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Glucocorticoid therapy in respiratory illness: bench to bedside

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ABSTRACT

Each year, hundreds of millions of individuals are affected by respiratory disease leading to approximately 4 million deaths. Most respiratory pathologies involve substantially dysregulated immune processes that either fail to resolve the underlying process or actively exacerbate the disease. Therefore, clinicians have long considered immune-modulating corticosteroids (CSs), particularly glucocorticoids (GCs), as a critical tool for management of a wide spectrum of respiratory conditions. However, the complex interplay between effectiveness, risks and side effects can lead to different results, depending on the disease in consideration. In this comprehensive review, we present a summary of the bench and the bedside evidence regarding GC treatment in a spectrum of respiratory illnesses. We first describe here the experimental evidence of GC effects in the distal airways and/or parenchyma, both in vitro and in disease-specific animal studies, then we evaluate the recent clinical evidence regarding GC treatment in over 20 respiratory pathologies. Overall, CS remain a critical tool in the management of respiratory illness, but their benefits are dependent on the underlying pathology and should be weighed against patient-specific risks.

INTRODUCTION

Glucocorticoids (GCs) are a class of endogenous or synthetic steroid hormones that exhibit potent anti-inflammatory effects by regulating expression of inflammation-related genes. The GCs also influence metabolism, homeostasis, development and cognition.¹ Synthetic GCs include dexamethasone, methylprednisolone, prednisolone, hydrocortisone, cortisone, and betamethasone.² Natural GCs are produced by the adrenal gland and released into the systemic circulation. Natural and synthetic GCs both diffuse from the bloodstream to the cellular cytoplasm, where they bind GC receptors and form a protein complex with glucocorticoid receptor α (GR α). This GC-receptor-chaperone complex shuttles to the nucleus where it can bind DNA, promoters, transcription factors and other regions to regulate transcription of inflammation-related genes.^{3,4} The GCs can suppress the transcription of inflammatory genes such as STAT and NF- κ B and increase the transcription of anti-inflammatory genes

such as the NF- κ B inhibitor I κ B α , interleukin (IL)-10; IL-12, and other immune-controlling genes. They have become the backbone of the management of many acute and chronic respiratory illnesses, with an excellent safety profile and ample evidence for their effectiveness at suppressing pathologic inflammation.^{5,6}

MECHANISMS OF ACTION

General molecular mechanisms

The GCs modulate transcription and translation of inflammation-related genes through a myriad of molecular interactions with the cellular membrane and its DNA, RNA and proteins (figure 1). GCs are known for their ability to complex with GR α and its chaperone proteins in the cytoplasm. This complex then shuttles GCs into the nucleus where it may interact with DNA in three primary ways to ultimately modulate the transcription machinery and influence the transcription of inflammation-related genes.^{3,7} First, the GR-GC complex may directly bind to accessible DNA to influence transcription. This is termed *direct binding*. Second, the GR-GC complex may bind a transcription factor that in turn binds DNA. This is termed *tethering*. Finally, the GR-GC complex may bind DNA directly, while also associating with a DNA-bound transcription factor. This is termed *composite binding* (figure 1A). All three of these DNA binding mechanisms are capable of promoting or downregulating transcription. Indeed, many canonical proinflammatory genes are downregulated (NF- κ B, AP1, STAT, C/EBP, and NFAT inflammatory pathways), but GCs are also known to upregulate anti-inflammatory genes including TLR signaling inhibitors (DUSP1, MAPK1, IRAK3) and NF- κ B inhibitors (I κ B α , GILZ).³

GCs can also exert substantial non-genomic effects outside the nucleus through interaction with cellular membranes, cytoplasmic proteins, and mRNA (figure 1B). Interestingly, it was recently shown that GCs can destabilize cytoplasmic mRNA, resulting in the downregulated translation of proinflammatory mRNA. This mechanism involves the complexing of cytoplasmic GC with GR and chaperone proteins that then directly bind to mRNA and induce its degradation.^{8–10} GCs also modulate the expression of the mRNA-degrading protein *tristetaprolin* (TTP in figure 1B), which can increase degradation of proinflammatory

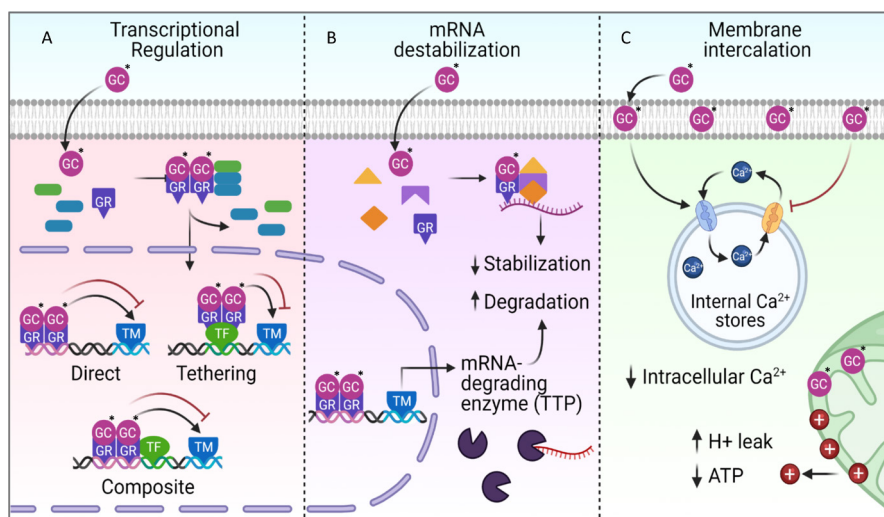


Figure 1 Molecular mechanisms of glucocorticoid (GC) action. (A) GCs are most well known for their effects on DNA transcription of inflammation-related genes. GCs in the cytoplasm associate with chaperone proteins and glucocorticoid receptor α (GR). This complex translocates to the nucleus to bind promoter regions of proinflammatory and anti-inflammatory genes. The GR-GC complex can promote or inhibit gene expression through directly binding the DNA promoter region (Direct); by binding to a transcription factor (Tethering); or by binding both the DNA and the transcription factor (Composite). (B) GCs can also interrupt inflammatory cascades by intercepting mRNA transcripts for proinflammatory genes such as NF- κ B. GCs complex with GR and other chaperones to form a protein complex that binds to mRNA causing it to lose stability and degrade.^{8,9} GR-GC protein complexes also promote the transcription of the mRNA-degrading enzyme TTP, thereby increasing the degradation of cytoplasmic mRNA. (C) GCs induce immediate, non-genomic changes by intercalating in the cell membrane's lipophilic interior. The intercalating GCs promote a reduction in intracellular calcium and ATP levels (* marks the GC).

genes in the cytoplasm. Many proinflammatory mediators are controlled by this mechanism including tumor necrosis factor- α (TNF- α), interferon- β (IFN- β), interleukin (IL)-1 α , IL-1 β , IL-6, iNOS, and COX2.¹¹⁻¹³

Additionally, GCs can exert virtually instantaneous effects on cellular energy metabolism, agonist-induced Ca^{2+} mobilization and reactive oxygen species (ROS) production. These effects are proposed to result from the intercalation of lipophilic GCs in cellular and mitochondrial membranes that induce complex signaling cascades¹⁴⁻¹⁶ (figure 1C). In GC-treated bronchial epithelial cells, for example, ATP consumption is reduced and Ca^{2+} is inhibited from cycling through intracellular stores into the cytoplasm.¹⁵ These rapid transcription-independent responses likely influence substantially the overall effects of GCs.

The GC effects greatly depend on the variant of GC, GR and cell phenotype.^{1,3,17} There are many types of GCs with specific molecular properties such as lipophilicity and binding affinity that influence their effects. Also, many variants of GR- α are possible through alternative splicing and post-translational modification. In kind, many genomic regulations are possible depending on the cell phenotype. Different cells may have variable accessibility of GC complex binding sites on chromatin that are regulated by epigenetic histone modifications, histone loops and other mechanisms.¹ As a result, GC effects are cell, tissue and patient specific. A more comprehensive discussion of GC mechanisms can be found in the articles by Newton and Cruz-Topete and Cidlowski.^{3,6}

Cellular mechanisms in the pulmonary microenvironment

GCs induce functional changes to each cell type in the distal airways and alveoli. In vitro studies of isolated cell

types have identified both positive and negative physiologic effects in the distal lung microenvironment (figure 2). GCs enhance epithelial barrier function,^{18,19} reduce inflammatory cell infiltration,²⁰⁻²² and suppress production of proinflammatory cytokines.¹⁷ However, GCs also appear to induce epithelial apoptosis,^{23,24} reduce airway cell proliferation,^{25,26} and suppress type I to type II pneumocyte transdifferentiation²⁷ for the coverage of desquamated regions. These effects in aggregate may interfere with tissue regeneration after acute lung injury. Indeed, it is well known that delay dermal wound healing, although this is hypothesized to be an effect of suppressed fibroblast proliferation.²⁸ However, recent clinical evidence does suggest that GCs have a net positive effect in acute lung injury.²⁹

GCs also regulate immune and endothelial cells to suppress and promote inflammation. In vitro, GCs appear to enhance leukocyte adhesion to the endothelium by upregulating adhesion markers.³⁰⁻³² They also increase the production of procoagulant factors including tissue factor and von Willebrand factor (VWF).³⁰⁻³³ Conversely, GCs inhibit neutrophil recruitment by suppressing the production of chemokines in the tissue and by resident immune cells. Finally, GCs suppress proliferation of lymphocytes, perhaps contributing to GC-induced lymphopenia.^{5,33} GC effects on fibroproliferation are contradictory and appear situation dependent.^{28,34-36}

However, many of the effects observed in monocultures do not appear to translate to physiologic effect in vivo. For instance, there is little evidence of procoagulant effects in human subjects due to GCs despite ample evidence in vitro.³⁷ Additionally, despite evidence that GCs induce enhanced endothelial expression of adhesion factors, neutrophil infiltration is substantially reduced at sites of

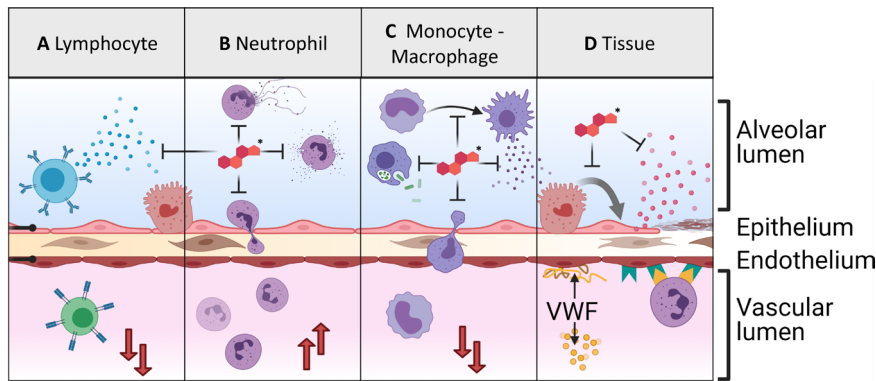


Figure 2 Glucocorticoid mechanism and cellular effects. (A) Glucocorticoids (GCs) inhibit lymphocytes' production and release of inflammatory cytokines and reduce circulating lymphocyte counts by redirecting circulating lymphocytes to the lymphoid organs. (B) GCs inhibit inflammatory neutrophil behaviors such as degranulation, NETosis, and recruitment. They also increase circulating neutrophil counts by enhancing the maturation of neutrophils in the bone marrow. (C) GCs inhibit inflammatory macrophage and monocyte behaviors including the activation of monocytes into macrophages; the phagocytosis of bacteria; the release of cytokines by activated macrophages; and the recruitment of monocytes to inflamed areas. (D) GCs inhibit the transdifferentiation of alveolar type II pneumocytes into type I to cover damaged tissue. They also inhibit the release of proinflammatory cytokines. However, they also appear to increase the release of von Willebrand factor (VWF) and the expression of endothelial adhesion proteins (* marks the GC).

inflammation following GC administration.²² Finally, while GCs appear to inhibit antibacterial capabilities of immune cells *in vitro*, there is little clinical evidence for increased risk of nosocomial infection in patients receiving GC treatment for acute respiratory failure, although opportunistic infections are possible with long-term treatment.^{38–40} Generally, while *in vitro* evidence can provide motivation for animal and human studies, it is limited in its ability to provide clinically useful insight independently (table 1).

GCS IN PULMONARY PATHOLOGY

Granulomatous and allergic inflammation

Granulomatous lesions are organized aggregates of primarily monocytic leukocytes and their derivatives, along with lymphocytes, multinucleated giant cells, epithelioid cells, and fibroblasts.⁴¹ Lesions form in response to foreign bodies, certain pathogens, smoke or toxin exposure, or as a consequence of allergic hypersensitivity. Granulomatous inflammation appears in the lung parenchyma, airways and/or lymphoid organs depending on etiology and generally responds well to corticosteroids (CSs).⁴² This is unsurprising given that GCs exhibit potent effects on the primary actors of granulomatous inflammation. Significantly for the clearance of granuloma tissue, GCs increase macrophages' phagocytosis capacity to engulf apoptotic cells.⁴³ GCs also reduce the proliferation and migration of inflammatory cells into granulomas by inhibiting monocyte and macrophage signaling of proinflammatory mediators, including IL-1 β , IL-6, IL-12, TNF α , and GM-CSF, and down-regulate the expression of chemokines like IL-8, RANTES, and MCP-1. Finally, GCs stimulate macrophages to produce anti-inflammatory mediators including Annexin-1, IL-10, and CD163.⁴³

Pulmonary sarcoidosis

Several studies have suggested clinical benefits of CSs in pulmonary sarcoidosis. Randomized controlled trials (RCTs) exploring their efficacy were primarily conducted several decades ago, comprising heterogeneous populations,

dosing, duration of therapy, and clinical follow-up.^{44–48} Regardless, overall outcomes generally support short-term improvements in symptoms, chest radiography, and pulmonary function. In a Cochrane review incorporating these

Table 1 Cell-specific GC effects

Cell type	Effects
Global	<ul style="list-style-type: none"> ↓ Proinflammatory and chemotactic factors¹⁷ ~ Coagulopathy³⁷ ↓ Wound healing²⁸ ↑ Infection risk (long term)⁴⁰
Lymphocyte	<ul style="list-style-type: none"> ↑ Apoptosis³ ↓ Proliferation³³ ↓ Circulating counts⁵
Neutrophil	<ul style="list-style-type: none"> ↓ Recruitment^{21,22} ↓ Inflammatory genes²² ↓ Apoptosis²⁷⁵ ↑ Circulating counts²²
Monocyte, macrophage	<ul style="list-style-type: none"> ↓ ROS, inflammasome²⁰ ↓ Shift M1, M2²⁷⁶ ↓ Chemotactic factors⁴³ ↓ Adhesion, recruitment, accumulation^{5,43} ↓ Efferocytosis, phagocytosis⁴³ ↓ Circulating counts⁵
Alveolar and airway epithelium	<ul style="list-style-type: none"> ↑ Barrier integrity^{18,19,277–279} ↑ SPA, SPD^{280,281} ↑ Type II maturation²⁸² ↓ MUC5AC²⁸³ ↓ Type I>type II^{27,282} ↑ Apoptosis²³ ↓ Proliferation, repair^{24–26}
Fibroblast	<ul style="list-style-type: none"> ↑ Contractility³⁵ ↓ Collagen deposition²⁸ ~ Proliferation^{28,34}
Endothelium	<ul style="list-style-type: none"> ↓ NOS/vasoconstriction¹⁵ ↓ Angiogenesis²⁸⁴ ↑ VWF, TF, ICAM, VCAM^{30–32} ↑ Neutrophil adhesion^{30–32}
GC, glucocorticoid; ROS, reactive oxygen species; VWF, von Willebrand factor.	

studies, data analysis particularly favored treatment in those with parenchymal disease (stage II or III) with mean difference improvements in percent predicted of vital capacity and diffusion capacity increasing by 4.2% (CI 0.4% to 7.9%) and 5.7% (CI 1.0% to 10.5%), respectively.⁴⁹

While evidence supports short-term improvements, data are lacking regarding CS treatment's effect on long-term outcomes or modulating the natural progression of pulmonary sarcoidosis. Earlier RCTs demonstrated no persisting benefit on long-term follow-up after initial treatment with oral CSs for 3–24 months. However, certain key factors limit interpretation such as the inclusion of patients without parenchymal disease (stage I) or treating patients up-front without an observational period during which time many patients show partial or complete resolution. A 5-year longitudinal follow-up study of 149 patients with newly diagnosed parenchymal sarcoidosis aimed to address this gap.⁵⁰ In this study, patients were initially observed for a 6-month period after which those who had persisting radiographic abnormalities on chest radiographs (39%) were allocated to receive oral CSs (regardless of symptoms) for 18 months or continued observation (with selective treatment if symptoms developed). Patients in the treated group experienced mild and comparative symptomatic and radiographic improvement with an average adjusted increase in vital capacity by 9% at the end of 5 years. Notably, the untreated group also tended toward higher fibrotic scores, although not reaching statistical significance. Similar results were reported in another RCT wherein patients with stage II and III disease were randomized to receive oral prednisone for 3 months followed by 15 months of inhaled CSs or placebo.⁵¹ After 5 years, patients that received immediate treatment had significant improvements in forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO) and less subsequent requirements for CSs. Although CSs appear to have a marginal benefit for early treatment in parenchymal disease, clinical heterogeneity of disease and difficulty in selecting for patients with a tendency for progressive, refractory, or fibrotic phenotypes limit definitive interpretation.

The optimal dose and duration of therapy are unknown, so treatment guidelines make no specific recommendations. However, the typical initiating dosage varies from 20 mg daily (0.3 mg/kg/day) for those with indolent progressive symptoms, 40 mg daily (0.6 mg/kg/day) for those with rapidly progressive disease, and 80–100 mg daily for those with acute respiratory failure.^{52–54} This dose is usually maintained for 4–6 weeks after which steroids are slowly tapered over a 12 month period by 5–10 mg every 4–12 weeks once symptomatic, physiologic, or radiographic parameters improve. Recurrences appear in up to 50%–60% of patients as the dosage is reduced or once CSs are discontinued altogether. Monotherapy with inhaled CSs have also been explored as alternative therapy, although results appear conflicting. Clinical benefits have been reported in some patients, but evidence for clear and objective improvement is lacking.^{55–58}

Acute hypersensitivity pneumonitis

The role of CSs has been primarily evaluated in farmer's and bird fancier's lung, although the data are fairly limited.^{59–62}

In one randomized control study in patients presenting with farmer's lung comparing 8 weeks of prednisolone (n=20) to placebo (n=16), prednisolone treatment was associated with an improvement in forced expiratory volume in 1 s (FEV1), FVC, and DLCO at 1 month. Thereafter, these differences diminished and no disparities in pulmonary function were noted at 1 and 5 years.⁶⁰ Another study reported similar initial benefits without significant long term differences in symptoms or pulmonary function with 4 weeks, 12 weeks, or no therapy.⁵⁹ These findings suggest that although CSs do not improve long-term outcomes, they provide short-term relief in those with severe or persistent symptoms.

Chronic hypersensitivity pneumonitis (cHP)

Although unrecognized and untreated acute episodes may evolve into cHP, many patients have no acute episodes and present with progressive and chronic respiratory insufficiency over several weeks to months resulting from persistent, low level antigen exposure.⁶³ These patients can be further classified into either a non-fibrotic or fibrotic disease pattern. The latter is associated with reduced survival, especially accompanied by usual interstitial pneumonia (UIP)-like histology.⁶⁴ Antigen avoidance remains key to management. Patients lacking an identifiable inciting antigen have increased mortality and adverse outcomes.⁶⁵ For those with progressive symptoms, CSs have been the primary immunosuppressive therapy for decades. Despite this, no randomized trials or observational studies have evaluated CS efficacy in cHP. However, the lymphocytic disease process suggests steroid responsive disease process and positive studies in acute HP support its use.^{66–69}

CS efficacy in non-fibrotic (nfHP) and fibrotic (fHP) phenotypes of HP is now an important distinction that is predictive of treatment responsiveness and long-term outcomes.⁶⁴ Only one observational study to date has evaluated the role of CSs in those with nfHP and fHP.⁷⁰ In this report of 202 patients, the nfHP cohort (n=93) treated with CSs experienced a monthly improvement in FVC of 0.84% compared with a 0.35% monthly decline prior to initiation of treatment. A non-significant trend toward increased DLCO was also noted. Conversely, patients with fHP (n=109) continued to experience a decline in both FVC and DLCO irrespective of CS dose or duration of therapy. Those treated with CSs trended toward worse survival in comparison to untreated patients with fHP. These results distinctly vary from another study that evaluated outcomes in patients with cHP treated with prednisone, azathioprine, or mycophenolate mofetil.⁷¹ The cohort treated with prednisone alone experienced a FVC decline of 10.8% ($\pm 2.7\%$) over 36 months. Notably, this analysis did not distinguish patients based on a predominant non-fibrotic or fibrotic phenotype despite 85% of patients having ground glass opacities on high-resolution CT and 51% having honeycombing. As a result, there is a possibility that the magnitude of decline may have been driven by a proportion of patients with a predominant fibrotic phenotype. These outcomes in pulmonary function were similar to the mycophenolate only group, but in those receiving prednisone and subsequently commenced on mycophenolate or azathioprine, the slope of monthly decline in FVC was significantly reduced (-0.7% vs

–0.2%) along with a reduction in treatment associated adverse events.

Overall, these data suggest that corticosteroids have greater utility in treating patients with a predominant non-fibrotic phenotype which is in line with acute HP. In patients with fibrotic HP, CSs do not seem to reduce decline in pulmonary function and could be associated with increased mortality. In all patients with cHP irrespective of phenotype, prednisone monotherapy may be inferior to mycophenolate or azathioprine in reducing the rate of decline in pulmonary function.

GPA and MPA

Historically, no RCTs have evaluated corticosteroid monotherapy for the treatment of granulomatous polyangiitis (GPA) and microscopic polyangiitis (MPA). Initial, observational and anecdotal experiences in acute episodes of vasculitis described very high rates of relapses and mortality, prolonging survival by only several months.^{72–74} Further disease phenotype characterizations, the description of ANCA and the introduction of combination therapy including cyclophosphamide transformed the therapeutic landscape, with significantly improved remission and mortality.^{72 75–77} Resultantly, CSs are now predominantly used as adjunctive therapy with additional immunosuppressants such as cyclophosphamide, rituximab, azathioprine, or methotrexate in induction and maintenance phases of therapy.

For patients with organ or life-threatening disease, commonly used induction regimens consist of combination therapy with either cyclophosphamide or rituximab in addition to high-dose oral CS therapy of 1 mg/kg/day prednisone maintained for at least 1 month slowly tapered over several months to a lower maintenance dose between 5 and 10 mg/day.^{75 78–81} High-dose pulse intravenous steroids (ie, methylprednisolone 7–15 mg/kg up to 1000 mg/day for 1–3 days) are generally used in cases of alveolar hemorrhage, rapidly progressive glomerulonephritis, optic neuritis, or mononeuritis multiplex. In the landmark RAVE trial that demonstrated non-inferiority of rituximab to cyclophosphamide (in addition to CS), and which included patients with pulmonary manifestations in 50% of patients, this approach resulted in similar rates of remission at the end of 6 months (64% vs 53%).⁷⁹ In the 25% with alveolar hemorrhage (none of whom required ventilatory support), 57% of those with rituximab (vs 41%) achieved the study endpoint. Similarly, in the absence of organ or life-threatening generalized disease, studies evaluating the use of cyclophosphamide and methotrexate used an initial oral prednisone or prednisolone dose of 1 mg/kg/day.^{75 82}

Maintenance therapy following 3–6 months of induction consists of methotrexate, azathioprine, or mycophenolate in addition to low-dose corticosteroids with the goal of preventing disease relapse and minimizing cumulative CS exposure. Although there are no standardized protocols or strong evidence for long-term use, a meta-analysis of 13 RCTs and observational studies suggested that early withdrawal of CSs was associated with higher rates of disease relapse.⁸³ Only 14% of patients receiving CSs (vs 43% of controls) experienced at least one relapse. While these findings suggest that CSs play an important role in maintaining

disease remission, interpretation of these results may be limited due to heterogeneity in treatment regimens. This question remains to be answered in RCTs.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Similar to GPA and MPA, CSs are used in conjunction with additional immunosuppressive therapy in the presence of poor prognostic factors (Five Factor Score (FFS) ≥ 1) or life-threatening or organ-threatening disease such as alveolar hemorrhage or cardiac, gastrointestinal, central nervous system, or renal (glomerulonephritis) involvement.^{84 85} In the absence of these factors, single-agent anti-inflammatory monotherapy is often successful. For example, in the only trial (n=72) evaluating the efficacy of systemic CSs alone without poor prognostic factors (FFS=0) and in which 67% of patients had pulmonary infiltrates, 93% achieved clinical remission (absence of active vasculitis for 3 months) with initial high-dose prednisone monotherapy alone (1 mg/kg/day for 3 weeks, tapered to minimal effective dosage).⁸⁶ Five patients failed to respond and 25 (total 42%) had relapsed symptoms following tapering or termination of CSs requiring randomization to receive adjuvant azathioprine or cyclophosphamide. While relapses and long-term CS use is not uncommon and predominantly driven by difficult to control asthma, alveolar manifestations appear to respond well to therapy with only four patients found to have new pulmonary infiltrates—a phenomenon that has been reported elsewhere.^{87 88}

Although alveolar hemorrhage is infrequently encountered, it remains a life-threatening and under-recognized complication in patients with EGPA. Data evaluating outcomes in this subset of patients are sparse and only described in case reports. As a result, current understanding of optimal therapy and long-term outcomes is limited and largely extrapolated from anecdotal reports and experiences gathered from alveolar hemorrhage in GPA and MPA. Current EGPA Task Force Consensus Guidelines recommend using combination therapy with high-dose systemic CSs and cyclophosphamide followed by maintenance therapy with azathioprine or methotrexate for patients with alveolar hemorrhage.⁸⁴

Asthma

Historically, oral cortisone was first introduced as routine therapy for chronic bronchial asthma in the 1950s.^{89 90} Although effectively used as mainstay therapy for the subsequent two decades, adverse effects of chronic systemic therapy paved the development and routine application of inhaled corticosteroid (ICS) therapy. The first of these was beclomethasone, with initial randomized studies in the 1970s confirming the efficacy of inhaled monotherapy by demonstrating improvement in symptom control, lung function (FEV₁), and dose reduction of chronic oral CSs.^{91–94} Since, several inhaled CS of varying potency have been developed and used as monotherapy and in combination with short-acting and long-acting beta agonists (SABA, LABA), long-acting muscarinic antagonists (LAMA), leukotriene inhibitors, and biologics. Cumulative evidence has solidified these initially noted benefits; in addition, it has demonstrated improved quality of life, reduced rates of acute exacerbation, and providing a protective effect against

severe exacerbations.^{95 96} For example, in a Cochrane analysis of 68 studies comprising 11,104 subjects, monotherapy with inhaled fluticasone propionate in patients with mild and moderate disease was associated with a dose-dependent increase in FEV₁ (0.13–0.45 L), morning peak expiratory flow (27–47 L/min), symptom scores, reduction in rescue beta-2 agonist use (reduction between 1.2 and 2.2 puffs/day), and reduction in the number of patients dependent on systemic therapy.⁹⁷ Large population-based studies have also suggested a mortality benefit for maintenance therapy in patients with persistent disease. In an analysis of a cohort comprising 30,569 individuals from Saskatchewan, Canada, the rate ratio of death from asthma exceeded 2.5 for patients who received no ICS therapy and decreased to 0.25 in patients that used ICS consistently (12 cannisters per year). It was estimated that with each additional cannister of ICS used in the previous year, there was a 21% reduction in the rate of death.⁹⁸ Underlying these clinical benefits, the use of ICS therapy, even in short durations, has consistently shown to effectively reduce airway inflammation and chronic airway remodeling particularly in patients with an atopic and eosinophilic phenotypes.^{95 99–101} In summary, existing data strongly support the use of ICS as mainstay therapy in the treatment of persistent asthma and as such, comprises the backbone of treatment recommendations set forth by Global Initiative for Asthma (GINA) guidelines.¹⁰²

While the role of systemic CSs as part of maintenance therapy for severe persistent disease has diminished with the introduction of biologics-based therapy, oral CSs play a vital role in the management of acute exacerbations. In outpatients treated for mild to moderate exacerbations presenting to the emergency room, short courses equivalent to 40–60 mg/day for 5–7 days are associated with a reduction in symptom severity, SABA usage, and probability of subsequent exacerbations requiring additional therapy or further healthcare utilization.^{103–106} While the data in regard to the optimal dosage and duration of therapy for those treated for severe exacerbations leading to hospital admission are not as robust, expert opinion has often advocated for higher dose requirements, particularly in patients with respiratory failure requiring intensive care unit (ICU) admission (ie, methylprednisolone 60–80 mg every 6–8 hours).^{107 108}

In summary, CSs are the mainstay of therapy in asthma, especially in the eosinophilic pheno-endotypes, while in more severe or non-eosinophilic asthma, CS may in fact fail to suppress the neutrophilic inflammation and may even promote neutrophil survival.

Chronic obstructive pulmonary disease (COPD)

In vitro studies show that airway inflammation in COPD is generally unresponsive to CS, and that drugs such as beta-2 adrenergic agonists, macrolides and theophylline may increase the CS sensitivity, yet these observations have not had major implications on the current standard of care.^{109 110}

In vivo studies found that dose–response relationships and long-term (>3-year duration) safety of ICS therapy in COPD are still unclear and require further investigation.¹¹¹ As such, because the effects of ICS in COPD could be modulated by concomitant use of long-acting bronchodilators, these combinations are discussed separately.

ICS monotherapy

Most studies found inconclusive evidence of benefit in COPD, as ICS monotherapy does not change FEV₁ decline or general mortality over time.¹¹² In the TORCH study,¹¹³ a trend toward higher mortality was noted in the fluticasone propionate alone arm versus those on placebo or on salmeterol plus fluticasone propionate combination. However, in the SUMMIT trial,¹¹⁴ the increase in mortality was non-observed in patients with COPD treated with fluticasone furoate; furthermore, in moderate COPD, the groups on fluticasone furoate alone or fluticasone furoate plus vilanterol had slower declines in FEV₁ versus placebo or vilanterol alone.

ICS in combination therapy with long-acting bronchodilators

ICSs are frequently prescribed for patients with COPD in combination with inhaled LAMA and LABA therapy. Long-term randomized control trials evaluating the use of ICS monotherapy in patients with COPD have demonstrated varying effects on clinical endpoints, however, have failed to demonstrate a modifying effect on lung function.^{115–118} Similarly, two meta-analyses, including one large Cochrane review of 55 RCTs have confirmed a lack of benefit of ICS therapy in attenuating the rate of decline in FEV₁ (mean difference 5.80 mL/year with ICS vs placebo, 95% CI –0.28 to 11.88) in 2333 participants.^{112 119} In addition, in this Cochrane analysis, long-term use was not associated with a mortality benefit, although there were additional benefits in secondary outcomes, including a reduction in both the rate of annual exacerbation (–0.26; 95% CI, –0.37 to –0.14) and the rate of decline in the quality of life, as measured by St. George’s Respiratory Questionnaire (SGRQ; mean difference –1.22 units/year, 95% CI –1.83 to –0.60).¹¹²

In the subset of patients with moderate to very severe COPD and history of exacerbations, LAMA and/or ICS combination therapy with LABA appears to be more effective than either component alone. A meta-analysis evaluating 14 RCTs comparing ICS/LABA to LABA monotherapy found a reduction in annual exacerbation rates (rate ratio 0.76, 95% CI 0.68 to 0.84) in 9921 participants, and an improvement in SGRQ (1.58 to 2.69 units lower), dyspnea, symptoms, and rescue inhaler use without a difference in mortality.¹²⁰ Likewise, triple therapy (ie, ICS, LAMA and LABA combination) is associated with similar clinical benefits, in addition to providing a mortality benefit in this population. This was first demonstrated in the IMPACT trial, which evaluated the role of triple therapy to ICS/LBA and LAMA/LABA.¹²¹ All-cause mortality was significantly lower in those treated with triple therapy than LAMA/LABA (HR 0.58, 95% CI 0.38 to 0.88) in addition to reducing the annual rate of severe exacerbation resulting in hospitalization (rate ratio 0.66, 95% CI 0.56 to 0.78).¹²² Further, in the ETHOS trial that evaluated the role of triple therapy at two doses of budesonide (160 and 320 µg budesonide), a reduction in mortality was only noted in patients treated with higher dose budesonide triple therapy compared with LABA/LAMA (HR 0.54; 95% CI 0.34 to 0.87).¹²³

Despite the benefits attributable to ICS, their widespread use has been limited by a potential undesired increased risk of developing pneumonia, especially in those with severe COPD.¹²⁴ The first major study that brought to light such a

relationship was the TORCH study,¹¹³ and numerous others have added evidence in support of this observation.¹²⁴

Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines advocate for use of ICS therapy in patients that have factors that are predictive of a therapeutic response.³² Evidence suggests that ICS therapy has little effect in patients with peripheral blood eosinophil counts of <100 cells/ μ L, with incremental benefits noted in those with higher counts.^{32 125–127} Blood eosinophil counts \geq 300 cells/ μ L have been suggested to distinguish patients that may have the greatest probability of benefiting with ICS therapy.³² Moreover, a beneficial therapeutic response has been shown for patients with high exacerbation risk (\geq 2 exacerbations and/or 1 hospitalization within the previous year).^{32 125–127}

Systemic CSs are frequently used in the management of acute exacerbations of COPD. Data support a reduction in recovery time, improvement in FEV1, risk of relapse, treatment failure, and length of hospitalization.^{128–130} Shorter durations of 5 approximately days have been advocated after the REDUCE trial demonstrated non-inferiority compared with previously accepted 14-day courses.^{32 131}

In summary, regular treatment with ICS may increase the risk of pneumonia, especially in those with severe COPD; ICS combined with a LABA is more effective than either individual component in improving lung function and health status, and in reducing the exacerbation rate in moderate to very severe COPD; and triple therapy with inhaled ICS/LABA/LAMA improves lung function, health status and symptoms, and reduces exacerbations compared with dual or LAMA monotherapy; long-term use of oral CS has numerous side effects and questionable benefits.¹²⁴

Diffuse alveolar inflammation/infection

Acute, severe inflammation of the alveo-capillary tissue, termed acute lung injury (ALI), describes the condition of the alveoli wherein there is induce a rapid efflux of neutrophils and their mediators; activation of resident macrophages and the tissue barrier itself, leading to loss of alveo-capillary barrier function, and an efflux of proteinaceous fluid in the airspace.¹³² This is caused by a range of etiologies ranging from acute exposure, infection, trauma or septic shock to chemical exposure, drowning, or pneumonia. In severe ALI, heightened presence and activation of inflammatory cells results in an overexpression of inflammatory mediators that can cause breakdown of the epithelial-endothelial barrier, resulting in fulminant respiratory failure, termed acute respiratory distress syndrome (ARDS).¹³³

Glucocorticoids have shown promise at resolving ALI in experimental studies. In animal models, GCs attenuate diffuse alveolar inflammation and reduce the risk of progression from ALI to ARDS.^{134 135} In vitro studies indicate that neutrophilic inflammation is tempered by GCs.¹³⁶ Additionally, although GCs induce maturation of neutrophils from the bone marrow resulting in peripheral neutrophilia, they also tightly regulate the migration of neutrophils to sites of inflammation. GCs prevent neutrophil accumulation in tissues by downregulating L, P and E-selectin from the cells' surface, reducing neutrophil attachment to the endothelium and therefore preventing extravasation. GCs also reduce endothelial expression of selectin ligands including ICAM

and VCAM. Finally, GCs reduce the activation of neutrophils by tamping proinflammatory cytokines and reduce superoxide release and ROS levels.²² It is well known that GCs inhibit the mRNA transcription of proinflammatory genes, which may be significant to reducing neutrophilic inflammation due to evidence that lung-transmigrated neutrophils exhibit a rapid burst of inflammatory transcription on arrival in the airspace.¹³⁷ However, GCs have generally failed to show efficacy in ALI/ARDS in human clinical studies.¹³⁸ Indeed, the influence of GCs in infection-induced acute injury appears pathogen-dependent. In murine studies, GCs did not improve lung injury pathology score of H5N1-infected mice but GCs improved the score of H1N1 pandemic influenza-infected mice^{139–141} (online supplemental table S1). Similarly, GCs improved lung injury score for mice infected with SARS-CoV-2 and not fungal pneumonia models^{142–145} (online supplemental table S1).

COVID-19

While viral load clears within 3–5 days of the initial infection, the serious sequelae of COVID-19 emerge days later when viral titers are low or undetectable, suggesting that pathophysiologic mechanisms are linked to the dysregulated immunity following infection.^{146 147} As such, there is great interest in immunomodulatory therapies,^{148 149} and CSs have been evaluated in several case series, studies and trials.^{150 151} Initial results from case studies were negative, prompting the WHO to recommend against CS therapy in COVID-19.¹⁵² These guidelines were reversed afterward, in July 2020, when the RECOVERY Collaborative Group published positive results in its preliminary report on the open-label, controlled trial of dexamethasone for COVID-19.^{153 154} They reported that in 2104 patients receiving dexamethasone versus 4321 in the usual care group, dexamethasone reduced mortality among patients on invasive mechanical ventilation (rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (rate ratio, 0.82; 95% CI 0.72 to 0.94).¹⁵⁴ Due to these findings, similar trials of GCs for COVID-19^{155–157} were halted, and international clinical practice guidelines were modified to support the use of GCs in moderate to severe COVID-19.^{151 158} While the most attention has been focused on dexamethasone since the influential RECOVERY trial, similar studies using methylprednisolone^{29 159 160} and hydrocortisone^{155 157} have also suggested benefit in COVID-19, although the quality of evidence for these studies is low to moderate, as the studies were either halted prematurely or were observational.

As evidence continues to emerge, GCs have become a first-line treatment in moderate to severe COVID-19. Indeed, a recent systematic review and meta-analysis by Cano *et al*¹⁶¹ that evaluated 73 studies on 21,350 patients with COVID-19 concluded that CSs provide mortality benefit in severely ill patients (OR 0.65; 95% CI 0.51 to 0.83, $p=0.0006$).

Influenza

CSs as adjunct therapy to neuraminidase inhibitors were primarily used during the Influenza A/H1N1 pandemic of 2009, with some epidemiologic studies estimating its use in 18%–53% of critically ill patients requiring mechanical

ventilation.^{162–164} Unfortunately and despite their widespread use, several meta-analyses have raised the issue of a potentially augmented risk of death with or without the use of concomitant neuraminidase inhibitors and irrespective of timing and dosage of CS therapy (relative risk (RR) or equivalent OR of 1.53–4.22).^{66–68 165} This is also associated with an increased risk of nosocomial infection (RR 1.98–3.15),^{66 67 165} rate of ICU admission,¹⁶⁵ higher proportion of patients requiring mechanical ventilation,¹⁶⁵ and increased ICU length of stay.⁶⁶ To our knowledge, there are no RCTs that have assessed the benefits of CSs in viral influenza. Data incorporated into these analyses are heterogeneous and almost exclusively based on case-control or cohort studies, of which none proved unequivocally favorable effects. Overall, this is in stark contrast with data applicable to community acquired pneumonia of general etiologies (bacterial and mixed), and from animal models, which have shown improvement in histopathologic scores and survival rates.^{69 141}

Pneumocystis jirovecii

Classically known as an opportunistic infection in HIV individuals, *Pneumocystis jirovecii* (previously called *P. carinii*) pneumonia (PCP or PJP) is increasingly recognized as posing a substantial risk to transplant recipients, patients with malignancies, and in those receiving chronic immunosuppression or cytotoxic therapy. Affected individuals can present with a wide spectrum of disease severity, ranging from an insidious onset of dyspnea in HIV-infected individuals, to fulminant respiratory failure in HIV-uninfected patients, with mortality approaching 50%–80% in this population.^{166 167}

CSs used in a 21-day tapered regimen have been used as established adjuvant therapy for patients with HIV and moderate to severe PJP pneumonia, which is defined by (1) a partial pressure of oxygen <70 mmHg on room air or (2) an alveolar-arterial (A-a) gradient of ≥ 35 mmHg.^{168 169} Presumptively, the anti-inflammatory benefits may mitigate an enhanced inflammatory response and subsequent clinical deterioration known to occur within 3–5 days in response to microbial death caused by the initiation of anti-*Pneumocystis*-specific therapy.^{168 170} Earlier RCTs evaluating the use of adjuvant CS therapy in HIV-associated PJP showed significant reductions in the mortality rate at 1 month (RR 0.21–0.48)^{171–173} and need for mechanical ventilation (RR 0.24–0.35).^{171 173} Furthermore, aggregate data in a Cochrane review with three additional RCTs^{170 174 175} mirrored these favorable benefits with an overall reduction in the relative risk of death of 44% (RR 0.56) at 1 month and 41% (RR 0.59) at 3–4 months.¹⁷⁶ This subsequently translated into a number needed to treat to prevent 1 death in 9 patients not on highly active antiretroviral therapy and 1 in 23 in those on it, along with a robust reduction in the need for mechanical ventilation at 1 month by 62% (RR 0.38).¹⁷⁶

Despite clear-cut benefits in the HIV-infected population, the role of adjunctive CSs in HIV-uninfected patients remains controversial. Current evidence is weak and predominantly based on retrospective cohort studies, with a large majority failing to demonstrate favorable effects on mortality and need for mechanical ventilation.^{177–182} In a study of 323

HIV-negative patients with PJP, early CS therapy (within 48 hours of diagnosis) was not associated with any survival benefit, length of hospital stay, admission to the ICU, and need for mechanical ventilation by 1 month or physiologic improvement in respiratory Sequential Organ Failure Assessment (SOFA) score at day 5 following initiation of CS and pneumocystis-specific therapy.¹⁸¹ Conversely, in a larger study on 1299 participants, CSs were associated with improved 60-day mortality in patients with severe disease, as defined by a $\text{PaO}_2 \leq 60$ mmHg HR 0.71) but not in those with moderate disease.¹⁸³

Meta-analyses have also failed to demonstrate a survival benefit, suggesting in fact an increased risk of death (OR 1.37, CI 1.07 to 1.75).^{184 185} This analysis¹⁸⁵ also revealed a survival benefit in patients with respiratory failure (OR 0.63), although the definition of respiratory failure was relatively heterogeneous among included studies, and a majority of cases (55%) originated from the study conducted by Inoue and colleagues, which defined respiratory failure as $\text{PaO}_2 \leq 60$ mmHg.¹⁸⁶

Community-acquired pneumonia (CAP)

CSs have been proposed as adjunctive therapy for the treatment of CAP for many years. Several animal models have demonstrated decline in circulating and pulmonary proinflammatory cytokine levels and reduction in histopathologic severity scores with adjunctive CS therapy.^{187–190} Similar reductions have been noted in prospective cohort studies for patients presenting with CAP and septic shock.^{191–193}

Despite evidence for favorable pathophysiologic responses attributed to CS therapy, effects on mortality remain controversial. With the exception of two studies (Confalonieri *et al*,¹⁹⁴ Nafae *et al*¹⁹⁵) that demonstrated a positive effect on mortality, most RCTs did not replicate these results in patients with severe CAP.^{194–204} Results from pooled meta analyses remained controversial for patients treated for severe CAP, however, have demonstrated no effect on mortality in those with non-severe CAP.^{205–209} The presence of differences can primarily be attributed to variability in study methodology and likely to poorly defined study populations due to heterogeneity in CS type, dosing, treatment duration, and criteria for defining CAP severity among individual RCTs. Irrespective of these potential confounding factors, CSs have demonstrated beneficial effects in improving time to clinical stability, reducing hospital length of stay, need for mechanical ventilation, and progression to acute respiratory distress syndrome, without increasing the risk for gastrointestinal bleeding or contributing to treatment failure.^{194–196 201 202 205–209} These results mirror data currently available for stress-dose CS therapy in patients with refractory septic shock.^{153 210} At the same time, one should remember that CS use in the intensive care setting could be associated with critical illness polyneuropathy, critical illness myopathy and/or delirium.

Fibrotic inflammation

Fibrotic inflammation is a dysregulated response to tissue injury that results in uncontrolled deposition of extracellular matrix (ECM) that interrupts tissue function. In the distal airways and alveoli, such fibrotic inflammation can result from acute or chronic exposure, infection, or trauma.

These insults produce inflammation that activates fibroblasts to proliferate and produce ECM components. The resultant fibrotic pathologies are varied with a common theme of disruption of normal tissue structure by fibrotic processes.^{211–213} Despite the fact that inflammation seems to drive early fibroproliferation through the signaling of cytokines such as IL-1 β and IL-6, CS treatment has proven ineffective in most fibrotic lung diseases.²¹⁴ Further, animal models of pulmonary fibrosis are limited, slowing the progress toward antifibrotic therapeutics. The most common model is bleomycin injury that does not recapitulate the non-resolving IPF-associated fibroproliferation. Future studies of anti-fibrotic therapeutics are aimed at microphysiological systems incorporating human cells and tissues.²¹⁵

Usual interstitial pneumonia (UIP)

Almost universally, the presence of UIP, especially in IPF, is accompanied by a progressive clinical course resulting in chronic respiratory failure with poor long-term prognosis and response to several immunosuppressive therapies, including CSs. Hallmark histologic characteristics include a heterogeneous appearance of fibroblastic foci (both geographically and temporally), composed of dense collagen, fibroblasts, and myofibroblasts alternating with areas of normal lung parenchyma in a predominantly peripheral and subpleural distribution. Interstitial inflammatory infiltrates comprised of lymphocytes and plasma cells are generally mild and considered a non-dominant feature, highlighting support behind poor responses to immunosuppressive treatments.²¹⁶

Idiopathic pulmonary fibrosis (IPF)

For many years, CSs were considered to be the backbone of conventional therapy based on retrospective observational studies that suggested a mild clinical benefit in approximately 15%–30% of patients.^{217–219} Notably, patients that responded to treatment were found to be younger and with a cellular-appearing biopsy,²¹⁷ which is inconsistent with the typical demographic profile for IPF and current pathologic understanding and definition of UIP. As a result, it seems likely that those that responded favorably may have done so if they had steroid responsive histologic patterns such as desquamative interstitial pneumonia (DIP) or non-specific interstitial pneumonia (NSIP), which were not clearly delineated as separate entities until mid-1990s.^{220–221} Additional factors that limit interpretation of these results included heterogeneous definitions of treatment response and lack of objective, validated endpoints.

As a result, owing to a potential benefit in a disorder with a poor prognosis, no RCTs directly explored GC use versus placebo until the late 1980s, when CSs were used in the control arms of several trials evaluating both immunosuppressive (cyclophosphamide, azathioprine, colchicine) and non-immunosuppressive (N-acetylcysteine, D-penicillamine) adjunctive therapies.^{221–226} None of these studies demonstrated a clinically meaningful symptomatic, physiological, or survival advantage from any combination of therapy. Two trials evaluating (1) high-dose prednisolone versus a combination of low-dose prednisolone and cyclophosphamide²²³ and (2) high-dose prednisone versus colchicine²²¹ demonstrated a trend toward a decline in pulmonary

function and shortened survival, while a third and more recent study (PANTHER) evaluating the use of combination N-acetylcysteine to prednisone and azathioprine revealed an increased risk of hospitalization and death.²²⁵

Finally, one retrospective cohort study evaluating outcomes in patients that were either treated with or without CSs prior to a presentation of an acute exacerbation of IPF (AE-IPF), suggested that those treated with CSs had significantly adverse outcomes, with a 25% survival rate (HR 3.54). Survivors were also noted to have worse 1-year survival rates, although these comparative cohorts included small number of patients.²²⁷ Current treatment practices have shifted away from routine use of general immunosuppressive agents to targeted anti-fibrotic therapy, although robust data in support for effective long-term outcomes are still lacking.^{228–230}

A small minority of patients with IPF can experience acute and rapid deterioration in lung function (acute exacerbation, AE-IPF) characterized by increased areas of ground glass on CT correlating with acute or organizing diffuse alveolar damage (DAD) or less commonly, organizing pneumonia.²³¹ High-dose steroids (prednisone 1 mg/kg/day to methylprednisolone 1 g/day) have been suggested by international guidelines; however, this recommendation is weak and based on anecdotal evidence from uncontrolled retrospective cohort studies.^{231–235} Despite treatment with high-dose steroids, AEs-IPF carry significant morbidity and mortality. One study evaluating outcomes of patients with exacerbations of interstitial pneumonias admitted to the hospital revealed that those presenting with an AE-IPF were found to have an overall 90-day mortality of 69%.²³⁴ In another cohort of 25 patients admitted to the ICU with 84% needing mechanical ventilation, 24 (96%) died. All patients received high-dose CSs, with eight also receiving additional immunosuppressive therapy with cyclophosphamide.²³²

Connective tissue disease–usual interstitial pneumonia (CTD–UIP)

CSs are frequently used for management of extrapulmonary manifestations; however, definitive evidence supporting use in CTD–UIP is lacking although there is justification in using immunosuppression to control underlying autoimmunity in mitigating further decline of lung function. To date, no RCTs have been conducted, while several studies do not differentiate UIP from non-UIP subtypes which makes interpretation of the results difficult. Current management practices are now incorporating the use of antifibrotics such as nintedanib and pirfenidone particularly with experiences extrapolated from patients with IPF–UIP and the INBUILD and SENSICIS trials.²³⁶

While no RCTs have evaluated the utility of CSs in the treatment of COP, several case series have supported the use of CSs as effective treatment in controlling disease activity.^{237–243} From pooled data comprising of 12 case series and approximately 160 patients with histologically confirmed COP, treatment with CSs was associated with a complete response (generally with resolution of presenting symptoms and pulmonary opacities without leaving significant physiologic or imaging sequelae) in 59.4% of patients while a partial response was noted in 26.9%. Of the remaining 20%, only 6% had a fatal outcome.^{244–245}

The optimal dosage of CSs is unknown; however, most experiences and collaborative practice guidelines propose initiating high-dose prednisone equivalent to 0.75–1 mg/kg/day.^{237 238 241 244–246} Although the duration of therapy is also uncertain, the initial dose is typically maintained for 1–3 months with a gradual taper advocated over a 6–12 month period during which time frequent disease relapses are known to occur, particularly as steroids are discontinued or dose reduced under 20 mg/day.^{238 239 241} In one of the largest and well-described series of 48 patients, 42% (n=20) that were treated with high-dose CSs had complete recovery without disease relapse—typically classified by the reappearance of new infiltrates with compatible clinical features. Of the remaining 58% (n=28), 15 (31%) had one relapse, whereas 13 (27%) experienced two or more relapses with 5 patients (10%) experiencing four or more. The majority of relapses occurred within the first year of diagnosis with the probability of a relapse-free course being 65% at 6 months, 49% at 1 year, 32% at 2 years, and 16% at 4 years after initial diagnosis.²³⁸ These data have been similarly described elsewhere in the literature, although with some variability. For example, in a larger series originating from China of 73 patients with CS-treated COP with a similar treatment protocol, 31.5% (n=23) developed relapses, with only 3 having two or more.²⁴¹

Respiratory bronchiolitis–interstitial lung disease (RB-ILD)

CS therapy's role in management remains controversial and with variable results. For example, in a series of 12 patients of whom 11 were treated with CSs, initial improvement was observed in 6 (54%); however, sustained benefit as defined by ATS/ERS criteria at the end of the follow-up period was notable in only 2 (18%). Approximately two-thirds were still smoking.²⁴⁷ In another study, 43% (9) of patients treated with steroids, demonstrated improvement in the extent of centrilobular nodules and ground glass opacities on follow-up CT.²⁴⁸ Conversely, in the largest study reporting characteristics of 25 cases of RB-ILD, 15 (60%) patients were treated with oral prednisone. Overall symptomatic improvement was noted in only 2 patients (13%), whereas a significant number (10, 67%) reported symptomatic worsening with 8 experiencing a decline in pulmonary function. Sixty-four per cent of patients in this series were successful in quitting smoking.²⁴⁹ To our knowledge, data regarding dosing, duration, and criteria for initiation of CS therapy have not been clearly defined in any reported studies nor have any RCTs directly evaluating the role of corticosteroids. As a result, significant treatment heterogeneity may exist and contribute to the variability in the reported data and our current understanding of this rare disorder.

Desquamative interstitial pneumonia (DIP)

The largest study to date is a prospective longitudinal study of 40 patients with biopsy-proven DIP who were followed up over a 24-year period and were not treated at presentation.²⁵⁰ In this study, 22% recovered spontaneously (15% had complete remission), 15% remained unchanged, while 62% had progressive disease necessitating treatment with long-term systemic CSs (30–60 mg prednisone tapered to 20 mg/day for at least 6 months). Among the 26 patients that

were treated for a mean period of 3.1 (\pm 2.8) years, 61.5% improved, 11.5% remained unchanged, and 27% worsened based on longitudinal changes in clinical, physiologic, and radiographic data. Notably, the extent of fibrosis on diagnostic histopathology correlated with favorable treatment outcomes in those with mild or moderate fibrosis, whereas none of the patients with severe fibrosis improved—a finding supported in another clinicopathologic analysis.²⁵¹ On a radiological standpoint, two studies comprising 19 patients demonstrated that CS therapy resulted in improvement in areas of ground glass attenuation in more than half the cases on follow-up chest CT, while areas of cystic and fibrotic changes were generally left unaffected.^{252 253} Several other series have echoed utility of long-term therapy with high-dose CSs. Recent composite data from almost 200 patients included in eight series and several individual cases revealed that 57% improved, 22% remained stable, and 20% worsened with CS therapy.²⁵⁴ While the lack of RCTs do raise a question whether this benefit is due to smoking or exposure limitation, corticosteroid treatment, or the natural course of disease, CSs do remain a reasonable therapeutic option for those with progressive disease. The lack of RCTs raises the question whether this benefit is due to smoking cessation, exposure limitation, CS treatment or the natural course of disease; however, several series have added in support of long-term therapy in those with progressive therapy. Indeed, recent composite data from almost 200 patients included in eight series and several individual cases revealed that 57% improved, 22% remained stable, and 20% worsened with CS therapy.²⁵⁴

Non-specific interstitial pneumonia (NSIP)

Due to the lack of robust prospective data and clinical heterogeneity of this subtype, the overall impact of treatment has been difficult to evaluate; however, in comparison to other idiopathic interstitial pneumonia (IIP)s, CSs have favorable disease-modifying effects. Current practices are largely based on clinical experience and extrapolated from retrospective studies. In those with idiopathic NSIP, these studies comprise varying populations of cellular and fibrosing phenotypes along with variable and loosely defined treatment regimens or meaningful clinical endpoints which limit interpretation. However, universally, CS treatment was associated with symptomatic, physiologic, and radiographic improvement in a majority of included patients.^{255–259} These effects have also been observed in those with NSIP associated with a variety of connective tissue disorders in which CSs comprise backbone therapy in treating both lung and systemic disease.

The optimal dose and duration of therapy is unknown and are often variable based on individual practice experiences. In the absence of respiratory failure, which is generally treated with pulse dose steroids, a reasonable initiating dose of prednisone at 0.5–1 mg/kg of ideal body weight (up to 60 mg/day) is maintained over a 1-month period.^{258–260} Thereafter, higher doses comprising 30–40 mg/day are maintained for an additional 1–2 months after which a gradual taper over several months to low dose prednisone can be implemented in those improving or stabilized disease.^{258 259} In patient's that are unable to be tapered from higher doses of prednisone, those with frequent relapses,

Table 2 Summary: corticosteroids in lung disease

Benefit?	Indication	Effect	Evidence strength	Unanswered questions
✓	Sarcoidosis	Short-term improved symptoms, chest imaging and pulmonary function	Short term: Strong Long term: Weak	Long-term efficacy; dosage and duration
✗	Pulmonary tuberculosis	No benefit	Strong	TB-infected ALI patients
✓	<i>Pneumocystis jirovecii</i>	In HIV-infected individuals, reduction in mortality rate and need for mech vent at 1 month	Strong	Role in non-HIV infected individuals
✗	Influenza	No benefit, possible harm: increased risk of nosocomial infection, rate of ICU admit, and req. for mech vent	Moderate	No RCT on viral influenza with CS
✓	Community acquired pneumonia	Improved time to clinical stability, reduced hospital length of stay and req. for mech vent, reduced progression to ARDS	Moderate	
✓	Acute hypersensitivity pneumonitis	Improved FEV1, FVC, DLCO at 1 month that diminishes at 1 and 5 years	Weak	
✗	Chronic hypersensitivity pneumonitis	No benefit in fibrotic phenotype	Weak	
✓	Acute eosinophilic pneumonia	Resolution of symptoms including respiratory failure, normalization of chest radiographs, lack of frequent recurrence, and minimal residual abnormalities on pulmonary function testing	Strong	
✓	Chronic eosinophilic pneumonia	Complete response; relapse on cessation; improvement in restrictive abnormalities on pulmonary function	Strong	CEP with coexisting asthma
✓	Desquamative interstitial pneumonia	Effective in mild/moderately fibrotic cases	Moderate	Confounding with smoking cessation
✓	Microscopic polyangiitis and granulomatosis with polyangiitis	In combination with cyclophosphamide, improved remission and mortality outcomes	Moderate	Evidence for long-term use
✓	Asthma	Improved quality of life, decreased rate of acute exacerbations, and providing a protective effect against severe exacerbations	Strong	
✓	Chronic obstructive pulmonary disease	Controversial efficacy; more effective in combination with LABA and/or LAMA and in eosinophilic patients	Strong	
✓	Eosinophilic granulomatosis with polyangiitis (Churg Strauss Syndrome)	Clinical remission in patients without poor prognostic factors	Moderate	Dosage and duration; use in alveolar hemorrhage
✓	COVID-19	Reduced risk of death in severe COVID-19 induced ARDS	Strong	Combination therapies, use in non-life-threatening COVID-19
✗	Seasonal and pandemic influenza	Increased risk of death, nosocomial infection, rate of ICU admit, mech vent	Weak	Missing RCT for viral influenza GCS
✓	<i>Pneumocystis jirovecii</i>	Reduced risk of death, vent dependence	Strong (HIV) Weak (non-HIV)	
✓	Community acquired pneumonia	Improving time to clinical stability, reducing hospital length of stay, need for mechanical ventilation, and progression to acute respiratory distress syndrome,	Moderate	Controversial effect on mortality
✗	Usual interstitial pneumonia	No benefit	Weak	
✗	Idiopathic pulmonary fibrosis	Possible harm—reduced survival	Strong	Effect of GCs in acute exacerbation of IPF
✓	Connective tissue disease—UIP	Regularly used but weak evidence	Weak	Rare—only case studies, no differentiation between IPF-UIP and CTD-UIP
✓	Cryptogenic organizing pneumonia	Complete response (generally with resolution of presenting symptoms and pulmonary opacities without leaving significant physiologic or imaging sequelae)	Moderate	Dosage and duration unknown

Continued

Table 2 Continued

Benefit?	Indication	Effect	Evidence strength	Unanswered questions
✗	Respiratory bronchiolitis– Interstitial lung disease	Decline in pulmonary function possible	Weak	Lack of studies—rare condition
✓	Non-specific interstitial pneumonia	Benefit to symptoms and radiographic movement	Weak	Optimal dosage

ARDS, acute respiratory distress syndrome; CEP, chronic eosinophilic pneumonia; CS, corticosteroid; CTD-IUP, connective tissue disease—usual interstitial pneumonia; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GC, glucocorticoid; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; RCT, randomized controlled trial; TB, tuberculosis.

or those with contraindications to long-term CS therapy, additional steroid-sparing immunosuppressants can be supplemented.

Acute eosinophilic pneumonia (AEP)

While reports of successful remission with smoking cessation and exposure limitation without therapy have not been infrequently reported in those with mild disease, a significant portion of patients present with acute respiratory failure with progressive disease often requiring mechanical ventilation and treatment with GCs.^{261–265} The utility of CSs has not been evaluated in RCTs, but several reports and series have demonstrated efficacy as mainstay therapy.^{261 262 264 265}

The largest is a series comprised of 137 young military personnel in the Korean Army, 93% of whom were treated with high-dose CSs in a protocolized manner.²⁶² Those that were admitted with respiratory failure (58%, 3 requiring mechanical ventilation) as defined by P/F ratio ≤ 300 and/or tachypnea (respiration rate >30 breaths/min) were treated with intravenous methylprednisolone 60 mg every 6 hours for 3 days prior to transitioning to high-dose oral prednisolone tapered over either 2 or 4 weeks. Reported outcomes were favorable with all patients experiencing improvement in all symptoms within a median of 7 days with defervescence occurring within 48 hours and quick reversal of respiratory failure. All patients were discharged with complete resolution of symptoms and radiographic abnormalities with only one patient experiencing a relapse after resuming smoking. No significant differences in clinical outcomes were appreciable in patients that received the shorter 2-week course. In another series of 22 patients comprising a greater population of those requiring mechanical ventilation (8 intubation, 6 NIPPV), 16 were treated with CSs for a mean of 89 days. All patients irrespective of therapy were discharged from the hospital with most being followed at a mean of 12.7 months. All but one had normalized chest radiographs with a mean delay of 27 days. No relapses occurred and all patients receiving pulmonary function testing had no abnormalities in measured FEV1 and FVC.²⁶¹ These clinical outcomes (resolution of symptoms including respiratory failure, normalization of chest radiographs, lack of frequent recurrence, and minimal residual abnormalities on pulmonary function testing) have been consistently reported among other studies.^{264 265}

In summary, CSs are effective in the treatment of AEP. Several series have consistently suggested favorable outcomes in relation to quick resolution of symptoms (including respiratory failure), normalization of chest radiographs, lack of frequent recurrence, and minimal residual

abnormalities on pulmonary function. To date, the optimal dosage and length of therapy is not known. In general, treatment with high-dose intravenous steroids (60–125 mg every 6 hours) is reserved to patients with severe hypoxemia and those requiring mechanical ventilation, whereas in the absence of respiratory failure, high-dose oral CSs (40–60 mg daily) or supportive care in those with mild disease is reasonable approach. A 2-week regimen appears to be effective; however, in those presenting with peripheral eosinophilia (>500 cells/ μ L) at presentation, early cessation on clinical stabilization has been advocated by some authors.²⁶⁴ Notably, patients in this cohort had milder disease compared with patients that did not have peripheral eosinophilia at presentation with only a small minority meeting criteria for respiratory failure.

Chronic eosinophilic pneumonia (CEP)

The efficacy of CSs in treating CEP has been universally accepted and described in the literature, although no formal management guidelines exist. Responses are often dramatic with most patients experiencing symptomatic and radiographic improvement in as little as 48 hours and 1 week, respectively, after institution at an initial dose of 0.5–1.0 mg/kg/day.^{266–272} Subsequent disease activity is usually well controlled on maintenance therapy; however, a substantial portion of patients require prolonged treatment with low-dose CSs given the high frequency of relapses (50%–80%) on cessation or tapering of therapy.²⁷³ In the largest series of 133 patients, 64% required oral prednisolone for more than 1 year with 37% requiring therapy for more than 3 years.²⁶⁸ Despite the high frequency of relapses, favorable response are often noted with resumption or increased dose adjustments without a substantial impact on disease-related outcomes.^{266–272} Long-term studies have also demonstrated improvement in restrictive abnormalities on pulmonary function testing as parenchymal abnormalities recover. Interestingly, obstructive defects which are not uncommon at time of diagnosis increase in frequency at follow-up highlighting the prevalence of asthma and role of eosinophils in the pathogenesis and modulation of bronchial obstruction in this condition.^{268 271}

To date, only one randomized trial in CEP has been conducted.²⁷² In this open-labeled, parallel group study, 55 patients with CEP were treated with an initial dose of 0.5 mg/kg/day and tapered over either 3 or 6 months. All patients responded to initial treatment and no significant differences were noted in either rates or median times to relapse (182 days vs 211 days) in either group at the end of a 2-year observation period. These results coupled with

favorable outcomes and responses to retreatment, suggest that a shorter treatment duration may be more suitable to mitigate the consequences of extended corticosteroid therapy. ICSs are frequently prescribed in patients with CEP and coexisting asthma. Their utility has been explored to facilitate dose reduction of oral CSs in several retrospective studies, although data have been conflicting. Successful reports have been described^{267 269} but not consistently reflected or replicated in others. A small series evaluating the role of high-dose inhaled beclomethasone monotherapy did not demonstrate any efficacy in controlling disease activity.²⁷⁴

Acute respiratory distress syndrome (ARDS)

ARDS is in part the end-result of an innate immune cell-mediated inflammatory response that causes damage to the alveoli and the surround structures in response to a direct injury. It has long been hypothesized that treatment with CS may be beneficial in patients with ARDS, regardless of the etiology. A more recent systematic review and meta-analysis is the first to support this hypothesis, indicating that CS may reduce mortality and the duration of mechanical ventilation in all patients with ARDS. Furthermore, corticosteroids likely cause few side effects, except for an increase in hyperglycemia. This effect on mortality appears to be consistent across COVID-19 ARDS (regardless of strict ARDS criterion) and non-COVID-19 patients, and between corticosteroid type, timing and dose, although a longer duration of therapy may be more beneficial compared with a shorter course. Given the consistency of the results between ARDS etiology, this analysis supports the hypothesis that CSs should be considered in all patients with ARDS, assuming no contraindications.

CONCLUSIONS

GCs are powerful immunosuppressants that work by modulating the transcription and translation of inflammation-related genes. They have revolutionized the standard of care for many inflammatory conditions, but their effects in the distal lungs depend on the type of inflammatory pathology and the individual patient (table 2). Results from clinical studies across several diseases suggest that GCs are effective at reducing granulomatous inflammation. Evidence is emerging that diffuse alveolar damage can be reduced or prevented with early GC treatment during acute lung injury in certain cases and on a pathogen-dependent basis. However, few to no studies have shown benefit in reducing fibrosis-driven inflammatory pathologies like IPF and ARDS-induced fibroproliferation. Results from these studies are, however, difficult to compare directly due to inconsistencies in study design, patient population, and outcome measures. Further investigation is required to elucidate the optimal dosing method, dosing strategy, drug choice, and timing of intervention in most pulmonary pathologies that might benefit from GC intervention.

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