The association between CD4 counts of less than 200 cells/mm^3 is less evident in people without HIV [141] as 40% and 60% of patients with connective tissue disease and PJP had CD4 counts of less than 300 and less than 400 cells/mm^3, respectively [142]. Shared decision making with patients should be done due to the lack of consensus to determine who may benefit from prophylaxis, poor outcomes associated with PJP, and the potential for adverse events related to TMP/SMX. Further data are needed to determine whether glucocorticoid injection or pulse therapy [66, 68] and concurrent lymphopenia (CD4 count) [143] are helpful for predicting the risk of PJP in patients receiving glucocorticoids. As in our case, primary PJP prophylaxis should be discussed with the patient with consideration for lower doses or shorter durations of glucocorticosteroids (or concomitant immunosuppressive medications). Ongoing use of glucocorticoids necessitates secondary PJP prophylaxis. The optimal time to discontinue PJP prophylaxis remains unclear but can be considered, in conjunction with patient preferences, once doses are decreased to less than 15 mg PEQ/day in those without additional risk factors for PJP. Since other PJP risk factors are present in our case, PJP prophylaxis would be indicated despite receiving less than 15 mg PEQ/day.

PJP prophylaxis is also indicated for patients who develop irAEs after CPI therapy and requires 20 mg or more PEQ/day for 4 or more weeks [94]. However, in 1 report, 14 patients received TMP/SMX for PJP prophylaxis, in whom 43% developed an OI (2 patients with oral candidiasis and 1 with Varicella zoster virus) or non-OI (1 patient with sinusitis, 1 with cellulitis and *Clostridioides difficile* colitis, and 1 with bacteremia secondary to osteomyelitis) [95]. One patient developed PJP but was not receiving prophylactic therapy. Overall, the incidence of OIs in patients receiving glucocorticoids for irAEs is low despite weeks of glucocorticoids. Recent concerns have emerged about the association with antimicrobial therapy, before or with CPIs regardless of glucocorticoid use, and poor overall survival due to gut dysbiosis [144, 145]. Unnecessary antimicrobial therapy should be avoided, but more data are needed to examine whether similar deleterious effects on CPI

Table 5. Recommendations to Prevent Acute Infections or Reactivation of Opportunistic Infections in Patients Requiring Glucocorticoids

Opportunistic Infection	Recommended Indications	Recommendations for Prevention
Patients with AIIRD requiring glucocorticoids		
Latent TB	• Patients treated with ≥15 mg PEQ/d for ≥28 d, but preferably before initiating glucocorticoid therapy • Screening for latent TB may be indicated in those treated with <15 mg PEQ/d with a history of alcohol abuse, smoking, and living with people with TB or in endemic countries • Screening for latent TB may be indicated before initiating pulse dose glucocorticoid therapy in those already receiving glucocorticoid therapy at baseline	• IGRA preferred over TST • Further recommendations are available from the US Preventive Services Task Force [125] and EULAR [54]
PJP	• Patients treated with ≥15 mg PEQ/d for ≥14 to 28 d • Prophylaxis may be indicated in patients with a history of PJP, those treated with lower doses of glucocorticoids if 1 or more additional risk factors for PJP are present (eg, solid-organ transplantation, acute lymphocytic leukemia, lymphopenia [< 600 lymphocytes/mm^3 or <300–350 CD4 cells/mm^3 before or during treatment with glucocorticoids], concomitant immunosuppressive medications, underlying pulmonary disease, older age), or individuals treated with glucocorticoid injection or pulse therapy	• TMP/SMX 40 mg/200 mg once daily or 80 mg/400 mg once daily or 3 times weekly • TMP/SMX 80 mg/400 mg 3 times weekly in patients with renal dysfunction (CrCl: 15–30 mL/min) • Higher doses (160 mg/800 mg) are not expected to provide added benefit but may increase the risk of adverse effects • Further recommendations are available from EULAR [54]
Cryptococcosis	Symptomatic patients treated with glucocorticoid therapy who are at risk of cryptococcosis	• Serum CrAg test
HZ	• Patients treated with glucocorticoid therapy, but preferably before initiating glucocorticoid therapy • Vaccination may be indicated in those with additional risk factors for HZ (eg, age, chronic comorbidities, or concomitant immunosuppressive medications)	• Vaccination with RZV (Shingrix, GlaxoSmithKline (GSK)) • Antiviral prophylaxis is not routinely recommended • Further recommendations are available from EULAR [54]
SHS	Patients treated with glucocorticoid therapy who were born or residing for more than 6 mo in endemic countries (eg, Asia, Oceania, Africa, South America, the Caribbean, and Mediterranean countries), but preferably before initiating glucocorticoid therapy	• Stool sample should be screened for ova and parasites in addition to serum IgG against *Strongyloides stercoralis* • Nonpharmacological preventive measures should be discussed to prevent *Strongyloides* infection (eg, avoid contact with fecal matter or sewage, wear protective clothing around soil) • Further recommendations are available from CATMAT [148]
Patients treated with glucocorticoid therapy for irAEs associated with CPIs		
Latent TB	Before initiating glucocorticoid therapy, but preferably before starting CPIs	• IGRA • Further recommendations are available from the NCCN [94]
PJP	Patients treated with ≥20 mg PEQ/d for ≥28 d	• TMP/SMX 80 mg/400 mg once daily or 160 mg/800 mg 3 times weekly, or if TMP/SMX intolerant, then • Atovaquone 1500 mg once daily, or • Dapsone 100 mg once daily, or • Pentamidine (aerosolized inhalation or intravenous)
Cryptococcosis	Symptomatic patients treated with glucocorticoid therapy who are at risk of cryptococcosis	• Serum CrAg test
HZ	Before initiating glucocorticoid therapy, but preferably before starting CPIs	• Vaccination with RZV (Shingrix) before initiating glucocorticoid therapy • Antiviral prophylaxis is determined by standard prevention protocols in specific hematologic malignancy populations or those receiving concomitant alemtuzumab • Further recommendations are available from the NCCN [94]
SHS	Before initiating glucocorticoid therapy, but preferably before starting CPIs	• Stool sample should be screened for ova and parasites in addition to serum IgG against *Strongyloides stercoralis* • Nonpharmacological preventive measures should be discussed to prevent *Strongyloides* infection (eg, avoid contact with fecal matter or sewage, wear protective clothing around soil)

Abbreviations: AIIRD, autoimmune inflammatory rheumatic disease(s); CATMAT, Committee to Advise on Tropical Medicine, and Travel; CrAg, cryptococcal antigen; CPI, checkpoint inhibitor; CrCl, creatinine clearance; EULAR, European Alliance of Associations for Rheumatology; HZ, herpes zoster; IgG, immunoglobulin G; IGRA, interferon-γ release assay; irAE, immune-related adverse event; NCCN, National Comprehensive Cancer Network; PEQ, prednisone equivalents; PJP, *Pneumocystis jirovecii* pneumonia; RZV, recombinant zoster vaccine; SHS, *Strongyloides stercoralis* hyperinfection syndrome; TB, *Mycobacterium tuberculosis*; TMP/SMX, trimethoprim/sulfamethoxazole; TST, tuberculin skin test.

efficacy extend to prophylactic treatments against OIs with concomitant glucocorticoids.

The incidence of fungal OIs is low in patients with AIIRD treated with glucocorticoids and does not warrant routine prophylaxis. Alternatively, prophylactic strategies for IA are predominantly limited to patients with hematologic malignancies and should follow NCCN recommendations [94]. Routine prophylaxis against cryptococcosis in patients receiving glucocorticoids is not recommended. However, serum cryptococcal antigen (CrAg) testing may be beneficial in detecting

cryptococcal antigenemia in symptomatic patients treated with glucocorticoids with concomitant lymphopenia [146]. However, the sensitivity of serum CrAg is unknown in this population.

The risk of herpes simplex virus or CMV infection in patients treated with glucocorticoids alone is not well established. Therefore, antiviral prophylaxis among those at risk is determined by standard prevention protocols in specific hematological malignancy populations or those receiving concomitant alemtuzumab [94]. Since multiple studies have shown an increased risk of HZ in patients taking glucocorticoids [72–75], patients with autoimmune, inflammatory, hematologic, or oncologic diseases treated with glucocorticoids should be vaccinated against HZ with recombinant zoster vaccine (Shingrix; GSK) ideally before the initiation of immunosuppressive medications [147]. Antiviral prophylaxis is not routinely recommended and should be deferred based on the primary immunodeficiency guideline and setting [54].

Glucocorticoids are a recognized risk factor for SHS. Case reports have documented SHS during COVID-19 treatment with dexamethasone [111]. While the minimum dose and duration required to reactivate *Strongyloides stercoralis* are unknown, Canadian guidelines recommend 20 mg or more PEQ/day for 2 or more weeks [148]. Screening with an ova and parasite test and serology or preemptive therapy with ivermectin before starting glucocorticoids is recommended in people born or residing in endemic countries for more than 6 months. The synergistic effect of glucocorticoids with other immunosuppressive therapies increases the risk for reactivation of Chagas disease in patients with AIIRD [89, 149]. Further prospective studies are needed to determine if serologic screening for *Trypanosoma cruzi* is warranted before treatment with glucocorticoids.

Descriptions of disparate risks for OIs in patients receiving glucocorticoids are lacking. However, Black and Hispanic patients with SLE had more persistent glucocorticoid use with higher doses than White individuals over a 12-month period (17 ± 33 and 17 ± 39 vs 14 ± 14 mg PEQ/mo, respectively) [150]. Rates of PJP prophylaxis were similar among racial and ethnic groups, but fewer Black and Hispanic persons received 1 or more vaccination than White persons (4% and 6% vs 10%, respectively). More evidence is needed to evaluate and mitigate barriers and facilitators contributing to inequities in preventive strategies to reduce the risk of OIs among patients treated with glucocorticoids.

CONCLUSIONS

The challenge of determining the glucocorticoid dose and duration that predispose patients to the risk of developing an OI remains elusive as studies are confounded by disease severity, limited details about glucocorticoid treatments, inconsistent periods for determining glucocorticoid exposure, and the definition and distribution of OIs. Collaboration and shared decision making across specialties involving patients should be utilized to discuss interventions to prevent acute infection or reactivation of OIs. Alternatively, limiting the glucocorticoid dose, duration, and intensity may help reduce the risk of OIs. The differential effects of various glucocorticoids on lymphocyte subpopulations must be accounted for in future studies to better quantify the risk of OIs attributable to glucocorticoids versus underlying comorbidities or other immunosuppressive medications.

The increase in neutrophils following treatment with glucocorticoids is multifactorial. Glucocorticoids blunt the inflammatory response by obstructing PMN recruitment and movement across the vascular endothelium, stimulating the release of immature neutrophils from the bone marrow into the bloodstream, and inhibiting apoptosis [11–14]. Glucocorticoids exert apoptogenic effects on eosinophils by diminishing the synthesis of IL-5 [16, 17] and reducing the number of circulating basophils. However, histamine content per basophil is not affected (notably, this effect of glucocorticoids makes it a potent therapy for allergic reactions) [18]. Glucocorticoids lead to increased circulating macrophages and monocytes due to fewer resident tissue macrophages and macrophage migration inhibition [22, 23]. Production of inflammatory mediators, including IL-1 and TNF, from macrophages and monocytes is decreased, although macrophages resist glucocorticoid-induced apoptosis [11, 12, 24–26]. While phagocytic function and phagocyte recruitment by macrophages are not impacted by glucocorticoids [27, 28], phagocytic uptake of apoptotic debris by macrophages may be upregulated, promoting the resolution of inflammation [29, 30]. Glucocorticoids impair the elimination of opsonized bacteria by macrophages of the reticuloendothelial system [31].

Following treatment with glucocorticoids, the number of circulating T cells is decreased due to migration back to bone marrow and secondary lymphoid tissues and glucocorticoid-associated apoptosis of both T_H cells and cytotoxic T cells [35–37]. The binding of the glucocorticoid receptor in T cells inhibits IL-2 production affecting T-cell activation [38]. In addition, glucocorticoids impair the activity of dendritic cells (the most efficient antigen-presenting cells, which stimulate T-cell responses) by blocking maturation and inducing apoptosis, resulting in diminished T-cell activity [39]. T_H cells, vital components of adaptive immunity, can differentiate into T_H1, T_H2, T_H17, or T-regulatory (Treg) cells [40]. T_H1 cells promote immunologic responses against intracellular pathogens residing in the phagocytic vesicles within cells, often macrophages, by releasing IFN-γ and IL-12 and activating effector T cells, NK cells, and macrophages [40, 41]. T_H2 cells express IL-4, IL-5, IL-10, and IL-13 to eliminate extracellular pathogens and activate B-cell–mediated antibody responses [44]. T_H17 secretes IL-17A and aids in defense against extracellular pathogens, particularly in mucosal and epithelial immunity [43].

Glucocorticoids trigger higher rates of apoptosis in T_H1 cells than in T_H2 and T_H17 cells and suppress cytokine production by T_H1 and T_H2 cells. Consequently, the immune response is shifted from T_H1-cell–mediated immunity to T_H2 humoral-mediated immunity [45].

Glucocorticoids decrease B-cell receptor signaling and TLR-7 signaling while increasing expression of IL-10 and B-lymphocyte–induced maturation protein 1 (Blimp1) [4, 46]. In addition, glucocorticoid administration leads to decreased concentration of immunoglobulins (Ig), impairing humoral immune response, and disrupts B-cell activating factor (BAFF) responsible for B-cell maturation, antibody production, and T-cell stimulation [47].

Alternatively, glucocorticoids promote inflammation resolution by enhancing apoptotic PMNs and secretion of anti-inflammatory cytokines, although wound healing is impaired as glucocorticoids limit collagen deposition, angiogenesis, and re-epithelialization.

Notes

Author contributions. D. B. C.: conceptualization (lead), writing—original draft (lead), writing—review and editing (lead). M. S.: writing—original draft (equal), writing—review and editing (equal). H. A.: writing—original draft (equal), writing—review and editing (equal). A. F. H.-M.: conceptualization (lead), writing—original draft (lead), writing—review and editing (lead).

Acknowledgments. The authors thank Ella Marushchenko and Alex Tokarev, PhD, from the Ella Maru Studio, for their design and creation of the figure illustrating the immunological impacts of glucocorticoids.

Financial support. The authors received no financial support for the research, authorship, and/or publication of this article.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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