

Glucocorticoids and invasive fungal infections

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Since the 1990s, opportunistic fungal infections have emerged as a substantial cause of morbidity and mortality in profoundly immunocompromised patients. Hypercortisolaemic patients, both those with endogenous Cushing's syndrome and, much more frequently, those receiving exogenous glucocorticoid therapy, are especially at risk of such infections. This vulnerability is attributed to the complex dysregulation of immunity caused by glucocorticoids. We critically review the spectrum and presentation of invasive fungal infections that arise in the setting of hypercortisolism, and the ways in which glucocorticoids contribute to their pathogenesis. A better knowledge of the interplay between glucocorticoid-induced immunosuppression and invasive fungal infections should assist in earlier recognition and treatment of such infections. Efforts to decrease the intensity of glucocorticoid therapy should help to improve outcomes of opportunistic fungal infections.

Introduction

Cushing's syndrome is a metabolic condition featuring persistently excessive plasma cortisol levels (normal morning values: 138–607 nmol/L). Its origins fall into two categories. First, endogenous Cushing's syndrome is caused primarily by pituitary adenoma (Cushing's disease), and, less commonly, by hormonally active adrenal neoplasms or ectopic production of adrenocorticotrophic hormone (ACTH). Second, the far more common exogenous or iatrogenic Cushing's syndrome is seen mainly with long-term glucocorticoid therapy at supraphysiological doses, for inflammatory, autoimmune, and neoplastic conditions.¹

Endogenous and iatrogenic hypercortisolism have long been recognised to predispose patients to invasive fungal infections (IFIs).^{2–4} Although supraphysiological glucocorticoid levels undoubtedly result in increased susceptibility to IFIs, the prevalence and attributed mortality of such infections with glucocorticoid excess, and the minimum required glucocorticoid exposure for IFI development, are difficult to quantify. This difficulty is further complicated by the frequent comorbidities and additional risk factors for IFIs in affected patients. Herein we review the spectrum and presentation of IFIs in patients with hypercortisolism and how glucocorticoids contribute to their pathogenesis.

Components of immunity that control fungal infections

In immunocompetent hosts, there are two lines of defence against inhaled moulds. First, resident lung macrophages facilitate phagocytosis and, primarily, nonoxidative killing of conidia (asexual spores).^{5,6} These cells have a very

efficient phagocytic capacity, phagocytosing more than 10^8 conidia daily.⁵ Still, some conidia escape phagocytosis, germinate to hyphae, and establish an invasive infection. Then, neutrophils are chemotactically attracted and attach to the hyphae, which are subsequently destroyed by the oxidative cytotoxic mechanisms of polymorphonuclear leucocytes (PMNs).^{5,6}

The monocytes and macrophages, PMNs, and T lymphocytes also control yeast infections.^{6–8} Their protective mechanisms comprise phagocytosis and intracellular killing by oxidative and oxygen-independent processes and extracellular growth inhibition or destruction by cytokines.^{6–8} Unlike monocytes and neutrophils, which are critical in resistance to early-stage yeast infections, more differentiated macrophages, which are activated by cytokines secreted by T lymphocytes, participate in acquired host resistance to yeasts.⁸

Effects of glucocorticoids on immunity

Glucocorticoids exert many complex quantitative and qualitative immunosuppressive effects that induce cellular immunodeficiency, increasing host susceptibility to IFIs. These effects have been shown in studies both at cortisol levels typically encountered in patients with endogenous Cushing's syndrome and at glucocorticoid levels achieved in patients receiving pharmacological concentrations of glucocorticoids.^{9–18} The mechanism by which glucocorticoids exert regulatory effects is transcriptional

Search strategy

The MEDLINE and PubMed databases (from 1966 to February, 2003) and abstracts from major infectious diseases meetings held from 1992 to 2002 were searched for published reports pertaining to the association between glucocorticoid-induced immunosuppression and IFIs. Articles describing the effects of glucocorticoids on the host's immune responses and the spectrum and clinical presentation of IFIs with hypercortisolism were reviewed. Studies were selected based on significance of data (as determined by citation frequency by subsequent publications in the specialty) and originality. Additionally, review papers written by thought-leaders in mycology were included in our search.

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Panel 1: Glucocorticoid-induced effects that result in increased susceptibility to invasive fungal infections

Effects on host

Lymphocytes

- Reversible lymphopenia, CD4 depletion (>50% reduction)^{10,13}
- Decreased proliferation and migration of lymphocytes^{5,11–13,26}
- Impaired delayed-type hypersensitivity^{14,27}
- Impaired natural killer cell cytotoxicity¹⁵
- Decreased lymphokine production (interleukin-2, TNF α , interleukin-12, interferon γ)^{9,28–30}
- Th1/Th2 dysregulation of T-helper cells^{9,28–30} (decreased Th1 and increased Th2 cytokine production)
- Impaired phagocyte effector cell function and cellular immune response^{5,9–13,28}

Neutrophils

- Impaired phagocytosis, degranulation, and oxidative burst^{12,16}
- Reduced cytokine production¹⁶
- Impaired formation of nitric oxide^{22,36}
- Defective adherence to endothelium, extravasation, chemotaxis^{16,19–21}
- Inhibition of apoptosis³¹

Monocytes/macrophages

- Reversible monocytopenia (>40% reduction)²⁵
- Impaired phagocytosis and oxidative killing^{13,17,25,34,35}
- Decreased chemotaxis and migration to sites of inflammation^{13,17,25,34,35}
- Impaired formation of nitric oxide^{22,36}
- Impaired maturation of monocytes to macrophages^{13,17,25,34,35}
- Inhibition of pro-inflammatory cytokine production (interleukin-1, interleukin-6, TNF α)^{23,24,30,37,38,90}

Other immune effector cells

- Decreased counts for alveolar dendritic cells, central nervous system microglial cells, and Langerhans' epidermal cells^{39–41}
- Impaired antigen-presenting capacity of dendritic and Langerhans' cells (decreased expression of MHC II on their surface)^{39,40}
- Defective microglial cell-killing capacity (impaired nitric oxide formation)⁴¹

Other effects

- Inhibition of prostaglandin production²
- Inhibition of host's inflammatory response²
- Attenuation of clinical (ie, fever) and radiological signs of infection^{2,45}
- Potential delay of diagnosis^{2,45}

Effects on fungi

Aspergillus species

- In vitro increased growth rates of *A fumigatus* and *A flavus*⁶⁷

Candida species

- Increased colonisation rates of the oral mucosa and gastrointestinal tract of mice by *Candida albicans* and increased bloodstream translocation from the gastrointestinal tract^{92,93}
- Increased adherence capacity to mucosal cells⁹¹

upregulation or repression of specific genes. First, glucocorticoids bind to and activate their cognate intracellular receptors. Then, after translocation to the nucleus, the glucocorticoid-receptor complex modulates transcription through binding to specific elements within target-gene promoter regions. Particularly, the transcription factor nuclear factor κ B (NF κ B) has been implicated in multiple gene induction as part of the

immune and inflammatory response processes. There is mounting evidence that several immunosuppressive and anti-inflammatory effects of glucocorticoids may be exerted through inhibition of NF κ B and other transcription factors.^{19–24}

Glucocorticoids affect virtually every cell type involved in immune and inflammatory response (panel 1). Glucocorticoids affect the number of mononuclear leukocytes, causing reversible lymphopenia and monocytopenia.^{13,25} They rapidly redistribute lymphocytes from the circulation, depleting circulating CD4+ and, to a lesser extent, CD8+ T lymphocytes.¹³ Greater than 50% reduction in circulating lymphocytes has been reported 4 h after injection of 400 mg of hydrocortisone, which lasts for 24 h.¹³ Higher doses and longer durations of glucocorticoid administration do not affect the extent of lymphopenia; nevertheless, lymphopenia persists throughout glucocorticoid exposure.¹³ Monocytes are reduced by more than 40% after administration of glucocorticoid, an effect that persists for 24 h.²⁵ However, glucocorticoids mainly affect cellular immunity qualitatively through functional impairment of many effector immune cells, such as T lymphocytes, PMNs, and monocytes and macrophages.

Glucocorticoids potently inhibit T-lymphocyte activation, decreasing T-lymphocyte proliferation, lymphokine production, and migration.^{5,11–13,26} Delayed-type hypersensitivity is severely impaired, and anergy is common.¹⁴ For example, tuberculin skin test results are frequently false-negative in patients with tuberculosis receiving glucocorticoids.²⁷ Natural-killer-cell cytotoxicity is also hindered.¹⁵ Glucocorticoids also cause Th1/Th2 dysregulation of T-helper cells by favouring a Th2-predominant cytokine response, that causes suppression of phagocyte effector-cell function and leads to poor outcomes of fungal infections.^{9,28} Glucocorticoids decrease secretion of interleukin-2, interleukin-12, tumour necrosis factor α (TNF α), and interferon γ , and increase that of interleukin-4, interleukin-5, and interleukin-10.^{28–30} Although the exact mechanisms leading to this cytokine dysregulation have not been entirely delineated, data showing that glucocorticoids inhibit NF κ B and activator protein 1 (AP1), the principal mediators of interleukin-1 transcriptional activation in monocytes and macrophages, seem to be important.^{29,30}

Glucocorticoids also suppress several PMN functions, such as antibody-dependent cytotoxicity, adherence to vascular endothelium, extravasation, phagocytosis, oxidative burst and free radical generation, degranulation, nitric oxide release, cytokine production, and chemotaxis.^{12,16} Impaired migration to inflamed sites is believed to result from reduced endothelial activator and macrophage chemoattractant release following glucocorticoid administration.¹⁶ Glucocorticoid-induced impairment of NF- κ B has been implicated in dysfunctional migration of PMNs through inhibition of the expression of chemoattractants like cytokine-induced neutrophil chemoattractant/growth-related oncogene (CINC/gro).¹⁹ Moreover, by suppressing NF- κ B, glucocorticoids may inhibit expression of adhesion molecules like E-selectins, CD18, and intracellular adhesion molecule (ICAM)-1 on the endothelial surface.^{20,21} Furthermore, recent studies in human beings and animal models showed that annexin-1, an endogenous glucocorticoid-induced protein also called lipocortin-1 (a pivotal mediator of neutrophil activation, transmigration, and phagocytosis), might account for some functional defects of PMNs, including extravasation and oxidative killing.¹⁶ Finally, by inhibiting PMN

apoptosis, glucocorticoids prolong the survival of dysfunctional neutrophils.³¹ These anti-apoptotic effects are also thought to be exerted through modulation of the expression of several genes, including *BCL2* and *NFκB*.³² Hence, there is a discrepancy between the leucocytosis seen in the blood of glucocorticoid-treated patients and these neutrophils' capability to mount an efficient immune response. This PMN-function defect may be somewhat reversible. Roilides and colleagues³³ demonstrated that interferon γ or granulocyte-colony-stimulating factor (G-CSF), or both, prevented suppression of PMN oxidative damage of *Aspergillus fumigatus* hyphae in the presence of glucocorticoids.

The monocyte-macrophage axis is also impaired in hypercortisolaemic patients, because glucocorticoids suppress phagocytosis, superoxide production, and oxidative killing by these cells.^{13,17,25,34} Notably, by promoting the stabilisation of lysosomal membranes, glucocorticoids prevent phagolysosomal fusion in macrophages during phagocytosis. This has been shown to be reversed with interferon γ .³⁵ Moreover, glucocorticoids cause dose-dependent inhibition of nitric oxide production by macrophages.³⁶ This is caused by glucocorticoid-induced downregulation of *NFκB*, resulting in decreased expression of a gene that encodes for inflammation-inducible nitric oxide synthase.³⁶ Dandona and co-workers²² further showed that glucocorticoid-induced *NFκB* inhibition accounts for diminished generation of reactive oxygen species by mononuclear cells and PMNs, via suppression of the NADPH oxidase p47 subunit.²² Furthermore, glucocorticoids inhibit monocytes' maturation to macrophages and impair their chemotaxis and migration to inflamed sites. Glucocorticoids also hinder macrophages' ability to clear antibody-coated particles and decrease their secretion of proinflammatory cytokines like interleukin-1, interleukin-6, and *TNFα*.^{13,17,25,34} This defect in cytokine secretion also seems to be based on inhibition of assorted transcription factors.^{23,24,30} Moreover, glucocorticoids downregulate interleukin-1-induced expression of the *IL6* (interleukin-6) and *IL8* (interleukin-8) genes by inhibition of *NFκB*.^{23,24} Granulocyte-macrophage (GM)-CSF can prevent glucocorticoid-induced suppression of cytokine production by bronchoalveolar macrophages after challenge with *A fumigatus* conidia.³⁷ This in-vitro observation has been confirmed in vivo in mice.³⁸ Specifically, GM-CSF prevented dexamethasone-induced and cortisone acetate-induced suppression of the production of the pro-inflammatory cytokines interleukin-1 α and *TNFα* and the chemotactic chemokine macrophage-inflammatory-protein-1 α by bronchoalveolar macrophages in response to *A fumigatus* conidia.³⁸ Finally, glucocorticoids decrease the absolute epidermal Langerhans' and alveolar dendritic cell count and hinder their antigen-presenting capacity by decreasing expression of MHC II molecules on their surface.^{39,40} They also reduce the microglial cell count in the CNS and negatively affect their function by inhibiting nitric oxide formation.⁴¹

Not all glucocorticoid compounds have equal anti-inflammatory potencies.⁴² Likewise, different glucocorticoid preparations have differential effects on cellular immunity.^{9,11} Such differences might be due to differing interaction between transcriptionally active complexes of glucocorticoid receptors with each glucocorticoid compound and *NFκB*.⁹ For example, Fauci¹⁰ showed that although hydrocortisone, prednisone, and dexamethasone (administered in equivalent pharmacological doses) similarly suppressed lymphocyte counts in human beings, dexamethasone caused much

more marked functional defects in lymphocyte-mediated cytotoxicity than did the other two compounds.¹⁰ Methylprednisolone has been reported to have a greater suppressive effect on lymphocyte proliferation and cytotoxicity than does dexamethasone, although methylprednisolone is less potent.¹¹ Furthermore, different glucocorticoids have been implicated in differing suppression of cytokine secretion by lymphocytes.⁹ Again, dexamethasone inhibited Th1 (interleukin-2, *TNFα*) and pro-inflammatory cytokine (interleukin-6) secretion more than did prednisone.⁹

Nevertheless, not all glucocorticoid-induced immunosuppression variables are fully elucidated. Glucocorticoid-receptor gene mutations or polymorphisms might account for differences in patients' responses to glucocorticoids.^{43,44} For instance, patients with glucocorticoid resistance have specific germline mutations in the glucocorticoid-receptor gene.⁴³ Other evidence comes from studies in patients with glucocorticoid-resistant asthma, in which the glucocorticoid-receptor β variant has been proposed to affect glucocorticoid sensitivity.⁴³ Other mutations could be associated with increased glucocorticoid sensitivity in vivo.⁴⁴ Specifically, carriers of the N363S polymorphism in the glucocorticoid-receptor gene appear to have increased sensitivity to the suppressive effects of dexamethasone on lymphocyte proliferation.⁴⁴ Whether additional genetic polymorphisms in this gene account for significant genetic differences in the extent of glucocorticoid-induced immunosuppression remains unknown.

Invasive fungal infections in endogenous Cushing's syndrome

Compared with patients with iatrogenic Cushing's syndrome, fewer IFIs arise in those with endogenous Cushing's syndrome. However, the endogenous syndrome typically results in much higher plasma cortisol levels than does iatrogenic glucocorticoid therapy.² Thus, whenever IFIs arise in endogenous Cushing's syndrome, they carry a high fatality rate if left undiagnosed due to substantial net immunosuppression.^{2,45} Dimopoulos and colleagues⁴⁶ reported a high incidence of severe IFIs in patients with small-cell lung carcinoma and paraneoplastic Cushing's syndrome soon after initiation of

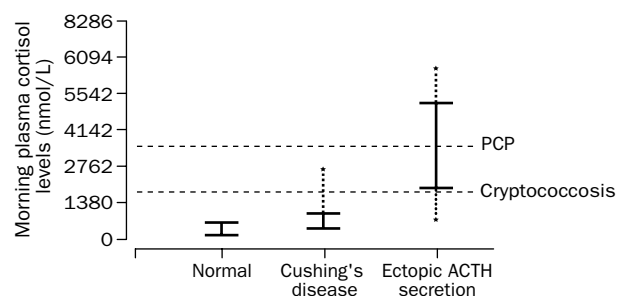


Figure 1: Morning plasma cortisol levels in healthy people, in Cushing's disease,* and in endogenous hypercortisolism†

*Pituitary ACTH-dependent hypercortisolism. †Due to ectopic production of ACTH. Solid bars show the range of typical values, dotted vertical lines show the extension of this range by outlier values occasionally recorded in clinical practice. As shown, Cushing's disease patients can occasionally have normal levels of plasma cortisol. Overlap can exist between these levels in Cushing's disease and ectopic ACTH production. The highest reported plasma cortisol levels in ectopic ACTH Cushing's syndrome are also shown, but some patients might have even higher levels. Horizontal dotted lines show approximate cortisol thresholds for clinical emergence of cryptococcosis and PCP. Based on data reported by Graham and Tucker.²

Panel 2: Opportunistic fungal infections reported in endogenous Cushing's syndrome

Superficial fungal infections

Oropharyngeal candidiasis
Oesophageal candidiasis
Cutaneous candidiasis
Candida onychomycosis
Tinea versicolor
Cutaneous alternariosis
Cutaneous sporotrichosis
Chromoblastomycosis
Dermatophytic infections

IFIs

Cryptococcosis
Pneumocystis carinii pneumonia, pneumocystosis
Invasive aspergillosis
Candidaemia
Invasive candidiasis
Histoplasmosis
Scedosporium arthritis, osteomyelitis

chemotherapy, frequently causing clinical deterioration and death before the tumour responded to chemotherapy.

Among the endogenous Cushing's syndrome subtypes, IFIs are much more prevalent with ectopic ACTH production, probably due to extremely high plasma cortisol concentrations (morning levels may exceed 5524 nmol/L); such infections are less frequent in Cushing's disease (typical morning cortisol levels: 414–967 nmol/L; figure 1).² Thus, although Cushing's disease represents 70% of endogenous Cushing's syndrome cases, it represents only 9% of endogenous Cushing's syndrome-associated opportunistic infections (including IFIs).^{1,2}

Because endogenous Cushing's syndrome can now be diagnosed early, IFIs are infrequent. Therefore, an IFI is unlikely to be the presenting feature of otherwise silent endogenous hypercortisolism. However, when a severe opportunistic fungal infection arises with hypokalaemia, hyperglycaemia, hypertension, and other clinical features of hypercortisolism, endogenous Cushing's syndrome should be considered.

Several mucosal and invasive fungal infections have been reported in endogenous Cushing's syndrome (panel 2).⁴⁷ However, the preponderant IFIs are invasive aspergillosis, cryptococcosis, and *Pneumocystis carinii* pneumonia (PCP).^{2,45} The extent of immunosuppression, risk of acquisition, and type of opportunistic infection depend on the degree of excess cortisol. For instance, Graham and Tucker² reported different cortisol-level thresholds for each infection in ten patients with endogenous Cushing's syndrome who developed cryptococcosis and pneumocystosis. Particularly, cryptococcosis could occur with morning plasma cortisol levels of less than 1933 nmol/L. However, the PCP threshold was much higher, as morning cortisol levels above 3342 nmol/L were associated with pneumocystosis (figure 1). Others have suggested that prophylactic chemotherapy for PCP should be initiated when cortisol levels exceed 2486 nmol/L.⁴⁵

Sarlis and co-workers⁴⁸ reported that glucocorticoid-excess indices besides plasma cortisol levels, such as high daily urinary cortisol and urinary 17-hydroxysteroid per 1 g creatinine excretion ratios, predicted severe infections, including candidaemia, in patients with ectopic production of adrenocorticotropic hormone (ACTH).⁴⁸

Nonetheless, more studies are needed to correlate plasma cortisol levels and other glucocorticoid-excess indices with likelihood of occurrence and outcome of different IFIs in patients with endogenous Cushing's syndrome.

Fortunately, immunosuppression associated with endogenous Cushing's syndrome appears reversible with treatment of the underlying condition.^{2,18} Prompt correction of hypercortisolism with pharmacology, surgery, or both, and aggressive antifungal treatment, usually resolves infections and greatly reduces risk of recurrence. Therefore, early diagnosis of endogenous Cushing's syndrome with prompt initiation of treatment to reduce cortisol levels is recommended.

Invasive fungal infections after exogenous glucocorticoid therapy

Systemic glucocorticoids are extensively used in bone marrow transplantation, solid organ transplantation, and treatment of haematological malignancies (eg, leukaemia, lymphoma, multiple myeloma), vascular-collagen disorders (eg, systemic lupus erythematosus [SLE], rheumatoid arthritis), and chronic pulmonary conditions (eg, asthma, chronic obstructive pulmonary disease, sarcoidosis; figure 2). This widespread use of glucocorticoids has expanded the population of profoundly immunocompromised patients and array of IFIs (panel 3).

Different IFI thresholds seem to depend on both the glucocorticoid therapy intensity and relative virulence of the offending fungus. More specifically, IFIs associated with glucocorticoid therapy depend on the administration route, dose, potency, and duration of treatment. Additionally, the host's underlying disease state, which dictates dosage and duration of treatment, largely contributes to IFI variability in clinical practice. Inhaled glucocorticoids have a lower potential for causing IFIs than do systemic glucocorticoids. Nevertheless, invasive aspergillosis has been reported with high-potency inhaled glucocorticoids.^{49,50} Moreover, there is mounting evidence that high doses and long durations of systemic glucocorticoid therapy correlate with high risk and poor outcomes of IFIs.^{3,51–55} Several studies have shown that risk of opportunistic infection is lower when glucocorticoids are administered on alternate days rather than a daily schedule.^{14,56,57} Dale et al⁵⁷ postulated that the intermittently normal leucocyte kinetics seen with alternate-day glucocorticoid therapy might account for reduced susceptibility to such infections. Vincenti and colleagues⁵⁸ showed that rapid tapering of glucocorticoids in renal transplant recipients increased survival and markedly reduced infectious complications, including PCP. Moreover, the introduction of more selective immunosuppressive agents—such as cyclosporin and tacrolimus—in solid organ transplant recipients means that glucocorticoid doses needed to maintain graft function could be reduced, producing fewer infectious complications.^{59,60} Nevertheless, these differences between the older solid organ transplant recipients in older studies who received glucocorticoids as primary immunosuppressive therapy and those who received such selective agents could partly be explained by differences other than the type of immunosuppressive therapy. Furthermore, restriction of glucocorticoid administration to less than 21 days might reduce infectious complications, since prolonged suppression of T-lymphocyte-mediated cellular immunity has been suggested to be essential for opportunistic infections.⁶¹ Consequently, use of the lowest possible glucocorticoid dose for the shortest possible time should decrease the risk of IFIs. Research is needed to

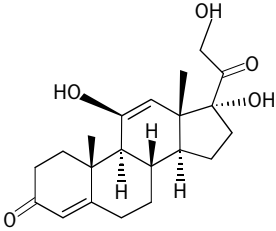
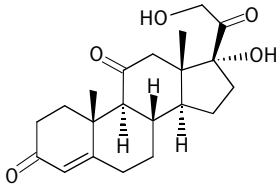
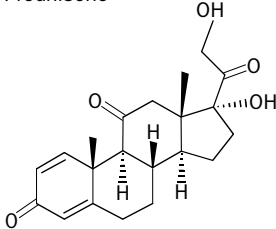
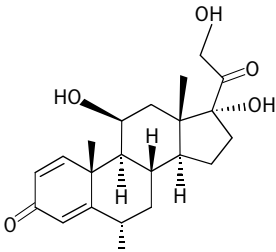
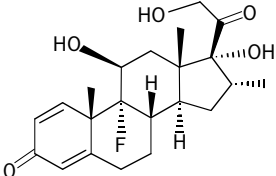
	Anti-inflammatory potency*	Equivalent dose*	Common therapeutic indications
Hydrocortisone (cortisol)	1	20 mg	Addison's disease, asthma, VCDs, allergic states, Bell's palsy, septic shock
			
Cortisone acetate	0.8	25 mg	Asthma, VCDs, leukaemias, nephrotic syndrome
			
Prednisone	4	5 mg	COPD, asthma, VCDs, BMT, SOT, hypercalcaemia, Addison's disease, Guillain-Barre syndrome, multiple sclerosis, autoimmune hepatitis, nephropathies, PCP
			
Methylprednisolone	5	4 mg	ARDS, COPD, VCDs, sarcoidosis, allergic states, asthma, shock, ulcerative colitis, Crohn's disease, BMT, SOT, GVHD, leukaemias, lymphomas, aplastic anaemia, haemolysis, nephropathies
			
Dexamethasone	25	0.75 mg	Leukaemias, lymphomas, multiple myeloma, meningitis, cerebral oedema, allergic states, asthma, ARDS, VCDs, pemphigus vulgaris, nephrotic syndrome, hypotension chemotherapy-induced emesis, PCP, idiopathic thrombocytopenic purpura
			

Figure 2: **Characteristics of common corticosteroid preparations**

ARDS=acute respiratory distress syndrome. COPD=chronic obstructive pulmonary disease. VCD=vascular-collagen disorders. BMT=bone-marrow transplantation. SOT=solid organ transplantation. GVHD=graft-versus-host disease. *Modified from Hardman JG, Gilman AG, Limbard LE. *Goodman and Gilman's the pharmacological basis of therapeutics*. 10th edn. McGraw-Hill Companies, 2001.

correlate the preceding cumulative dose and glucocorticoid therapy duration with risk of IFI acquisition or reactivation. This knowledge should aid prophylaxis and earlier recognition of IFIs. Finally, the dissipation of the relative infectious risk of IFIs after glucocorticoid tapering has not been assessed.

Besides the heightened risk of IFIs in glucocorticoid-treated patients, recognition of such infections may be delayed, since the anti-inflammatory properties of glucocorticoids usually blunt the signs and symptoms of IFI. For example, due to blockade of prostaglandin E₂ synthesis, which normally increases the set-point

Panel 3: Invasive fungal infections subsequent to exogenous glucocorticoid therapy, and associated clinical settings

Invasive aspergillosis

Acute leukaemia, allogeneic BMT and SOT, SLE, multiple myeloma, AIDS^{3,51-55,72-80}

Zygomycosis

Acute leukaemia, allogeneic BMT, liver and pancreas-kidney transplantation^{83,84}

Fusariosis

Acute leukaemia, allogeneic BMT and SOT^{71,73,74,77,85-87}

Scedosporiosis/other infections by rare moulds

Allogeneic BMT^{71,73,74,89}

Candidaemia-invasive candidiasis

Cancer, allogeneic BMT and liver transplantation, SLE^{3,53,77,95-100,103,105}

Cryptococcosis

Cancer, allogeneic BMT, SOT, sarcoidosis^{3,4,77,107,108,111,112}

Trichosporonosis

Cancer¹¹⁵

PCP

Brain tumours, chronic lymphocytic leukaemia, lymphoma, solid tumours, allogeneic BMT, liver transplantation, SLE, Wegener's granulomatosis, ARDS^{7116-121,123-126,128}

Endemic mycoses

SLE, cancer¹³⁰⁻¹³²

ARDS=acute respiratory distress syndrome. BMT= bone-marrow transplantation. SOT=solid organ transplantation. SLE=systemic lupus erythematosus.

temperature in the hypothalamus, hypercortisolaemic patients may not have raised temperatures.² Clinical and radiological signs of inflammation can also be ambiguous, and mental status alteration secondary to IFIs may be falsely attributed to glucocorticoids.² Therefore, IFIs should be anticipated in such patients.

In addition to potentially delaying diagnosis, hypercortisolism may negatively affect treatment of IFIs. For instance, O'Day and colleagues⁶² described an inverse relationship between topical corneal administration of glucocorticoid and the efficacy of several antifungals in a rabbit model of *Candida* keratitis. Additionally, Graybill and co-workers⁶³ reported hindrance of G-CSF activity in mice with invasive aspergillosis with glucocorticoid administration for immunosuppression.⁶³ G-CSF normally raises neutrophil counts; however, the increased dysfunctional neutrophils in these mice failed to kill hyphae, causing lung-abscess formation. Nevertheless, other investigators did not confirm this observation.⁶⁴

Furthermore, antifungals are known to be less effective in patients with neutropenia, and restoration of their efficacy depends on neutrophil recovery.⁶⁵ Since neutrophils are defective in hypercortisolism, glucocorticoids may hinder the efficacy of antifungals. In fact, neutropenia plus high cumulative glucocorticoid administration is associated with worse IFI outcomes. For example, Nucci and colleagues⁶⁶ recently reported that among patients with haematological malignancies and fusariosis, the mortality rate was 100% in those who had neutropenia while undergoing glucocorticoid administration and 70% in those with glucocorticoid exposure alone. Therefore, rapid glucocorticoid tapering plus measures to abrogate neutropenia in patients with IFIs should be attempted to improve therapeutic responses.

Invasive fungal infections caused by moulds

As mentioned, both lines of defence against invasive mould infections (macrophages and PMNs) are defective following glucocorticoid therapy, rendering glucocorticoid-treated patients at high risk for such infections.^{13,16,17,29} Glucocorticoids' primary role in predisposing to such infections is most likely impairment of macrophage anticonidial activity.^{5,35}

Invasive aspergillosis

Besides the immune dysfunction that contributes to invasive aspergillosis, glucocorticoids can induce alterations in the biology of *Aspergillus* species. Ng and colleagues⁶⁷ showed increased growth of *A fumigatus* and *A flavus* on in-vitro exposure to pharmacological doses of hydrocortisone, suggesting that glucocorticoids enhance the fungus' fitness to cause disease.

Invasive aspergillosis is the most common invasive mould infection associated with glucocorticoids.^{5,68,69} There are distinct differences between the histopathological features of pulmonary invasive aspergillosis in glucocorticoid-induced immunosuppression and invasive aspergillosis caused by neutropenia.⁷⁰ Specifically, pulmonary lesions in glucocorticoid-treated rabbits comprise mainly neutrophilic and monocytic infiltrates, inflammatory necrosis, scant intra-alveolar haemorrhaging, and a paucity of hyphae and angioinvasion.⁷⁰ However, coagulative necrosis, intra-alveolar haemorrhaging, scant mononuclear inflammatory infiltrates, and a higher invading hyphae burden are noted in granulocytopenic animals.⁷⁰

Perhaps the most striking and well-studied association between glucocorticoids and invasive aspergillosis in man arises in allogeneic bone-marrow transplantation. Invasive aspergillosis is now the most common cause of infectious death in the late post-transplant period, accounting for 10% of these deaths.^{5,51-53,68,69,71,72} High cumulative doses of glucocorticoid administered for prophylaxis or treatment of graft-versus-host-disease are associated with both risk of acquisition and poor outcome of invasive aspergillosis.^{3,4, 51-53,55,71-74}

In an analysis of 331 recipients of allogeneic bone-marrow transplants, use of high-dose prednisone (0.5–1.0 mg/kg per day) for graft-versus-host-disease prophylaxis was the most important risk factor for IFIs, including invasive aspergillosis—this treatment increased such infections sixfold compared with regimens with low-dose prednisone (0.25 mg/kg per day).³ Wald and co-workers⁵¹ showed that a prednisolone dose of greater than 1 mg/kg per day administered over 7 or more days before onset of invasive aspergillosis increased the risk of late acquisition of this infection threefold in allogeneic bone-marrow transplant recipients, compared with those who did not undergo glucocorticoid treatment. Likewise, Marr and colleagues⁵⁵ showed that glucocorticoids administered in the late post-bone-marrow-transplant period increase the risk of aspergillosis dose-dependently. Specifically, doses of less than 1.9 mg/kg per day, 1.9–3.0 mg/kg per day, and greater than 3 mg/kg per day were associated with risks of 5%, 10%, and 14%, respectively.⁵⁵ Furthermore, Ribaud and co-workers⁵² found that the risk of death was higher (60-day survival rate of 20%) in allogeneic bone-marrow transplant recipients with invasive aspergillosis who received a cumulative prednisolone dose of greater than 7 mg/kg during the week preceding onset of the infection, versus similar patients who received a cumulative prednisolone dose of 7 mg/kg or less (60-day survival rate of 88%).

Such findings are noted in other patients receiving intense glucocorticoid therapy, such as solid-organ transplant recipients and patients with vascular-collagen disorders and AIDS.^{54,75-78} Gustafson and colleagues⁵⁴ showed that a daily prednisolone dose of 1 mg/kg is a critical risk factor for invasive aspergillosis in renal transplant recipients. Likewise, preoperative administration of glucocorticoid and the total number of glucocorticoid boluses used to control rejection immediately after liver, heart, and lung transplantation were found to predispose patients to invasive aspergillosis.⁷⁵⁻⁷⁷ However, no study results correlating the exact glucocorticoid dose and duration of treatment with the risk for invasive aspergillosis in these populations have been published. Moreover, invasive aspergillosis is a known complication and common cause of infectious death in patients with SLE, accounting for 15% of deaths in a recent Brazilian autopsy study.⁷⁸ Patients with multiple myeloma treated with pulse dexamethasone are also at high risk of invasive aspergillosis.⁷⁹ In patients with AIDS, glucocorticoids are a risk factor in many of those with invasive aspergillosis.⁸⁰ Use of high-potency inhaled glucocorticoids for treatment of asthma and chronic obstructive pulmonary disease has been implicated in isolated cases of aspergillosis,^{49,50,81} whereas it has been reported that asthmatics receiving chronic treatment with glucocorticoids are at further risk for aspergillosis of the CNS.⁸²

Zygomycosis

The immune dysfunction and hyperglycaemic state induced by glucocorticoids account for the predilection for IFIs caused by *Mucorales* moulds. Glucocorticoid therapy is a well recognised risk factor for zygomycosis in cancer patients and solid-organ transplant recipients.^{83,84} A cumulative prednisone dose of greater than 600 mg, given during the month before onset of infection, predisposes cancer patients to zygomycosis.⁸³ Unlike rhinocerebral zygomycosis, which is typically seen with ketoacidosis, pulmonary zygomycosis arises most frequently in cancer patients, suggesting host-specific differences in phenotypic expression of *Zygomycetes* infections. Furthermore, Jimenez and colleagues⁸⁴ reported that all patients in their investigation who developed zygomycosis after liver or pancreas-kidney transplantation had previously received a total methylprednisone dose of 2-7 g.

Fusariosis and rare moulds

Glucocorticoids are associated with the development of fusariosis, especially in leukaemic patients and allogeneic bone-marrow and solid-organ transplant recipients.^{65,66,73,74,77,85,86} The drugs are also associated with poor fusariosis outcome; a multicentre study showed 70% mortality rate for fusariosis in haematological cancer patients receiving glucocorticoids and 33% rate in patients not receiving glucocorticoids.⁶⁶ However, host-specific differences do exist. *Fusarium* infections in solid-organ transplant recipients tend to remain localised and have a better outcome than do infections in allogeneic bone-marrow transplant recipients with graft-versus-host disease, which are characteristically disseminated and more fatal.⁸⁷

Other rare moulds, including *Scedosporium*, *Acremonium*, *Cladosporium*, *Alternaria*, *Curvularia*, and *Bipolaris* species, may also cause IFIs after glucocorticoid therapy.^{85,86,88} In fact, attention has been drawn to the increasing incidence of post-engraftment IFIs by these moulds in allogeneic bone-marrow transplant recipients.^{71,89} However, no assessments have been made of glucocorticoids' exact effect on the pathogenesis of IFIs by these moulds.

Invasive fungal infections caused by yeasts

As previously mentioned, all the immunity components responsible for controlling yeast infections (monocytes and macrophages, PMNs, and T lymphocytes) are dysfunctional after glucocorticoid therapy.^{13,16,17,29,35} Hence, glucocorticoid-treated patients are susceptible to invasive yeast infections.

Candidaemia and invasive candidiasis

Macrophages and PMNs (which are both defective after glucocorticoid use) are fundamental to the control of invasive candidiasis.^{7,8} Heidenreich and colleagues⁹⁰ showed that glucocorticoids principally affect the capacity of monocytes to control extracellular growth of *Candida* species by inhibition of TNF α secretion. Furthermore, glucocorticoid-induced augmentation of the biological fitness of *Candida* spp is possible. For example, glucocorticoids enhance adhesion of *Candida* spp to epithelial cells.⁹¹ Studies in mice have shown that glucocorticoids increase both the *Candida albicans* burden in the gastrointestinal tract and, indirectly, frequency of *C albicans* translocation from the gastrointestinal tract to the bloodstream.^{92,93} Moreover, further investigation is merited to find out whether the glucocorticoid-binding protein identified on the surface of *C albicans* enhances the fungus's virulence.⁹⁴

Glucocorticoids have long been recognised as a risk factor for candidaemia and invasive candidiasis.⁹⁵⁻⁹⁹ They predispose patients with cancer to candidaemia whether they have had previous antifungal prophylaxis or not,⁹⁵⁻⁹⁹ although, in one investigation, breakthrough candidiasis was more frequently associated with glucocorticoids (53%) than was de novo candidaemia (23%).¹⁰⁰ The association of glucocorticoids with candidaemia has been shown for *C albicans* and non-*albicans* *Candida* species.⁹⁶⁻⁹⁹ Furthermore, glucocorticoids can cause predisposition to candidaemia in other populations, including patients undergoing surgery,¹⁰¹ those with acute renal failure dependent on haemodialysis,¹⁰² and those with SLE.¹⁰³ In fact, Hellmann and colleagues¹⁰³ showed that invasive candidiasis is the most common deep-seated fungal infection in the latter group of patients. Furthermore, Botas and co-workers¹⁰⁴ reported that preterm neonates receiving glucocorticoids for hypotension were 7.5 times more likely to develop invasive candidiasis compared with those who were not receiving glucocorticoids.

Several studies have also shown that allogeneic bone-marrow transplant recipients receiving glucocorticoids are at risk for invasive candidaemia.^{3,53,73,74} Similarly, both preoperative and postoperative glucocorticoid administration predisposes patients to such infections following heart, lung, and, especially, liver transplantation.^{75-77,105}

Cryptococcosis

Cryptococcosis is common in patients with AIDS.¹⁰⁶ However, in glucocorticoid-treated patients without AIDS, fungaemia, overwhelming pneumonia, meningitis, disseminated cryptococcosis, and reactivation of cryptococcosis can occur.^{4,77,107,108} Particularly, *Cryptococcus neoformans* serotype D infections have been associated with previous treatment with glucocorticoids, suggesting host-specific phenotypic expression of *Cryptococcus* infections.¹⁰⁹

Some unique glucocorticoid-induced immunosuppressive characteristics are noted with cryptococcosis. For example, cortisone acetate has been shown to diminish alveolar macrophage capacity to attach to and ingest *C neoformans*, potentially leading to fungus

dissemination to the bloodstream.¹¹⁰ Similarly, Perfect and colleagues¹⁰⁷ showed that glucocorticoids pose a high risk for cryptococemia. Moreover, glucocorticoids predispose non-AIDS patients with cancer or sarcoidosis and recipients of allogeneic bone-marrow and solid-organ transplants to cryptococcosis.^{4,77,108,111,112}

Furthermore, glucocorticoid administration substantially reduces the chemotactic activity of cerebrospinal fluid toward PMNs and monocytes.¹¹³ This factor might contribute to the significant lack of PMN influx in cerebrospinal fluid and subsequent inability to eradicate fungi with tropism to the CNS, such as *C neoformans*. This attenuation is further intensified by glucocorticoid-induced abnormalities of microglial cells.⁴¹

Besides predisposing patients to cryptococcal meningitis, glucocorticoids are also a critical factor for adverse outcome of this infection. Diamond and Bennet¹¹⁴ reported that all cryptococcal meningitis relapses were associated with maintenance of glucocorticoid treatment beyond termination of antifungal therapy at daily prednisone-equivalent doses of greater than 20 mg.¹¹⁴

Other yeast infections

Trichosporon beigeli, *Malassezia*, and *Saccharomyces* species have also been reported to occasionally cause severe systemic infections in patients treated with glucocorticoids.^{85,86,115} In fact, high-dose glucocorticoid therapy in cancer patients was recently reported to correlate with a poor outcome of trichosporonosis.¹¹⁵

PCP

PCP is the most common opportunistic infection in patients with AIDS.¹⁰⁶ Although glucocorticoids are a well-recognised treatment modality in severely hypoxaemic patients with PCP, the findings of several studies have associated glucocorticoids with PCP development in patients with cancer and vascular-collagen disorders, and in those receiving allogeneic bone-marrow and solid-organ transplants.^{77,116-119} Therefore, prophylaxis with trimethoprim/sulfamethoxazole should be considered for patients receiving a long course of glucocorticoids, especially at high doses. Typically, PCP manifests during glucocorticoid tapering when the glucocorticoids' anti-inflammatory effects are attenuated.^{120,121} Possible justification for PCP prophylaxis during glucocorticoid tapering is the delayed lung clearance of *P carinii* in infected hosts. Walzer and colleagues¹²² showed prolonged lung clearance of the microorganism in rats after tapering of glucocorticoid immunosuppression, lasting longer than 6 weeks after glucocorticoid termination.¹²²

Sepkowitz and co-workers¹¹⁶ reported that glucocorticoids were a risk factor in 87% of their patients with cancer in whom PCP developed. Moreover, PCP is not uncommon in patients with brain tumours receiving high-dose dexamethasone.^{120,121} Anaissie and colleagues¹²³ also reported that administration of glucocorticoids and fludarabine was a risk factor for PCP in patients with chronic lymphocytic leukaemia. Similarly, bone-marrow transplant recipients receiving methylprednisolone for chronic graft-versus-host disease are at risk of PCP for 7-12 months after transplantation.¹²⁴ Additionally, Yale and Limper¹²⁵ showed that 90% of patients with various, mainly nonmalignant, conditions who had PCP had received glucocorticoids the month before PCP diagnosis. A daily prednisone-equivalent dose of 30 mg given for a median of 12 weeks was further associated with worse PCP outcome.¹²⁵

PCP is a recognised opportunistic pulmonary infection in glucocorticoid-treated patients with vascular-collagen disorders, especially SLE and Wegener's granulomatosis.^{117,118} Specifically, a median daily dose of 40 mg prednisone in patients with SLE is associated with development of PCP.¹²⁶ When rheumatological patients receive glucocorticoids plus a cytotoxic agent, the incidence of PCP is about 6%,¹¹⁷ and the mortality rate exceeds 30%.^{117,118} In patients with asthma and chronic obstructive pulmonary disease, PCP may arise, although rarely, with long-term high-potency systemic glucocorticoid treatment.¹²⁷ Finally, Hartel and colleagues¹²⁸ noted *P carinii* in bronchoalveolar lavage specimens in 40% of the cases of acute respiratory distress syndrome they treated. However, whether glucocorticoid use in treatment of this syndrome predisposes patients to PCP, further deteriorating the syndrome's clinical course, remains unclear.

Invasive infections caused by endemic and dimorphic fungi

Patients receiving glucocorticoids may develop primary or reactivated infections by endemic fungi. However, glucocorticoids' role in their pathogenesis is uncertain. Histoplasmosis is the primary endemic mycosis in patients receiving glucocorticoids.¹²⁹ In patients with SLE, a main risk factor for disseminated histoplasmosis is glucocorticoid treatment at doses of greater than 20 mg/day.¹³⁰ Furthermore, Torres and colleagues¹³¹ noted that 43% of their cancer patients with histoplasmosis had received glucocorticoids during the month before diagnosis. Histoplasmosis is also seen in patients undergoing bone-marrow and solid-organ transplants and in asthmatics receiving glucocorticoids.^{4,77,132} In glucocorticoid-treated patients, the pathological features of histoplasmosis are atypical, characterised by the absence of discrete granulomas, consistent with the glucocorticoids' anti-inflammatory properties.¹²⁹

Coccidioidomycosis is also associated with glucocorticoid use, especially in patients with vascular-collagen disorders¹³³ but also in those with cancer and asthma.^{131,132} Furthermore, blastomycosis, penicilliosis, and sporotrichosis are associated with glucocorticoids, whereas paracoccidioidomycosis is the least reported endemic mycosis after treatment with glucocorticoids.^{85,86,134,135}

Conclusions

Glucocorticoids have pleiotropic effects on immunity that account for hypercortisolaemic patients' propensity for life-threatening IFIs. However, the exact prevalence and attributed mortality of such infections are difficult to quantify. As our knowledge accumulates, better understanding of glucocorticoids' precise effect on IFI pathogenesis might lead to earlier detection and initiation of treatment. Because IFI severity is associated with intensity of glucocorticoid treatment, every effort should be made to use the lowest glucocorticoid dose for the shortest possible time in accordance with host characteristics.

Conflict of interest statement

None declared.

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