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Glucocorticoids as Adjunctive Therapy in Infectious Diseases—Immunomodulation in the Management of Infection-Related Inflammation

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Abstract: Glucocorticoids (GCs) represent a critical adjunctive strategy in the management of select infectious diseases, particularly those in which the host inflammatory response, rather than direct pathogen toxicity, is the primary driver of morbidity and mortality. This review synthesizes evidence-based indications for GC use across bacterial, viral, fungal, and parasitic infections, with emphasis on agent selection, dosing, duration, and the clinical principle that steroids must always be co-administered with definitive antimicrobial therapy. The conditions discussed include bacterial meningitis, tuberculosis (meningitis and pericarditis), PCP, COVID-19, septic shock, croup, and selected fungal and parasitic infections. Contraindications, most notably cerebral malaria, are highlighted. The evidence base ranges from landmark randomized controlled trials to consensus guidelines.

Keywords: Glucocorticoids; infectious disease; immunomodulation

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1. Introduction

Immunomodulation is the deliberate modification of immune system activity and encompasses both enhancement and suppression of the immune response. Glucocorticoids (GCs) are the most clinically relevant immunosuppressive agents used as adjuncts in infectious disease management. Their use is predicated on a fundamental principle: in certain infections, the host inflammatory cascade itself generates tissue damage that exceeds any harm caused directly by the pathogen.

GCs act as immunosuppressants across a spectrum of conditions, from septic shock and bacterial meningitis to fungal and parasitic disease. Their application should always be considered within the framework of risk and benefit: GCs are never used as monotherapy and should be initiated only when the inflammatory burden justifies the attendant risks of immunosuppression, hyperglycemia, adrenal suppression, secondary infection, and GI bleeding.

A recurring clinical theme is that timing is paramount. For many indications, including bacterial meningitis and *Pneumocystis jirovecii* pneumonia (PCP), maximum benefit is achieved when GCs are initiated before or concurrently with antimicrobial therapy.

2. Mechanism of Action and Efficacy

2.1. Mechanism of Action

Glucocorticoids exert anti-inflammatory effects through both genomic and non-genomic pathways. The dominant mechanism involves binding to intracellular glucocorticoid receptors, which translocate to the nucleus and suppress transcription of pro-inflammatory mediators. This results in a coordinated reduction in cytokine production and leukocyte activation (Table 1).

Table 1: Glucocorticoid mechanisms of action.

Mechanism	Details
Genomic (primary)	Binds glucocorticoid receptors → translocate to nucleus → inhibit NF-κB and AP-1 → suppress transcription of pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, TNF-α)
Eicosanoid Pathway	Suppress COX-2 expression → ↓ prostaglandin and leukotriene synthesis
WBC Trafficking	↓ Leukocyte adhesion to endothelium; ↓ egress to tissues; ↑ release from bone marrow
Adaptive Immunity	↓ MHC-II expression; ↓ antigen presentation; ↓ CD4+ T-cell activation; ↓ NK cell population

The net effect is a dysfunctional neutrophilia, elevated circulating neutrophil counts with impaired tissue migration and suppression of both innate and adaptive immune responses. This dual suppression underlies both the therapeutic utility and the infectious risks of systemic GC use.

2.2. Efficacy of GC Therapy

As delineated below and summarized in Tables 2 and 3, the efficacy and dosing of GC therapy for certain infections varies widely.

3. Bacterial Infections

3.1. Bacterial Meningitis

Adjunctive dexamethasone is the best-established GC indication in infectious disease. The pivotal European Dexamethasone in Adulthood Bacterial Meningitis study demonstrated a significant reduction in unfavorable outcomes (death and neurological disability) in patients treated with dexamethasone, with mortality benefit most pronounced for *Streptococcus pneumoniae* meningitis

in adults and *Haemophilus influenzae* meningitis in children [1]. Benefit was observed when dexamethasone was initiated before or within one hour of the first antibiotic dose.

Key clinical considerations include:

- Dose: 0.15 mg/kg IV q6h (~10 mg every 6 hours for 70 kg adult);
- Duration: 4 days;
- Pathogen uncertainty at initiation justifies empiric administration in most community-acquired cases;
- Caveat: *Listeria monocytogenes* meningitis: no proven benefit; caution warranted [2];
- Vancomycin CSF penetration is reduced by dexamethasone: optimize vancomycin dosing accordingly;
- There are no data supporting GC use in healthcare-acquired meningitis.

3.2. Tuberculosis (TB)

3.2.1. TB Meningitis

Dexamethasone significantly reduces mortality in adolescents and adults with TB meningitis [3]. Benefit was demonstrated across all disease severity grades in the landmark Thwaites et al. Trial.

3.2.2. TB Pericarditis

Prednisolone reduces the risk of constrictive pericarditis and hospitalization, as demonstrated in the IMPI Trial [4].

3.2.3. TB IRIS

Immune Reconstitution Inflammatory Syndrome (IRIS) following ART initiation can precipitate life-threatening pulmonary or CNS inflammation in patients with concurrent tuberculosis. GCs are indicated when inflammatory reactions are organ-threatening or life-threatening.

3.3. Severe Community-Acquired Pneumonia (CAP)

In CAP severe enough to require ICU admission (PSI Class V/CURB-65 $\geqslant$4) or with escalating oxygen requirements, adjunctive GCs reduce the duration of illness and risk of ARDS progression [5]. Hydrocortisone is most commonly used:

- Dose: 200 mg/day IV divided q6–8h;
- Duration: Through ICU course, or 7 days with subsequent 7-day taper (may transition to oral outpatient completion).

Recently, patients with documented mycoplasma pneumoniae CAP were found to benefit from a 5-day course of betamethasone therapy. Randomized patients had a more rapid resolution of hypoxemia and decreased hospital length of stay. In general, the evidence profile mirrors that observed in COVID-19 [6]. Any significant increase in oxygen demand should warrant consideration of GC therapy. In general, the type of glucocorticoid utilized and the duration of therapy are variable and should be tailored to the individual patients clinical response.

3.4. Septic Shock

Relative adrenal insufficiency is common in critical illness. The diagnosis is primarily clinical; laboratory thresholds (random cortisol <10 mcg/dL, ACTH stimulation) have poor predictive utility due to assay variability and altered protein binding kinetics in the critically ill.

Patient selection for GC therapy is guided by:

- Non-response to adequate fluid resuscitation;
- Persistent need for vasopressors.

Dosing: Hydrocortisone 200–300 mg/day IV in divided doses, q6–8h, for 7 days followed by a taper based on clinical stability [7]. Fludrocortisone may be added per the APROCCHSS trial protocol [8].

4. Viral Infections

4.1. Severe COVID-19

The RECOVERY Trial established dexamethasone as the standard of care for hospitalized COVID-19 patients requiring supplemental oxygen or mechanical ventilation. A 22% relative reduction in 28-day mortality was demonstrated in ventilated patients; no benefit was observed in patients who did not require oxygen. Dexamethasone 6 mg/day for up to 10 days is now a global treatment standard [6].

4.2. Croup (Viral Laryngotracheobronchitis)

A single dose of oral or intramuscular dexamethasone (0.6 mg/kg) is standard of care for moderate-to-severe croup. Meta-analyses confirm significant reductions in stridor, return emergency visits, and hospitalizations. Nebulized budesonide is an equivalent alternative [9].

4.3. *Pneumocystis jirovecii* Pneumonia

For HIV-positive patients with PCP and evidence of hypoxia (PaO_2 < 70 mmHg or alveolar-arterial oxygen gradient > 35 mmHg), adjunctive prednisone reduces the risk of respiratory failure and mortality (RR 0.56) [10]. The same criteria and approach are applied to HIV-negative immunocompromised hosts, though mortality benefit data are more limited in this population.

The standard regimen is as follows: Prednisone 40 mg bid $\times$5 days $\rightarrow$ 40 mg qd $\times$5 days $\rightarrow$ 20 mg qd $\times$11 days. GCs should be started within 72 h of PJP-directed therapy.

4.4. Infectious Mononucleosis (EBV)

GCs are not indicated for uncomplicated EBV infection. Indications are limited to the following complications: impending airway obstruction, severe thrombocytopenia, or hemolytic anemia.

5. Fungal and Parasitic Infections

5.1. Cryptococcal Meningitis and IRIS

Dexamethasone is used for severe inflammatory flares following antifungal therapy initiation in HIV patients beginning ART (Immune Reconstitution Inflammatory Syndrome). It is not indicated for standard cryptococcal disease management outside this context [11].

5.2. Allergic Bronchopulmonary Aspergillosis (ABPA)

Glucocorticoids are the cornerstone of ABPA management, suppressing IgE-mediated hypersensitivity to Aspergillus fumigatus in the airways. Prednisone reduces acute exacerbations, mucus plugging, and bronchiectasis progression [12].

5.3. Neurocysticercosis

Dexamethasone or prednisolone is given concurrently with antiparasitic therapy (albendazole or praziquantel) to blunt the intense inflammatory reaction as cysticerci degenerate [13]. GCs reduce peri-lesional edema and seizure risk during treatment.

5.4. Cerebral Malaria: Contraindication

Dexamethasone is contraindicated in cerebral malaria. Randomized trial data demonstrate increased adverse outcomes, including prolonged coma and higher rates of gastrointestinal bleeding, with GC use compared to placebo [14].

6. Evidence Summary and Dosing Reference

6.1. Evidence Summary by Indication

Table 2: Glucocorticoid use in infectious diseases—evidence summary.

Infection/Condition	Steroid Agent	Primary Benefit	Evidence Level
Bacterial Meningitis	Dexamethasone	↓ Hearing loss, neurological sequelae	High (RCTs)
TB Meningitis	Dexamethasone	↓ Mortality, severe disability	High (RCTs)
TB Pericarditis	Prednisolone	↓ Constrictive pericarditis	High (RCT)
PJP Pneumonia	Prednisone	↓ Respiratory failure	High (RCTs)
Severe COVID-19	Dexamethasone	↓ Mortality (ventilated)	High (RECOVERY Trial)
Croup	Dexamethasone	↓ Airway edema, hospitalizations	High (meta-analyses)
ABPA	Prednisone	↓ Hypersensitivity, mucus plugging	Moderate
Neurocysticercosis	Dexamethasone	↓ Peri-cyst edema, seizures	Moderate
EBV Mononucleosis (severe)	Prednisone	Airway/hematologic control	Low–Moderate
Community Acquired Pneumonia (severe)	Hydrocortisone	↓ Inflammatory lung injury	Moderate
Septic Shock (refractory)	Hydrocortisone	Vasopressor weaning, mortality	Moderate (APROCCHSS)
Typhoid Fever (severe)	Dexamethasone	↓ Mortality in shock/altered consciousness	Moderate (RCT)
Cerebral Malaria	—	**CONTRAINDICATED—worse outcomes**	High (RCT)

6.2. Dosing Quick-Reference

Table 3: Recommended dosing and duration by indication.

Indication	Agent	Dose	Duration/Notes
Bacterial Meningitis	Dexamethasone	0.15 mg/kg IV q6h (~10 mg q6h)	4 days; start before or with first antibiotic dose
TB Meningitis	Dexamethasone	0.4 mg/kg/day tapered over 6–8 wks	Gradual taper per Thwaites protocol
TB Pericarditis	Prednisolone	60 mg/day, taper over 11 weeks	Ref: [4]
PCP (HIV+)	Prednisone	40 mg bid $\times$5 d $\rightarrow$ 40 qd $\times$5 d $\rightarrow$ 20 qd $\times$11 d	Start within 72 h of PCP therapy if PaO < 70 or A-a >35
Severe COVID-19	Dexamethasone	6 mg/day IV or PO	10 days or until discharge
Septic Shock	Hydrocortisone	200–300 mg/day $\div$ q6–8h IV	7 days + taper based on clinical stability
Croup	Dexamethasone	0.6 mg/kg IM/PO (single dose)	Single dose; budesonide nebulized alternative

7. Key Clinical Principles

01	**Never Monotherapy** Glucocorticoids must always be paired with appropriate antimicrobial therapy. Steroids alone in an active infection can be fatal.
02	**Timing Matters** Maximum benefit is achieved when GCs are started early—ideally before or concurrent with the first antibiotic dose (e.g., bacterial meningitis, PCP).
03	**Inflammation Is the Target** GCs are indicated when the host's own immune response causes collateral damage, not when pathogen burden is the primary threat.
04	**Know the Contraindications** Contraindicated in cerebral malaria, most uncomplicated viral infections, and situations where immunosuppression outweighs benefit.

8. Limitations of the Evidence Base

Despite decades of use, the evidence guiding GC therapy in infections carries important limitations:

- Disease-specific populations are difficult to enroll in adequately powered trials, leading to variability in recommended doses, steroid preparations, and treatment durations.
- Many studies are underpowered to detect differences in subgroup populations (e.g., HIV-negative PCP, non-pneumococcal meningitis).
- Timing of initiation is consistently identified as a determinant of efficacy, but optimal windows remain imprecisely defined beyond key indications (meningitis, PCP).
- Heterogeneity in critically ill populations (septic shock, ARDS) complicates generalization from trial results.

The consistent signal across the literature is that early initiation, when GCs are indicated, improves outcomes. Clinicians must balance this evidence against individual patient risk factors for GC-related adverse effects.

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