Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Review: Oral Glucocorticoids

Date of Review: February 2022 **End Date of Literature Search:** 10/13/2021
Generic Names: See **Appendix 2** for a list of medications

Purpose for Class Review:
To identify appropriate utilization management strategies for oral glucocorticoids.

Research Questions:
1. What is the comparative efficacy and effectiveness for oral glucocorticoids used in management of anti-inflammatory and autoimmune conditions?
2. What are the comparative harms for oral glucocorticoids used in management of anti-inflammatory and autoimmune conditions?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which one oral glucocorticoid is more effective or associated with fewer adverse events?

Conclusions:
Systematic Reviews Focused on Efficacy
- There are over 100 Cochrane reviews that evaluate evidence for the safety and efficacy of oral glucocorticoids for various clinical conditions. After reviewing published literature, Cochrane reviewers determined there is low-quality or insufficient evidence for the use of oral glucocorticoids in treating the following conditions: shoulder pain,[1] periorbital and orbital cellulitis,[2] influenza,[3] acute gout,[4] tuberculosis pleurisy,[5] acute otitis media in children,[6] myasthenia gravis,[7] optic neuritis,[8] chronic inflammatory demyelinating polyradiculoneuropathy,[9] chronic rhinosinusitis,[10,11] pulmonary sarcoidosis,[12] primary biliary cirrhosis,[13] congenital adrenal hyperplasia,[14] dengue fever,[15] cancer-related pain in adults,[16] cancer-related dyspnea in adults,[17] viral myocarditis,[18] and postherpetic neuralgia.[19]
- Three Cochrane reviews concluded current evidence does not support the use of oral glucocorticoids for management of sore throat in adults and children,[20] to hasten recovery from Guillain-Barre syndrome (GBS),[21] or for management of acute sinusitis in children and adults.[22]
- Five Cochrane reviews cited moderate or high-quality evidence for the use of glucocorticoids in specific conditions including: treatment of croup in children;[23] recovery of facial motor function in patients with Bell's palsy;[24] prevention of respiratory complications in patients with cystic fibrosis;[25] promoting disability recovery in patients with relapsing-remitting multiple sclerosis (MS) experiencing acute relapse;[26] and after treatment of an acute asthmatic exacerbation.[27] In all of these reviews glucocorticoids were compared to placebo or no treatment.

Systematic Reviews Focused on Safety
- A 2019 systematic review aimed to investigate whether chronic use of oral glucocorticoids for more than 4 months would increase mortality and vertebral fracture risk in patients with stable chronic obstructive disease (COPD).[28] A meta-analysis of 5 studies (n=1,795) demonstrated that use of long-term oral

glucocorticoids increased the risk of mortality compared to placebo (risk ratio [RR], 1.63; 95% confidence interval [CI], 1.19 to 2.23; p<0.0001; I^2 = 86%).[29] A meta-analysis of 4 studies showed long-term use of oral glucocorticoids increased the rate of vertebral fractures (odds ration [OR], 2.31; 95% CI, 1.52 to 3.50; p=0.03; I^2 = 65%).[29] These results support the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommendations to not use systemic glucocorticoids in the treatment of COPD for extended, chronic use.[30]

- The primary outcome of a 2018 systematic review was to estimate the risk of different complications related to the long-term use of oral glucocorticoids in the treatment of asthma as an add-on to chronic maintenance therapy (high dose inhaled corticosteroids and other controller medications).[21] Duration of glucocorticoid therapy ranged from 3 months to 2 years in the 15 studies that met inclusion criteria. Combining unadjusted OR of adverse events among patients who were treated with glucocorticoid compared with patients who were not, there was an increased risk of peptic ulcers 2.86 (95% CI 1.39 to 5.90), hypertension 1.28 (95% CI 1.20 to 1.36), diabetes mellitus 1.30 (95% CI 1.02 to 1.64), cataracts 1.49 (95% CI 1.29 to 1.72), infections 1.68 (95% CI 1.51 to 1.87), and fractures 1.46 (95% CI 1.25 to 1.70); the risk of osteoporosis and glaucoma was not different between groups.[21] The use of oral glucocorticoids in the chronic management of asthma is associated with a higher risk of adverse effects.[21]
- A 2016 systematic review aimed to identify the most common and serious adverse drug reactions (ADRs) associated with a short course of oral glucocorticoids in children.[31] The most serious adverse effect associated with short courses of oral glucocorticoids was infection.[31] All the children returned to a normal level of endogenous cortisol secretion within 10–12 days after discontinuation of the glucocorticoids.[31] The 3 most common adverse drug effects (ADRs) were vomiting, changes in behavior and disturbed sleep.[31] Vomiting was the most common ADRs with an incidence of 5.4% and was the most frequent reason for early discontinuation of a glucocorticoid.[31]
- There is insufficient evidence to evaluate if there are subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities for which one oral glucocorticoid is more effective or associated with fewer adverse events.

Clinical Practice Guidelines

- The 2021 Global Initiative for Asthma (GINA) recommendations suggest a short course of oral glucocorticoids may be needed in addition to inhaled glucocorticoids for severe or uncontrolled asthma exacerbations.[32] Oral glucocorticoids should only be considered for adults with poor symptom control or frequent exacerbations despite good inhaler technique and adherence with appropriate guideline-recommended treatment, and after exclusion of other contributory factors and other add-on treatments including biologics.[32]
- In 2018, the Endocrine Society published updated clinical practice guidelines for management of congenital adrenal hyperplasia (CAH).[33] Management of classic CAH is a difficult balance between hyperandrogenism and hypercortisolism.[33] During childhood, the preferred glucocorticoid is hydrocortisone because its short half-life minimizes the adverse effects typical of longer-acting, more potent glucocorticoids, especially growth suppression.[33] Glucocorticoid maintenance therapy recommendations in fully grown patients with CAH are presented in **Table 2.**
- According to the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, oral glucocorticoids have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.[30] Long-term use of oral glucocorticoids has numerous adverse effects (Level of Evidence A) with no evidence of benefits (Level of Evidence C).[30] Long-term use of oral glucocorticoids is not recommended (Level of Evidence A).[30] Duration of therapy should not be more than 5-7 days (Level of Evidence A).[30]
- In 2017 the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) collaborated to update guidance for prescribing glucocorticoids in pregnancy and breastfeeding.[34] Prednisolone is compatible with each trimester of pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatologic disease in pregnancy.[34]
- In 2016 the Endocrine Society formulated clinical practice guidelines for hormonal replacement in adults with hypopituitarism.[35] Hydrocortisone is recommended for glucocorticoid replacement, usually as a 15 to 20 mg total daily dose in single or divided doses. (Strong Recommendation, Moderate-Quality Evidence).[35]

- The Endocrine Society published clinical guidelines that address the diagnosis and treatment of primary adrenal insufficiency in 2016.[36] Glucocorticoid therapy is recommended in all patients with confirmed primary adrenal insufficiency (Moderate Recommendation; High-Quality Evidence).[36]

Recommendations:

- Create a new Oregon Health Plan Fee-for-Service Preferred Drug List (PDL) entitled "Oral Glucocorticoids".
- Add at least one formulation of each glucocorticoid to the PDL after review of costs in the executive session.

Background:

Glucocorticoids are synthetic analogs of natural steroid hormones secreted by the adrenal cortex under the control of the hypothalamic-pituitary-adrenal (HPA) axis.[37] They have anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.[38] The clinical effects of glucocorticoids are predominantly achieved by regulating the transcription of anti-inflammatory genes to affect the downstream production of cytokines, cell adhesion molecules and other key enzymes involved in the host inflammatory response.[38] Glucocorticoids are used as replacement therapy in adrenal insufficiency (at physiologic doses) as well as in supraphysiologic doses for the management of dermatologic, ophthalmologic, rheumatologic, pulmonary, hematologic, and gastrointestinal disorders.[38] It is estimated that 1 to 2% of the population in the United States (US) population are on chronic glucocorticoid therapy.[39]

Glucocorticoids do not have significant mineralocorticoid, androgenic, or estrogenic activity; thus the major systemic adverse effects are from suppression of the HPA axis and Cushing's syndrome.[40] Use of glucocorticoids for greater than 2 weeks results in suppression of the HPA axis, which requires tapering of glucocorticoid doses prior to discontinuation of therapy.[40] Osteoporosis, adrenal suppression, cataracts, hyperglycemia, dyslipidemia, cardiovascular disease, psychiatric disturbances and immunosuppression are among the more serious adverse effects observed with systemic glucocorticoid therapy, particularly when used at high doses for prolonged periods.[38] Glucocorticoids are classified according to duration of effect, glucocorticoid activity and mineralocorticoid potency.[38] Dosing is expressed relative to hydrocortisone and is useful in determining comparable doses.[38] **Table 1** compares properties of oral glucocorticoids.

Table 1. Oral Glucocorticoid Properties Relative to Hydrocortisone[38]

Medication	Relative Glucocorticoid Activity	Equivalent Dose	Duration of Action	Relative Mineralocorticoid Activity
Short-acting				
Hydrocortisone	1	20 mg	8-12 hours	1
Cortisone	0.8	25 mg	8-12 hours	0.8
Intermediate-acting				
Prednisone	4	5 mg	18-36 hours	0.8
Prednisolone	4	5 mg	18-36 hours	0.8
Methylprednisolone	5	4 mg	18-36 hours	0.5
Long-acting				
Dexamethasone	30	0.75 mg	36-72 hours	0
Abbreviations: mg = milligrams				

Concomitant use of other medications should also be assessed before initiating glucocorticoid therapy as significant drug interactions have been noted with oral contraceptives, antiepileptic drugs, anticoagulants, antifungals, antibiotics, and antivirals.[38] Systemic glucocorticoids are eliminated primarily by hepatic CYP3A4 metabolism, and inhibition of the catalytic activity of CYP3A4 by other drugs can affect their elimination.[37] The drug-drug interactions mediated through CYP3A4 result either from induction (leading to a decrease in glucocorticoid availability) or from inhibition (leading to an increase in glucocorticoid availability) of this enzyme.[37]

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

SYSTEMATIC REVIEWS:

Efficacy of Oral Glucocorticoids

There are over 100 Cochrane reviews which evaluate the safety and efficacy of glucocorticoids for various clinical conditions. After reviewing published literature, Cochrane reviewers determined there is low-quality or insufficient evidence for the use of oral glucocorticoids in treating the following conditions: shoulder pain,[1] periorbital and orbital cellulitis,[2] influenza,[3] acute gout,[4] tuberculosis pleurisy,[5] acute otitis media in children,[6] myasthenia gravis,[7] optic neuritis,[8] chronic inflammatory demyelinating polyradiculoneuropathy,[9] chronic rhinosinusitis,[10,11] pulmonary sarcoidosis,[12] primary biliary cirrhosis,[13] congenital adrenal hyperplasia,[14] dengue fever,[15] cancer-related pain in adults,[16] cancer-related dyspnea in adults,[17] viral myocarditis,[18] and postherpetic neuralgia.[19] This class update will focus on publications that evaluate outpatient utilization of oral glucocorticoids. Three Cochrane reviews concluded current evidence does not support the use of oral glucocorticoids for management of sore throat in adults and children,[20] to hasten recovery from Guillain-Barre syndrome (GBS),[21] or for management of acute sinusitis in children and adults.[22] Five Cochrane reviews cited moderate or high-quality evidence for the use of glucocorticoids in specific conditions including: treatment of croup in children;[23] recovery of facial motor function in patients with Bell's palsy;[24] prevention of respiratory complications in patients with cystic fibrosis;[25] promoting disability recovery in patients with relapsing-remitting multiple sclerosis (MS) experiencing acute relapse;[26] and after treatment of an acute asthmatic exacerbation.[27] In all of these reviews glucocorticoids were compared to placebo or no treatment. Cochrane reviews citing moderate or high-quality evidence for the avoidance or utilization of glucocorticoids in specific conditions are summarized below.

Evidence Does Not Support Use in Specified Indication

Sore Throat

The objective of a 2020 Cochrane update was to assess the clinical benefit and safety of glucocorticoids in reducing the symptoms of sore throat in adults and children.[20] Randomized controlled trials that compared glucocorticoids to placebo or standard clinical management were included.[20] Nine trials involving 1319 participants (369 children, aged over 3 years and 950 adults) met inclusion criteria.[20] Trials were conducted in general practice or emergency department settings. Primary outcomes included: complete resolution of pain at 24 and 48 hours; mean time to onset of pain relief; and mean time to complete resolution of pain.[20] Secondary outcomes included adverse events, relapse rates and days missed from school or work.[20] Antibiotics were administered to both glucocorticoid and placebo group participants in all of the included trials.[20] Six trials used a single oral dose either dexamethasone (up to 10 mg) or prednisone 60 mg.[20] The other trials used a single intramuscular (IM) dose of betamethasone 8 mg or a combination of oral and IM glucocorticoid doses.[20] The included studies were assessed as moderate quality, but the small number of studies has the potential to increase the uncertainty, particularly if applying these results to children.[20]

Five trials reported resolution of pain at 24 hours and 4 RCTs reported pain resolution at 48 hours. In addition to any effect of antibiotics and analgesia, glucocorticoids increased the likelihood of complete resolution of pain at 24 hours compared to placebo (RR 2.4, 95% CI 1.29 to 4.47; p=0.006; I^2 = 67%; high-certainty evidence).[20] The number-needed-to-treat for an additional beneficial outcome (NNTB) was 4.8 (95% CI 2.85 to 14.28).[20] Similar results on pain resolution were observed at 48 hours (RR 1.50, 95% CI 1.27 to 1.76; p<0.001; I^2 = 0%; high-certainty evidence).[20] The NNTB at 48 hours was 4.1 (95% CI 2.4 to 16.7).[20] In a pooled analysis of 7 trials, the mean time to onset of pain relief was 6 hours earlier in participants taking glucocorticoids compared to placebo (MD −5.96, 95% CI −8.75 to −3.17; p<0.001; I^2 = 69%; moderate-certainty evidence).[20] The mean time to complete pain resolution with glucocorticoids was reduced by 21 hours compared to placebo (MD −21.01, 95% CI −26.42 to −15.61; p<0.001; I^2 = 9%; moderate-certainty evidence).[20] No differences were reported in relapse rates, days missed from work or school, or adverse events for participants taking glucocorticoids versus placebo.[20] However, the reporting of adverse events was poor, and only two trials included children or reported days missed from work or school.

In summary, a single dose of oral or intramuscular glucocorticoids, in addition to antibiotics, moderately increased the likelihood of both resolution and improvement of pain in participants with sore throat with an average difference of 6 hours in time to onset of pain relief compared to placebo.[20] Given the limited benefit, further research into the harms and benefits of short courses of steroids is needed to permit informed decision-making.[20]

Guillain-Barre Syndrome

A 2016 Cochrane review examined the ability of glucocorticoids to hasten recovery and reduce the long-term morbidity from Guillain-Barre syndrome (GBS).[41] Literature was searched through January 12 2016. Studies that evaluated of any form of glucocorticoid or adrenocorticotrophic hormone (ACTH) versus placebo or supportive care alone in GBS were included.[41] Eight RCTs with 653 participants met inclusion criteria.[41] The primary outcome of interest was change in disability grade on a 7-point scale after 4 weeks.[41] Secondary outcomes of interest included time from randomization until recovery of unaided walking, time from randomization until discontinuation of ventilation (for those ventilated), death, death or disability (inability to walk without aid) after 12 months, relapse, and adverse events.[41]

Six trials with 587 participants provided data for the primary outcome.[41] The first trial compared intramuscular ACTH daily for 10 days with placebo.[41] Four trials with between 14 and 46 participants compared oral prednisolone versus placebo, or supportive treatment without glucocorticoids and no placebo.[41] The oral regimens varied but all consisted of the equivalent of prednisolone 40 mg daily for at least 2 weeks.[41] A trial with alternate allocation included 10 participants treated with methylprednisolone 1500 mg daily for five days and 10 participants who received supportive care.[41] A trial with 242 participants compared intravenous methylprednisolone 500 mg daily for five days with an identical placebo.[41] This trial did not show a difference in any outcome assessed between

glucocorticoid and placebo groups.[41] One trial with 225 participants differed from the others in that all participants received intravenous immunoglobulin 0.4 g/kg daily for 5 days in accordance with current practice and were randomly allocated to receive intravenous methylprednisolone 500 mg daily for 5 days, or an identical placebo.[41] In this trial, the authors reported a one disability grade improvement after 4 weeks in 63 of 113 (56%) of control- and 76 of 112 (68%) methylprednisolone-treated participants (RR 1.2, 95% CI 1.0 to 1.5, p=0.06).[41] The trials could not demonstrate a difference in other outcomes between the groups, including the proportion of participants requiring ventilation, becoming able to walk unaided, and improving by 1 or more disability grades during the first year.[41]

According to moderate quality evidence, the change in disability grade after 4 weeks in the glucocorticoid groups was not different from that in the control groups (MD 0.36; 95% CI 0.16 to 0.88).[41] In 4 trials (n=120) of oral glucocorticoids, there was very low quality evidence of less improvement after 4 weeks with glucocorticoids than without glucocorticoids (MD 0.82; 95% CI 0.17 to 1.47).[41] In 2 trials (n=467), there was moderate quality evidence of no difference of disability improvement after 4 weeks with intravenous glucocorticoids (MD 0.17, 95% CI -0.06 to 0.39).[41] According to moderate quality evidence, there was also no difference between the glucocorticoid treated and control groups for improvement by 1 or more grades after 4 weeks (RR 1.08, 95% CI 0.93 to 1.24) or for death or disability after 1 year (RR 1.51, 95% CI 0.91 to 2.5).[41] High quality evidence showed the occurrence of diabetes was more common (RR 2.21, 95% CI 1.19 to 4.12) and hypertension less common (RR 0.15, 95% CI 0.05 to 0.41) in the participants treated with glucocorticoids.[41]

Based on moderate quality evidence, glucocorticoids given alone do not significantly hasten recovery from GBS or affect long-term outcomes.[41] Based on very low quality evidence, oral glucocorticoids may even delay recovery.[41] Diabetes requiring management with insulin was more common and hypertension less common with glucocorticoids based on high quality evidence.[41]

Acute Sinusitis

The objective of a 2014 Cochrane update was to assess the safety and efficacy of systemic glucocorticoids on clinical response rates in children and adults with acute sinusitis.[22] Acute sinusitis was defined by clinical diagnosis alone, or confirmed by additional radiological or nasal endoscopic examination.[22] Literature was searched for RCTs that compared systemic glucocorticoids to placebo or standard clinical care through February 2014.[22] Five RCTs (n= 1,193 adults) met inclusion criteria.[22] None of the trials included children. Three French trials performed in ear, nose and throat (ENT) outpatient clinics also used radiological assessment as part of their inclusion criteria.[22] The other 2 RCTs were conducted in primary care settings located in South Africa and the Netherlands. The primary outcome of interest was the proportion of participants with resolution or improvement of any patient-related symptoms, including total change in clinical status, measured at two time points: short-term (2 weeks or less) or long-term (more than 2 weeks).[22] All participants were assigned to either oral glucocorticoids (prednisone 24 mg to 80 mg daily or betamethasone 1 mg daily) or the control treatment (placebo in 4 trials and non-steroidal anti-inflammatory drugs in 1 trial).[22] In 4 trials antibiotics were prescribed in addition to oral glucocorticoids or control treatment, while 1 trial investigated the effects of oral glucocorticoids as a monotherapy.[22] Methodological quality was judged as moderate in 4 trials and high in 1 trial.[22]

When combining data from the 4 placebo-controlled trials, participants treated with oral glucocorticoids and antibiotics were slightly more likely to have short-term resolution or improvement of symptoms than those receiving the control treatment at days 3 to 7 (RR 1.2, 95% CI 1.1 to 1.3; $I^2 = 0\%$; absolute risk difference [RD] 11%; 95% CI 4% to 17%) and at days 4 to 14 (RR 1.1, 95% CI 1.0 to 1.2; $I^2 = 30\%$; RD 8%, 95% CI 2% to 13%).[22] Only one high-quality trial reported on the long-term effects (more than 2 weeks) of oral glucocorticoids.[22] At 8 weeks, the proportions of patients with resolution of facial pain/pressure and total symptoms were higher in the placebo group than in the oral glucocorticoid monotherapy group, although the differences were not found to be different (RD -2.2%, 95% CI -12.6% to 8.1% and RD -9.9%, 95% CI -24.7% to 4.9%, respectively).[22] Neither of the groups differed significantly in the proportion of patients who received prescriptions for antibiotics (17/88 vs. 16/86) or intranasal glucocorticoids (6/88 vs. 15/86).[22] No trial reported effects on relapse or recurrence rates.[22]

Reported adverse effects in patients treated with oral glucocorticoids were mild (nausea, vomiting, gastric complaints) and did not significantly differ from those receiving placebo.[22]

Oral glucocorticoids as monotherapy appear to be ineffective for adult patients with acute sinusitis.[22] Oral glucocorticoids in combination with antibiotics may be modestly beneficial for short-term relief (< 14 days) of symptoms from acute sinusitis.[22] Until high-quality trials demonstrate oral glucocorticoids to be beneficial in patients with acute sinusitis, their use is not supported by current evidence.[22]

Evidence Supports Use in Specified Indication

Croup in Children

A 2018 Cochrane review examined the effects of glucocorticoids in the treatment of croup in children aged 0 to 18 years.[23] This was an update of a Cochrane Review published in 1999 and previously updated in 2004 and 2011.[23] Literature was searched through April 3, 2018.[23] Randomized controlled trials which investigated children aged 0 to 18 years with croup and measured the effects of glucocorticoids, alone or in combination, compared to placebo or another pharmacologic treatment were included.[23] For inclusion in the systematic review the studies needed to report at least 1 of the following outcomes: change in croup score from baseline; return visits or admissions or both; length of stay; patient improvement; use of additional treatments; and adverse events.[23] Five new RCTs with 330 children met inclusion criteria. This review now includes 43 RCTs with a total of 4,565 children.[23] Dexamethasone and budesonide were the most widely studied glucocorticoids in this population.[23] Most (98%) studies were assessed as having a high or unclear risk of bias due to issues with study methods, reporting or both.[23]

Compared to placebo, glucocorticoids improved symptoms of croup at 2 hours (standardized mean difference [SMD] -0.65; 95% CI-1.13 to -0.18; 7 RCTs; 426 children; moderate-certainty evidence), and the effect lasted for at least 24 hours (SMD -0.86; 95% CI -1.40 to -0.31; 8 RCTs; 351 children; low-certainty evidence).[23] Compared to placebo, glucocorticoids reduced the rate of return visits, admissions or both (RR 0.52; 95% CI 0.36 to 0.75; 10 RCTs; 1679 children; moderate-certainty evidence).[23] Glucocorticoid treatment reduced the length of stay in hospital by about 15 hours (mean difference [MD} -14.90; 95% CI -23.58 to -6.22; 8 RCTs; 476 children; quality of evidence not reported).[23] Serious adverse events were infrequent.[23] Uncertainty remains with regard to the optimal type, dose, and mode of administration of glucocorticoids for reducing croup symptoms in children.[23] In summary, glucocorticoids reduced symptoms of croup at 2 hours, shortened hospital stays, and reduced the rate of return visits to care.[23] Previous version of this review reported that glucocorticoids reduced symptoms of croup within 6 hours.[23]

Bell's Palsy

A 2016 Cochrane update evaluated the effectiveness and safety of glucocorticoid therapy in people with Bell's palsy.[24] This was an update of a review first published in 2002 and updated in 2010.[24] Literature was searched through March 2016.[24] Seven trials, including 895 participants with one-sided mild, moderate or severe Bell’s palsy met inclusion critiera.[24] Participants ranged in age from 2 to 84 years.[24] They were treated with a short course of glucocorticoids or placebo, either alone or in combination with other therapies (e.g., antivirals).[24] Glucocorticoids used in the RCTs included prednisone, cortisone, methylprednisolone, and prednisolone. One trial only involved children, from 24 months to 74 months old.[24] The duration of follow-up for the included studies from 157 days to 12 months.[24] The primary outcome of interest was incomplete recovery of facial motor function 6 months or more after randomization.[24]

Moderate- to high-quality evidence showed short-term use of glucocorticoids reduced the number of people left with facial weakness after Bell's palsy compared to placebo.[24] Overall, 79/452 (17%) participants allocated to glucocorticoids had incomplete recovery of facial motor function 6 months or more after randomization; which was fewer than the 125/447 (28%) participants in the control group (RR 0.63, 95% CI 0.50 to 0.80, 7 RCTs, n=895).[24] The number of people

who need to be treated with glucocorticoids to avoid one incomplete recovery at 6 months was 10 (95% CI 6 to 20).[24] The reduction in the proportion of participants with cosmetically disabling sequelae 6 months after randomization was very similar in the glucocorticoid and placebo groups (RR 0.96, 95% CI 0.40 to 2.29, 2 trials, n=75, low-quality evidence).[24] However, there was a reduction in motor synkinesis (i.e., crocodile tears) during follow-up in participants receiving glucocorticoids (RR 0.64, 95% CI 0.45 to 0.91, 3 trials, n=485, moderate-quality evidence).[24]

Three studies explicitly recorded adverse effects attributable to glucocorticoids.[24] One trial reported that 3 participants receiving prednisolone had temporary sleep disturbances and 2 trials gave a detailed account of adverse effects occurring in 93 participants, all non-serious.[24] The combined analysis of data from these 3 trials could not find a difference in adverse effect rates between people receiving glucocorticoids and people receiving placebo (RR 1.04, 95% CI 0.71 to 1.51, n=715).[24] Glucocorticoid courses in Bell's palsy are short and the dosed are quickly tapered, making the likelihood of adverse effects in practical use less than in longer-term indications.[24] The available moderate- to high-quality evidence from 7 RCTs showed benefit from treating Bell's palsy with glucocorticoids.[24]

Long-Term Use In Cystic Fibrosis

A 2015 Cochrane systematic review updated a previous review that assessed the effectiveness of long-term use (over 30 days) of oral glucocorticoids in respiratory complications in patients with cystic fibrosis.[25] Literature was searched through August 28, 2015.[25] Primary outcomes of interest included: improved pulmonary function tests from baseline (i.e., forced expiratory volume at 1 second [FEV_1]and forced vital capacity [FVC]), and adverse events.[25] Three studies including 354 participants met inclusion criteria.[25] The ages of the participants ranged from 1 year to 19.5 years.[25] In each study oral glucocorticoids were compared with placebo.[25] The dose of prednisolone included 1mg/kg day on alternate days, 2 mg/kg on alternate days, and 2 mg/kg daily for 14 days followed by 1 mg/kg on alternate days for 10 weeks.[25] The duration of administration of oral glucocorticoids and follow-up ranged from 12 weeks in 1 RCT to 4 years in the other 2 RCTs.[25] Common outcomes were examined at different time-points and presented differently, so meta-analyses were not possible.[25] Of the 3 studies included in this review, only one was assessed to be of moderate quality.[25] Information to fully assess the quality of the other two studies was not available.[25]

All studies showed some improvement or delay in decline in lung function in the oral glucocorticoid-treated groups compared with placebo.[25] In one RCT, the mean absolute change in percent predicted FEV_1 at 14 days was 7.7% in the treatment group compared to -1.0% in the placebo group (95% CI, 15.08 to 2.32 for difference between groups) and at 12 weeks was 6.3% in the prednisolone group compared to -1.8% in the placebo group (95% CI, 15.75 to 0.45).[25] A second RCT reported that at 4 years the mean percent-predicted FEV_1 was higher in the prednisolone group at a dose of 2 mg/kg on alternate days (103%) compared to the placebo group (87%), ($p<0.005$).[25] An excess of adverse events resulted in premature discontinuation of high dose prednisolone (2 mg/kg on alternate days).[25] When the 3 groups were compared for the initial 24 months, the mean change in percent-predicted FVC was higher in the 1 mg/kg group than the placebo group at all 6 month time points ($p<0.0001$); and at all time points the mean change in percent predicted FVC was greater in the 2 mg/kg group than the placebo group ($p<0.01$).[25] When the 1 mg/kg prednisolone group and the placebo group were compared for the first 48 months of the study, the glucocorticoid-treated group had a greater change in percent-predicted FVC, which was sustained throughout the time period ($p<0.0025$).[25] At 24 months, 70.4% participants treated with 1 mg/kg prednisolone had an increase in percent predicted FVC, compared with 54.9% participants treated with 2 mg/kg prednisolone and 41.6% participants treated with placebo.[25]

Each study reported different adverse events. One RCT specifically sought to assess adverse events including elevated blood pressure, fluid retention, and serum sodium, potassium, and glucose abnormalities.[25] The second study regularly measured height and weight of participants, but other adverse effects were not recorded.[25] The third study monitored adverse events at each clinic visit, specifically serum glucose levels, presence of cataracts, liver enzyme abnormalities, or chest infections.[25] The development of a Cushingoid appearance was reported in one study and occurred in 4 of the prednisolone-treated participants (2 mg/kg on alternate days).[25] Development of cataracts was reported in 2 studies. Data from one RCT showed that during the first 24 months, cataracts were seen more often in participants in the 2 mg/kg prednisolone group (11 participants) compared to the 1 mg/kg group (3 participants).[25] Of note, 7 participants in the placebo

group developed cataracts in this RCT.[25] Osteoporosis was not specifically noted, but in the follow-up of one trial, 2 of the prednisolone-treated participants (2mg/kg on alternate days) developed multiple bone fractures.[25] All 3 RCTs noted varying degrees of glucose intolerance.[25]

In summary, oral glucocorticoids at prednisolone-equivalent dose of 1 to 2 mg/kg on alternate days appear to slow progression of lung disease in patients with cystic fibrosis; however, benefit should be weighed against occurrence of adverse events.[25] Current evidence suggests that oral glucocorticoids at a prednisolone equivalent dose of 2 mg/kg on alternate days is effective, but should not be used long term, due to the high risk of adverse effects.[25] A dose of 1 mg/kg on alternate days may be considered for up to 24 months, but close attention to the occurrence of adverse effects (glucose abnormalities, cataracts and growth retardation) is warranted.[25]

Oral Versus Intravenous Glucocorticoids for Acute Multiple Sclerosis Relapses

The primary objective of a 2012 Cochrane Review was to compare the safety and efficacy of oral versus intravenous glucocorticoids in promoting disability recovery after acute relapses in patients with relapsing-remitting MS.[26] Literature was searched through January 2012.[26] A total of 5 studies comprising 215 participants were identified.[26] In 4 RCTs, intravenous methylprednisolone was compared with oral methylprednisolone, and in 1 RCT the oral comparator was prednisone.[26] All trials were performed in the outpatient setting of a hospital-based MS care centers in the United Kingdom (UK), Italy, Canada and Spain.[26] Three RCTs had methodological limitations with respect to randomization, concealment of allocation, and incomplete followup.[26] Two trials were of moderate or high quality.

Only one endpoint, the proportion of patients with Expanded Disability Status Scale (EDSS) improvement at 4 weeks, was common to 3 trials.[26] The pooled analysis of 3 RCTs (n=165) resulted in a mean difference change in EDSS between groups at 4 weeks of -0.22 (95% CI -0.71 to 0.26; p=0.20).[26] Four RCTs (n=200) reported the proportion of patients experiencing improvement in EDSS and relapse recovery after steroid treatment.[26] The odds ratio of improvement with oral methylprednisolone versus intravenous methylprednisolone was 0.60 (95% CI 0.28 to 1.26).[26] Analysis of the 5 trials that compared intravenous versus oral glucocorticoid therapy for MS relapses do not demonstrate any differences in clinical outcomes or adverse events.[26] Based on this evidence, oral glucocorticoid therapy may be a practical and effective alternative to intravenous steroid therapy in this population.[26] However, only 2 of the 5 studies employed rigorous methodological techniques, so these results should be interpreted with some caution.[26]

Preventing Relapse Following Acute Exacerbations Of Asthma

A 2007 review evaluated the benefit of oral glucocorticoids for the treatment of patients with asthma discharged from an acute care setting (usually the emergency department) after treatment of an acute asthmatic exacerbation.[27] Six RCTs involving 374 children and adults met inclusion criteria.[27] Oral glucocorticoids (prednisone, methylprednisolone, and dexamethasone) were provided for 7 to 10 days, usually as a tapering dose.[27] The primary outcome was relapse to additional care, defined as a patient's perceived need for further assessment and treatment within the follow-up period.[27] Overall, the methodological quality of the studies was rated as high.[27] All 6 RCTs were double-blinded, placebo controlled, and demonstrated appropriate concealment of allocation.[27]

The meta-analysis showed fewer patients in the oral glucocorticoid group received additional care in the first 7 to 10 days following discharge compared with placebo-treated patients (RR 0.38, 95% CI 0.20 to 0.74).[27] This favorable effect was maintained over the first 21 days (RR 0.47, 95% CI 0.25 to 0.89) and there were fewer subsequent hospitalizations (RR 0.35, 95% CI 0.13 to 0.95).[27] Patients receiving glucocorticoids had less need for beta2-agonists (mean difference (MD) -3.3 activations/day, 95% CI -5.6 to -1.0). Differences in changes pulmonary function tests (SMD 0.045, 95% CI -0.47 to 0.56) and adverse effects (SMD 0.03, 95% CI -0.38 to 0.44) were not found between the groups.[27] No data were reported about the specific adverse effects associated with short courses of oral glucocorticoids.[27] From these results, as few as 10 patients need to be treated to prevent relapse to additional care after an exacerbation of asthma.[27]

Safety of Oral Glucocorticoids

Long-Term Oral Glucocorticoid Use In Patients With Chronic Obstructive Pulmonary Disease

A 2019 systematic review aimed to investigate whether chronic use of oral glucocorticoids for more than 4 months increases mortality and vertebral fracture risk in patients with stable COPD.[28] Literature was searched through November 2018.[29] Five studies met inclusion criteria for a mortality meta-analysis and 4 studies (n=17,764) were pooled for an analysis of the impact of long term glucocorticoid use on vertebral fracture.[29] Among the 5 studies assessing mortality, 4 were prospective cohort studies and one was a prospective case–control study.[29] The 4 studies assessing vertebral fracture were retrospective case–control studies.[29] No RCTs were identified, and the number of included observational studies was small.[29]

A meta-analysis of 5 studies (n=1,795) demonstrated that long-term use of oral glucocorticoids increased risk of mortality compared to placebo (RR, 1.63; 95% CI, 1.19 to 2.23; p<0.0001; I^2 = 86%).[29] In the 4 studies investigating vertebral fracture, 2,048 patients were on long-term oral glucocorticoids and 15,716 patients were in the placebo groups.[29] A meta-analysis of 4 studies showed that patients long-term use of oral glucocorticoids increased rate of vertebral fractures (OR, 2.31; 95% CI, 1.52 to 3.50; p=0.03; I^2 = 65%).[29]

Adverse Events Associated With Oral Glucocorticoids In Asthma

The primary outcome of a 2018 systematic review was to estimate the risk of different complications related to the use of long-term use of oral glucocorticoids in the treatment of asthma when used as add-on to chronic maintenance therapy (high dose inhaled corticosteroids and other controller medications).[21] Literature was searched through May 2017.[21] Fifteen studies met inclusion criteria. Of the 15 studies, 11 had a cohort design, 2 were cross-sectional studies, and 2 were case-control studies.[21] Duration of glucocorticoid therapy ranged from 3 months to 2 years in the various studies. Nine studies were performed in the United States, 5 in the UK, and 1 in South Africa.[21]

Combining unadjusted OR of adverse events among patients with glucocorticoid-use compared with non-glucocorticoid use from studies, there was an increased risk of peptic ulcers 2.86 (95% CI 1.39 to 5.90), hypertension 1.28 (95% CI 1.20 to 1.36), diabetes mellitus 1.30 (95% CI 1.02 to 1.64), cataracts 1.49 (95% CI 1.29 to 1.72), infections 1.68 (95% CI 1.51 to 1.87), fractures 1.46 (95% CI 1.25 to 1.70); the risk of osteoporosis and glaucoma was not different between groups.[21] The risk of any complication increased with higher doses of glucocorticoid, with pooled adjusted OR from 2 studies of 2.26 (95% CI 1.37 to 3.72), 2.94 (95% CI 2.62 to 3.29), and 3.35 (95% CI 2.94 to 3.82) for low dose (< 5 mg), medium dose (5–10 mg) and high dose (>10 mg), respectively, (compared with no glucocorticoid use).[21] The pooled adjusted OR from 2 studies that reported the relevant adverse events among high-dose glucocorticoid-users (>10 mg) compared with non-glucocorticoid users were as follows: for the development of any complications 3.35 (95% CI 2.94 to 3.82), infections 2.68 (95% CI 2.46 to 2.91), gastrointestinal complications 2.06 (95% CI 1.96 to 2.17), psychiatric complications 1.66 (95% CI 1.55 to 1.78), cardiovascular complications 1.82 (95% CI 1.67 to 1.98), metabolic complications 1.41 (95% CI 1.32 to 1.50), bone and muscle complications 2.30 (95% CI 2.18 to 2.42), and ocular complications 1.40 (95% CI 1.31 to 1.49).[21] The use of oral glucocorticoids in the management of asthma is associated with a higher risk of adverse effects.[21] This risk is higher as the oral glucocorticoid dose increases.[21]

Short-Course Oral Glucocorticoids In Children

A 2016 systematic review aimed to identify the most common and serious ADRs associated with short-course oral glucocorticoids in children.[31] Literature was searched up to December 2013.[31] Inclusion criteria were original research studies assessing glucocorticoid toxicity in children from 28 days up to 18 years of age.[31] Thirty-eight publications met inclusion criteria. Twenty-two RCTs accounted for over half of the studies, 89% of patients and 60% of ADRs.[31] Five prospective cohort studies included less than 10% of patients (n=305) but reported one-third of the ADRs.[31] Nine case reports and 2 case series were also included.[31] Glucocorticoids were used to manage various medical conditions, including asthma, bronchiolitis, croup, acute renal failure, allergic rhinitis, dengue

fever, infantile spasms, nephrotic syndrome, acute leukemia, acute idiopathic thrombocytopenic purpura and systemic lupus erythematosus.[31] Prednisolone and dexamethasone were the most commonly used glucocorticoids.[31]

The most serious adverse effect associated glucocorticoids was infection.[31] Five RCTs reported an incidence of infection of 0.9%.[31] Three cases were reported of children infected with varicella zoster, one of whom died and the other 2 were admitted to the intensive care unit with severe complications.[31] In 4 studies, 43 children showed a statistically significant biochemical suppression of the HPA axis.[31] One case series also showed a significant occurrence of transient HPA axis suppression in 3 of 11 children with a 5-day course of prednisolone (2 mg/kg/day).[31] All the children returned to a normal level of endogenous cortisol secretion within 10–12 days after discontinuation of the glucocorticoids.[31]

The 3 most common adverse effects were vomiting, changes in behavior and disturbed sleep.[31] Vomiting was the most common adverse effect with an incidence of 5.4% and was the most frequent reason for early discontinuation of glucocorticoids.[31] Prednisolone sodium phosphate solution was less likely to cause vomiting compared to other formulations (prednisolone base solution and dexamethasone solution).[31] Mood swings and behavioral disturbance were the second most frequently observed adverse events with an incidence of 4.7%. Mood swings (anxiety, hyperactivity and aggressive behavior) were significantly more frequent with higher doses (2 mg/kg/day or 60 mg/m²/day) of prednisolone than with lower doses (1 mg/kg/day).[31] Sleep disturbance was the third most frequent observed adverse event caused by glucocorticoids, with an incidence of 4.3%.[31] Two studies (one RCT and one cohort study) reported 101 children had sleep disturbances.[31] Three studies (one RCT, one cohort study and one case series) evaluated weight changes in patients.[31] Thirty of the 84 patients measured showed weight gain.[31]

After review, 6 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[42-47]

GUIDELINES:
High Quality Guidelines

Asthma

The GINA guidelines were updated in 2020.[32] The recommendations suggest if the initial asthma presentation is severely uncontrolled or an acute exacerbation, start regular controller treatment with medium dose inhaled glucocorticoid combined with a long-acting beta-agonist with as-needed short-acting beta-agonist.[32] Add-on low dose oral glucocorticoids (≤7.5 mg/day prednisone equivalent) may be effective for some adults with severe asthma (Evidence Level D: panel consensus judgement), but are often associated with substantial side effects (Evidence level A: based on rich body of data including RCTs and systematic reviews).[32] Oral glucocorticoids should only be considered for adults with poor symptom control or frequent exacerbations despite good inhaler technique and adherence with guideline-recommended treatment, and after exclusion of other contributory factors and other add-on treatments including biologics.[32] Patients should be counseled about potential side-effects.[32] They should be assessed and monitored for risk of glucocorticoid-induced osteoporosis, and those expected to be treated for 3 months or more should be provided with relevant lifestyle counselling and prescription of therapy for prevention of osteoporosis (where appropriate).[32]

Congenital Adrenal Hyperplasia

In November 2018, the Endocrine Society published updated clinical practice guidelines for management of CAH due to steroid 21-hydroxylase deficiency.[33] Congenital adrenal hyperplasia is a group of autosomal recessive disorders characterized by impaired cortisol synthesis.[33] Based on neonatal screening and

national case registries, the worldwide incidence in most studies ranges from ~1:14,000 to 1:18,000 births, but the condition is more prevalent in small, genetically isolated groups with a smaller gene pool, particularly in remote geographic regions (e.g., Alaskan Yupiks).[33] Proper treatment with glucocorticoids prevents adrenal crisis and virilization, allowing nearly normal growth and development during childhood.[33] Management of classic CAH is a difficult balance between hyperandrogenism and hypercortisolism.[33]

During childhood, the preferred glucocorticoid is hydrocortisone because its short half-life minimizes the adverse side effects typical of longer-acting, more potent glucocorticoids, especially growth suppression.[33] Although free-alcohol hydrocortisone suspensions achieve cortisol levels comparable to those achieved by hydrocortisone tablets, hydrocortisone cypionate oral suspensions were inadequate to control CAH in children due to uneven distribution in liquid form.[33] Good control can be achieved by orally administering crushed, weighed hydrocortisone tablets mixed with a small volume of liquid, if needed, immediately before administration.[33] Compounding pharmacies should be chosen for reliability in preparing very small doses or special drug formulations, as there have been reports of variable dose accuracy in compounded preparations.[33]

Patients with severe forms of CAH are unable to produce sufficient cortisol in response to stress, such as febrile illness, gastroenteritis with dehydration, surgery, or trauma, and therefore, require increased doses of glucocorticoids during such episodes.[33] In contrast to maintenance treatment given 3 times daily, it is recommended that stress dosing be given every 6 hours.[33] Specific recommendations by the Endocrine Society regarding glucocorticoid utilization in the management of CAH include:

- In growing individuals with classic congenital adrenal hyperplasia, use hydrocortisone as maintenance therapy. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In growing individuals with congenital adrenal hyperplasia, avoid the use of oral hydrocortisone suspension and avoid chronic use of long-acting potent glucocorticoids. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In adults with classic congenital adrenal hyperplasia, daily hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids are recommended, as clinically indicated. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In all individuals with classic congenital adrenal hyperplasia, monitor for signs of glucocorticoid excess, as well as for signs of inadequate androgen normalization, to optimize the adrenal steroid treatment profile. (Strong Recommendation, Moderate-Quality Evidence)[33]
- In pediatric patients with congenital adrenal hyperplasia, conduct regular assessments of growth velocity, weight, blood pressure, physical examinations, and biochemical measurements to assess the adequacy of glucocorticoid and mineralocorticoid replacement. (Strong Recommendation, Low-Quality Evidence)[33]
- In pediatric patients with congenital adrenal hyperplasia over the age of 2 years, advise annual bone age assessment until near-adult height is attained. (Ungraded Good Practice Statement)[33]
- In adults with congenital adrenal hyperplasia, conduct annual physical examinations, which include assessments of blood pressure, body mass index, and Cushingoid features in addition to obtaining biochemical measurements to assess the adequacy of glucocorticoid and mineralocorticoid replacement. (Strong Recommendation, Low-Quality Evidence)[33]
- Glucocorticoid maintenance therapy recommendations in fully grown patients with CAH are presented in **Table 2.**

Table 2. Glucorticoid Maintenance Therapy in Fully Grown Patients with Congenital Adrenal Hyperplasia[33]

Glucocorticoid	Suggested Dose (mg/day)	Daily Dosing Regimen
Hydrocortisone	15-25	2-3
Prednisone	5-7.5	2

Prednisolone	4-6	2
Methylprednisolone	4-6	2
Dexamethasone	0.25-0.5	1-2
Abbreviation: mg = milligram		

Chronic Obstructive Pulmonary Disease

According to the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, oral glucocorticoids have no role in the chronic daily treatment in COPD because of a lack of benefit balanced against a high rate of systemic complications.[30] Long-term use of oral glucocorticoids has numerous adverse effects (Evidence A; high quality evidence from 2 or more RCTs) with no evidence of benefits (Evidence C; observational studies).[30] Long-term therapy with oral corticosteroids is not recommended (Evidence A). In an acute COPD exacerbation, systemic corticosteroids improve lung function (FEV_1), oxygenation and shorten recovery time and hospitalization duration.[30] Duration of therapy should not be more than 5-7 days (Evidence A).[30]

Corticosteroids In Pregnancy And Breastfeeding

In 2017 the BSR and BHPR collaborated to update guidance for prescribing glucocorticoids in pregnancy and breastfeeding.[34] These recommendations were part of a series focused on drug safety of immunosuppressive drugs in pregnancy and breast feeding. Recommendations for men trying to conceive with their partner while taking glucocorticoids was also given where sufficient evidence was available.

Four cohort studies and 2 case series reported on outcomes from pregnancies (n=2,127) after paternal exposure to prednisolone and a case-control study and a case series reported on outcomes from pregnancies (n=4) after paternal exposure to methylprednisolone.[7] Overall, the quality of these studies was low, but, they did not identify an increased risk of adverse fetal outcomes.[34] Evidence for safe use of glucocorticoids in pregnancy was obtained from 47 studies on prednisolone (n=1503 pregnancies); 31 studies on dexamethasone (n=11,214 pregnancies); 27 studies on betamethasone (n=27,746 pregnancies); and 10 on general corticosteroids (n=785 pregnancies).[34] Types of studies included RCTs, systematic reviews, cohort studies, case-control studies, and case reports. The studies were confounded by multiple concomitant medications which are used to prevent or treat preterm labor and complications such as fetal lung immaturity.[34] Prednisolone, prednisone and methylprednisolone are metabolized in the placenta, so 10% or less of the active drug reaches the fetus, and they are considered to be compatible with pregnancy and breastfeeding.[34] Grading recommendations were based on the Scottish Intercollegiate Guidelines Network (SIGN) as follows:[48]

- Prednisolone is compatible with each trimester of pregnancy and is the preferred corticosteroid in the treatment of maternal rheumatologic disease in pregnancy (Level of Evidence: 1++, based on high quality meta-analyses, systematic reviews or RCTs with low risk of bias; Grade of Recommendation: A, based on at least 1 meta-analysis, systematic review or high quality RCT directly applicable to target population).[34]
- Prednisolone is compatible with breastfeeding (Level of Evidence: 2-, case control or cohort studies with high risk of confounding; Grade of Recommendation: D, based on extrapolated evidence from case reports or expert opinion).[34]
- Prednisolone is compatible with paternal exposure (Level of Evidence: 2+, based upon well conducted case-control or cohort studies with low risk of confounding; Grade of Recommendation D, based upon extrapolated evidence from case reports or expert opinion).[34]

Hypopituitarism in Adults

In 2016 the Endocrine Society formulated clinical practice guidelines for hormonal replacement in adults with hypopituitarism.[35] The guideline Task Force commissioned two systematic reviews to assist with summarizing the evidence base for this guideline.[35] Hypopituitarism results from complete or partial

deficiency in pituitary hormones and includes adrenal insufficiency, hypothyroidism, hypogonadism, growth hormone deficiency, and (more rarely) diabetes insipidus.[35] Hypopituitarism is the consequence of diseases that either reduce or destroy secretory function or interfere with the hypothalamic secretion of pituitary-releasing hormones.[35] Central adrenal insufficiency represents inadequate cortisol secretion due to ACTH deficiency. It can be secondary, when pituitary disease impairs the release of ACTH, or tertiary from inadequate hypothalamic corticotropin-releasing hormone.[35] Glucocorticoid replacement is just one aspect of the multi-pronged approach to managing this condition. Specific recommendations include:

- Hydrocortisone is recommended, usually 15–20 mg total daily dose in single or divided doses. Patients using divided doses should take the highest dose in the morning at awakening and the second in the afternoon (two-dose regimen) or the second and third at lunch and late afternoon, respectively (three-dose regimen). (Strong Recommendation, Moderate-Quality Evidence).[35]
- It is suggested to use longer-acting glucocorticoids in selected cases (e.g., nonavailability, poor compliance, convenience). (Weak Recommendation; Low-Quality Evidence).[35]
- Clinicians should teach all patients with adrenal insufficiency regarding stress-dose and emergency glucocorticoid administration and instruct them to obtain an emergency card/bracelet/necklace regarding adrenal insufficiency and an emergency kit containing injectable high-dose glucocorticoid (Strong Recommendation; Moderate-Quality Evidence).[35]
- It is suggested to test HPA axis functionality before and after starting GH replacement in patients who are not receiving glucocorticoid replacement and who have demonstrated apparently normal pituitary-adrenal function (Weak Recommendation; Low-Quality Evidence).[35]
- Clinicians should assess adrenal reserve or the adequacy of HC replacement, and take into consideration that total serum cortisol level can be elevated due to the effects of estrogen on glucocorticoid-binding globulin (CBG). (Weak Recommendation; High-Quality Evidence).[35]
- Clinicians should individually assess glucocorticoid replacement and avoid over-replacement to reduce the risk of osteoporosis. Low-dose hydrocortisone replacement is recommended because this approach might be associated with increased bone formation and a positive bone-remodeling balance (Weak Recommendation; Low-Quality Evidence).[35]

<u>Primary Adrenal Insufficiency (Addison' Disease)</u>

The Endocrine Society published clinical guidelines that address the diagnosis and treatment of PAI in 2016.[36] Adrenal insufficiency is defined by the inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids.[36] Primary adrenal insufficiency is a severe and potentially life-threatening condition due to the central role of these hormones in energy, salt, and fluid homeostasis.[36] Except for salt craving, the symptoms of PAI are rather nonspecific and include weakness, fatigue, musculoskeletal pain, weight loss, abdominal pain, depression, and anxiety.[36] As a result, the diagnosis is frequently delayed, resulting in a clinical presentation with an acute life-threatening adrenal crisis.[36] Primary adrenal insufficiency is a rare disease with a reported prevalence of about 100 to 140 cases per million and an incidence of 4:1,000,000 per year in Western societies.[36] The most common cause of PAI is autoimmunity (up to 90% in Western countries), followed by infectious diseases such as tuberculosis, adrenalectomy, neoplasia, and various genetic causes. Genetic causes are more likely to be present and diagnosed in children.[36] Glucocorticoid replacement regimen recommendations include:

- Start glucocorticoid therapy in all patients with confirmed PAI. (Moderate Recommendation; High-Quality Evidence)[36]
- Use hydrocortisone (15–25 mg) or cortisone acetate (20–35 mg) in two or three divided oral doses per day; the highest dose should be given in the morning at awakening, the next either in the early afternoon (2 h after lunch; two-dose regimen) or at lunch and afternoon (three-dose regimen). Higher frequency regimens and size-based dosing may be beneficial in individual cases. (Weak Recommendation; Low-Quality Evidence)[36]
- As an alternative to hydrocortisone, prednisolone (3–5 mg/day), administered orally once or twice daily, especially in patients with reduced compliance. (Weak Recommendation; Very Low-Quality Evidence)[36]

- Dexamethasone is not suggested for the treatment of PAI because of risk of Cushingoid side effects due to difficulties in dose titration. (Weak Recommendation; Low-Quality Evidence)[36]
- It is advised to monitor glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess. (Weak Recommendation; Moderate-Quality Evidence)[36]
- In children with PAI, treatment with hydrocortisone is suggested in 3 or 4 divided doses (total starting daily dose of 8 mg/m^2 body surface area) over other types of glucocorticoid replacement therapies, with doses adjusted according to individual need. (Weak Recommendation; Low-Quality Evidence)[36]
- In children with PAI, avoid synthetic, long-acting glucocorticoids (e.g., prednisolone, dexamethasone). (Weak Recommendation; Low-Quality Evidence)[36]
- Monitor glucocorticoid replacement by clinical assessment, including growth velocity, body weight, blood pressure, and energy levels. (Ungraded Best Practice Statement)[36]
- Pregnant patients with PAI should be monitored for clinical symptoms and signs of glucocorticoid over- and under-replacement (e.g., normal weight gain, fatigue, postural hypotension or hypertension, hyperglycemia), with at least one review per trimester. (Ungraded Best Practice Statement)[36]
- Based on the individual clinical course, an increase in hydrocortisone dose should be implemented, in particular during the third trimester. (Ungraded Best Practice Statement)[36]
- In pregnant women with PAI, use hydrocortisone over cortisone acetate, prednisolone, or prednisone (Weak Recommendation; Low-Quality Evidence) and recommend against using dexamethasone because it is not inactivated in the placenta. (Strong Recommendation; Low-Quality Evidence)[36]
- Hydrocortisone stress dosing is recommended during the active phase of labor, similar to that used in major surgical stress. (Strong Recommendation; Low-Quality Evidence)[36]

After review, 1 guideline was excluded due to poor quality.[49]

Randomized Controlled Trials:

A total of 207 citations were manually reviewed from the initial literature search. After further review, 205 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 2 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Paniagua et al.[50] OL,NI,RCT	1. Dexamethasone 0.6 mg/kg x 2 doses x 1 day 2. Prednisone 1.5 mg/kg/day x 1 day followed by 1 mg/kg/day x 4 days	Children aged 1-14 years old with Acute Asthma Exacerbation n=557	Percentage of patients with asthma symptoms and quality of life at day 7 assessed via telephonic consultation using PACT and ARQoL scales	Persistence of Symptoms (PACT) 1. 56.6% 2. 58.3% P=NS Mean Quality of Life score (ARQoL) 1. 80.0 2. 77.7 P=NS	• OL, NI design of study can lead to bias • Primary outcomes were based on subjective assessments reported by parents of the enrolled children • 43% of children were under 5 years of age, which may have made it difficult to

					assess self-reporting of symptoms • Adherence rates not assessed
Burmester G, et al.[51] DB, MC, RCT	1.Prednisone 5 mg/day x 24 weeks 2.Taper prednisone to 0 mg/day over 16 weeks	Adults with RA receiving tocilizumab and glucocorticoids 5-15 mg/day x 24 weeks or more with low disease activity (DAS28-ESR score $\leq$ 3.2) N=259	Difference in mean DAS28-ESR change from baseline to week 24	Mean change in DAS28-ESR from baseline to week 24: 1. -0.08 2. 0.54 Difference: 0.61; 95% CI: 0.35 to 0.88; p<0.0001 *Change in DAS28-ESR of 0.6 units considered clinically relevant	• Relatively short-term trial (6 months) • Cannot extrapolate results to patients taking different glucocorticoid doses or other RA treatments • Bone mineral density not assessed
Mathian A, et al.[52] OL, RCT	1.Prednisone 5 mg/day x 52 weeks 2. Prednisone withdrawal on Day 0, patients started on hydrocortisone 20 mg/day to prevent adrenal failure	Adult SLE patients who, during the year preceding the inclusion, had a clinically inactive disease and a stable SLE treatment including 5 mg/day prednisone N=124	Proportion of patients experiencing a flare defined with the SELENA-SLEDAI flare index at 52 weeks.	Proportion of patients experiencing a flare at 52 weeks: 1. 4/61 (7%) 2. 17/63 (27%) RR 0.2; 95% CI 0.1 to 0.7; P=0.003	• OL trial without a placebo group • Withdrawal of 5 mg of prednisone was relatively abrupt, cannot exclude possibility that slow prednisone tapering would have resulted in less flares. • Inclusion bias may have confounded results: the SLE patients were kept on low dose of steroids by their treating physician despite clinical remission. It is possible that these patients had a special lupus history with severe flares, major organ involvements and relapses that prompted the physician to maintain this long-term treatment.

Abbreviations: ARQoL=Asthma-Related Quality of Life tool; CI=confidence interval; DAS28-ESR=28 joint Disease Activity Score-Erythrocyte Sedimentation Rate; DB=double-blind; kg=kilogram; MC=multi-center; mg=milligram; NI=Non-inferiority; OL=open label; PACT= Pediatric Asthma Control Tool; RA=rheumatoid arthritis; RCT=randomized clinical trial; RR=RR; SLE=systemic lupus erythematosus					

Recent FDA-approved Indications and Formulations

- A new oral formulation of dexamethasone (HEMADY) received FDA approval October 2019.[53] This product is available as a 20 mg tablet and is indicated in combination with other anti-myeloma products for the treatment of adults with multiple myeloma.[53] The recommended dose is 20 or 40 mg once daily, on specific days depending on the protocol regimen.[53]
- A new formulation of hydrocortisone (ALKINDI SPRINKLE) received FDA approval September 2020. This product is indicated as replacement therapy in pediatric patients with adrenocortical insufficiency.[54] The recommended starting replacement dosage is 8 to 10 mg/m^2 daily.[54] Higher doses may be needed based on patient's age and symptoms of the disease.[54] Use of lower starting doses may be sufficient in patients with residual but decreased endogenous cortisol production.[54] Use of hydrocortisone sprinkles in pediatric patients is supported by use of another hydrocortisone product in pediatric patients with adrenocortical insufficiency and supportive pharmacokinetic and safety data in 24 pediatric patients with adrenocortical insufficiency.[54]

References:

1. Buchbinder R, Green S, Youd JM, Johnston RV. Oral steroids for adhesive capsulitis. *Cochrane Database Syst Rev.* 2006(4).
2. Kornelsen E, Mahant S, Parkin P, et al. Corticosteroids for periorbital and orbital cellulitis. *Cochrane Database Syst Rev.* 2021(4).
3. Lansbury L, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev.* 2019(2).
4. Janssens HJ, Lucassen P, Van de Laar FA, Janssen M, Van de Lisdonk EH. Systemic corticosteroids for acute gout. *Cochrane Database Syst Rev.* 2008(2).
5. Ryan H, Yoo J, Darsini P. Corticosteroids for tuberculous pleurisy. *Cochrane Database Syst Rev.* 2017(3).
6. Ranakusuma RW, Pitoyo Y, Safitri ED, et al. Systemic corticosteroids for acute otitis media in children. *Cochrane Database Syst Rev.* 2018;3(3):Cd012289.
7. Schneider-Gold C, Gajdos P, Toyka KV, Hohlfeld RR. Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev.* 2005(2).
8. Gal RL, Vedula SS, Beck R. Corticosteroids for treating optic neuritis. *Cochrane Database Syst Rev.* 2015(8):CD001430.
9. Hughes RAC, Mehndiratta MM, Rajabally YA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev.* 2017(11).
10. Head K, Chong LY, Hopkins C, Philpott C, Burton MJ, Schilder AG. Short-course oral steroids alone for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016;4:CD011991.
11. Head K, Chong LY, Hopkins C, Philpott C, Schilder AG, Burton MJ. Short-course oral steroids as an adjunct therapy for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016;4:CD011992.
12. Paramothayan NS, Lasserson TJ, Jones P. Corticosteroids for pulmonary sarcoidosis. *Cochrane Database Syst Rev.* 2005(2).
13. Prince M, Christensen E, Gluud C. Glucocorticosteroids for primary biliary cirrhosis. *Cochrane Database Syst Rev.* 2005(2).
14. Ng SM, Stepien KM, Krishan A. Glucocorticoid replacement regimens for treating congenital adrenal hyperplasia. *Cochrane Database Syst Rev.* 2020(3).
15. Zhang F, Kramer CV. Corticosteroids for dengue infection. *Cochrane Database Syst Rev.* 2014(7).
16. Haywood A, Good P, Khan S, et al. Corticosteroids for the management of cancer-related pain in adults. *Cochrane Database Syst Rev.* 2015(4).
17. Haywood A, Duc J, Good P, et al. Systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults. 2019;1:Cd012704.
18. Chen HS, Wang W, Wu S, Liu JP. Corticosteroids for viral myocarditis. *Cochrane Database Syst Rev.* 2013(10).
19. Han Y, Zhang J, Chen N, He L, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev.* 2013(3).
20. de Cassan S, Thompson MJ, Perera R, et al. Corticosteroids as standalone or add-on treatment for sore throat. *Cochrane Database Syst Rev.* 2020;5(5):Cd008268.
21. Al Efraij K, Johnson KM, Wiebe D, Sadatsafavi M, FitzGerald JM. A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma. *Journal of Asthma.* 2019;56(12):1334-1346.
22. Venekamp RP, Thompson MJ, Hayward G, et al. Systemic corticosteroids for acute sinusitis. [Review]. 2014;1(3):Cd008115.
23. Gates A, Gates M, Vandermeer B, et al. Glucocorticoids for croup in children. *Cochrane Database Syst Rev.* 2018(8).
24. Madhok VB, Gagyor I, Daly F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev.* 2016(7).

25. Cheng K, Ashby D, Smyth RL. Oral steroids for long-term use in cystic fibrosis. *Cochrane Database Syst Rev.* 2015(12):CD000407.
26. Burton JM, O'Connor PW, Hohol M, Beyene J. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. *Cochrane Database Syst Rev.* 2012(12).
27. Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev.* 2007(3).
28. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis care & research.* 2017;69(8):1095-1110.
29. Chang YP, Lai CH, Lin CY, et al. Mortality and vertebral fracture risk associated with long-term oral steroid use in patients with chronic obstructive pulmonary disease: A systemic review and meta-analysis. *Chron Respir Dis.* 2019;16:1479973119838280.
30. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *American journal of respiratory and critical care medicine.* 2017;195(5):557-582.
31. Aljebab F, Choonara I, Conroy S. *Archives of Disease in Childhood.* 2016;101(4):365-370.
32. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2020. Available from: www.ginasthma.org. Accessed November 8, 2021.
33. Speiser PW, Arlt W, Auchus RJ, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2018;103(11):4043-4088.
34. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology.* 2016;55(9):1693-1697.
35. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2016;101(11):3888-3921.
36. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism.* 2016;101(2):364-389.
37. Dineen R, Stewart PM, Sherlock M. Factors impacting on the action of glucocorticoids in patients receiving glucocorticoid therapy. *Clin Endocrinol (Oxf).* 2019;90(1):3-14.
38. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol.* 2013;9(1):30.
39. Overman RA, Yeh J-Y, Deal CL. Prevalence of oral glucocorticoid usage in the United States: A general population perspective. *Arthritis care & research.* 2013;65(2):294-298.
40. Williams DM. Clinical Pharmacology of Corticosteroids. *Respir Care.* 2018;63(6):655-670.
41. Hughes RAC, Brassington R, Gunn AA, van Doorn PA. Corticosteroids for Guillain-Barré syndrome. *Cochrane Database Syst Rev.* 2016(10).
42. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *American journal of respiratory and critical care medicine.* 2020;201(3):276-293.
43. Deng J, Silver Z, Huang E, et al. Pharmacological prevention of fractures in patients undergoing glucocorticoid therapies: a systematic review and network meta-analysis. *Rheumatology (Oxford, England).* 2021;60(2):649-657.
44. Bonovas S, Nikolopoulos GK, Lytras T, Fiorino G, Peyrin-Biroulet L, Danese S. Comparative safety of systemic and low-bioavailability steroids in inflammatory bowel disease: Systematic review and network meta-analysis. *Br J Clin Pharmacol.* 2018;84(2):239-251.

45. Castro-Rodriguez JA, Beckhaus AA, Forno E. Efficacy of oral corticosteroids in the treatment of acute wheezing episodes in asthmatic preschoolers: Systematic review with meta-analysis. *Pediatric pulmonology.* 2016;51(8):868-876.
46. Gøtzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Cochrane Database Syst Rev.* 2005(1).
47. Fernandes RM, Wingert A, Vandermeer B, et al. Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis. *BMJ Open.* 2019;9(8):e028511.
48. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ (Clinical research ed).* 2001;323(7308):334-336.
49. Aertgeerts B, Agoritsas T, Siemieniuk RAC, et al. Corticosteroids for sore throat: a clinical practice guideline. *Bmj.* 2017;358:j4090.
50. Paniagua N, Lopez R, Muñoz N, et al. Randomized Trial of Dexamethasone Versus Prednisone for Children with Acute Asthma Exacerbations. *The Journal of pediatrics.* 2017;191:190-196.e191.
51. Burmester GR, Buttgereit F, Bernasconi C, et al. Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. *Lancet (London, England).* 2020;396(10246):267-276.
52. Mathian A, Pha M, Haroche J, et al. Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial. *Ann Rheum Dis.* 2020;79(3):339-346.
53. HEMADY (dexamethasone) oral tablets. Prescribing Information. Acrotech Biopharma; East Windsor, NJ. June 2021.
54. ALKINDI SPRINKLE (hydrocortisone) oral granules. Prescribing Information. Eton Pharmaceuticals, Deer Park, IL. September 2020.
55. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed November 1, 2021.
56. Lexicomp Online. Wolters Kluwer Health, Hudson, Ohio, USA. Available at http://online.lexi.com. Accessed November 1, 2021.

Appendix 1. Oral Glucocorticoid Drug Information

Table 1. Clinical Pharmacology and Pharmacokinetics[55,56]

Drug Name	Mechanism of Action	Absorption	Metabolism	Excretion	• **Half Life** • **Volume of Distribution**
Short-acting					
Hydrocortisone	Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability	Bioavailability: 96% Protein Binding: 92%	Hepatic	Renal	• 1.5-2 hours • 0.5 L/kg
Cortisone		Bioavailability: 44% Protein Binding: 90%	Hepatic: to active metabolite hydrocortisone	Renal	• 0.5 hours • NR
Intermediate-acting					
Prednisone	Suppresses the immune system by reducing activity and volume of the lymphatic system; suppresses adrenal function at high doses	Bioavailability: 50-90% Protein Binding: 50%	Hepatic: to active metabolite prednisolone	Renal	• 2-3 hours • 0.4 -1 L/kg
Prednisolone		Bioavailability: 84-96% Protein Binding: 70-90%	Hepatic	Renal	• 2-4 hours • 0.22-0.7 L/kg
Methylprednisolone		Bioavailability: 88% Protein Binding: NR	Hepatic	Renal	• 2-3 hours • 1.5 L/kg
Long-acting					
Dexamethasone	Decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response	Bioavailability: 61-86% Protein Binding: 77%	Hepatic	Renal	• 4 hours • NR
Abbreviations: kg =kilogram; L=Liter; NR=not reported					

Drug Safety

Use in Specific Populations:

- Elderly: Use with caution in elderly patients with the smallest possible effective dose for the shortest duration. Steroid psychosis is more common in elderly patients, especially in those who are terminally ill.[56]

- Pediatric: May affect growth velocity; growth should be routinely monitored in pediatric patients.[56]
- Pregnancy: Some studies have shown an association between first trimester systemic glucocorticoid use and oral clefts. Systemic glucocorticoids may also influence fetal growth (decreased birth weight); however, information is conflicting. When systemic glucocorticoids are needed in pregnancy, it is generally recommended to use the lowest effective dose for the shortest duration of time, avoiding high doses during the first trimester.[56]
- Breast feeding: Glucocorticoids are excreted in breast milk. The manufacturer notes that when used systemically, maternal use of glucocorticoids have the potential to cause adverse events in a breastfeeding infant (e.g., growth suppression, interference with endogenous glucocorticoid production). Prednisone is one of the oral glucocorticoids preferred for use in breastfeeding women. Breastfeeding is acceptable for patients with rheumatic and musculoskeletal diseases taking prednisone <20 mg/day.[56]

Boxed Warnings and Risk Evaluation Mitigation Strategy (REMS) Programs: None of the glucocorticoid formulations have FDA boxed warnings or REMS programs.

Contraindications:

- Immunizations: Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of glucocorticoids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted.[56]
- Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.[56]
- May cause osteoporosis (at any age) or inhibition of bone growth in pediatric patients. Use with caution in patients with osteoporosis; high doses and/or long-term use of glucocorticoids have been associated with increased bone loss and osteoporotic fractures.[56]
- Increased mortality was observed in patients receiving high-dose IV methylprednisolone; high-dose glucocorticoids should not be used for the management of head injury.[56]

Table 2. Summary of Warnings and Precautions[56]

Warning/Precaution	Hydrocortisone	Cortisone	Prednisone	Prednisolone	Methylprednisolone	Dexamethasone
Adrenal Suppression	x	x	x	x	x	x
Psychiatric Effects	x	x	x	x	x	x
Cushingoid Features	x	x	x	x	x	x
Gastrointestinal Effects	x	x	x	x	x	x
Hyperglycemia	x	x	x	x	x	x
Infection	x	x	x	x	x	x
Neuromuscular and Skeletal Effects	x	x	x	x	x	x
Ocular Effects	x	x	x	x	x	x

Appendix 2: Current Preferred Drug List and Specific Drug Information

Generic	Brand	Route	Form
cortisone acetate	CORTISONE ACETATE	ORAL	TABLET
dexamethasone	DEXAMETHASONE INTENSOL	ORAL	DROPS
dexamethasone	DEXAMETHASONE	ORAL	ELIXIR
dexamethasone	DEXAMETHASONE	ORAL	SOLUTION
dexamethasone	DEXAMETHASONE	ORAL	TAB DS PK
dexamethasone	TAPERDEX	ORAL	TAB DS PK
dexamethasone	DEXAMETHASONE	ORAL	TABLET
dexamethasone	HEMADY	ORAL	TABLET
hydrocortisone	ALKINDI SPRINKLE	ORAL	CAP SPRINK
hydrocortisone	CORTEF	ORAL	TABLET
hydrocortisone	HYDROCORTISONE	ORAL	TABLET
methylprednisolone	MEDROL	ORAL	TAB DS PK
methylprednisolone	METHYLPREDNISOLONE	ORAL	TAB DS PK
methylprednisolone	MEDROL	ORAL	TABLET
methylprednisolone	METHYLPREDNISOLONE	ORAL	TABLET
prednisolone	PREDNISOLONE	ORAL	SOLUTION
prednisolone	MILLIPRED	ORAL	TABLET
prednisolone sodium phosphate	PEDIAPRED	ORAL	SOLUTION
prednisolone sodium phosphate	PREDNISOLONE SODIUM PHOSPHATE	ORAL	SOLUTION
prednisolone sodium phosphate	PREDNISOLONE SODIUM PHOS ODT	ORAL	TAB RAPDIS
prednisone	PREDNISONE INTENSOL	ORAL	ORAL CONC
prednisone	PREDNISONE	ORAL	SOLUTION
prednisone	PREDNISONE	ORAL	TAB DS PK
prednisone	PREDNISONE	ORAL	TABLET
prednisone	RAYOS	ORAL	TABLET DR

Appendix 3: Abstracts

Randomized Trial of Dexamethasone Versus Prednisone for Children with Acute Asthma Exacerbations[50]

Objective: To determine whether 2 doses of dexamethasone is as effective as 5 days of prednisolone/prednisone therapy in improving symptoms and quality of life of children with asthma exacerbations admitted to the emergency department (ED).

Study design: We conducted a randomized, noninferiority trial including patients aged 1-14 years who presented to the ED with acute asthma to compare the efficacy of 2 doses of dexamethasone (0.6 mg/kg/dose, experimental treatment) vs a 5-day course of prednisolone/prednisone (1.5 mg/kg/d, followed by 1 mg/kg/d on days 2-5, conventional treatment). Two follow-up telephone interviews were completed at 7 and 15 days. The primary outcome measures were the percentage of patients with asthma symptoms and quality of life at day 7. Secondary outcomes were unscheduled returns, admissions, adherence, and vomiting.

Results: During the study period, 710 children who met the inclusion criteria were invited to participate and 590 agreed. Primary outcome data were available in 557 patients. At day 7, experimental and conventional groups did not show differences related to persistence of symptoms (56.6%, 95% CI 50.6-62.6 vs 58.3%, 95% CI 52.3-64.2, respectively), quality of life score (80.0 vs 77.7, not significant [ns]), admission rate (23.9% vs 21.7%, ns), unscheduled ED return visits (4.6% vs 3.3%, ns), and vomiting (2.1% vs 4.4%, ns). Adherence was greater in the dexamethasone group (99.3% vs 96.0%, P < .05).

Conclusion: Two doses of dexamethasone may be an effective alternative to a 5-day course of prednisone/prednisolone for asthma exacerbations, as measured by persistence of symptoms and quality of life at day 7.

Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial[51]

Background: Patients with inflammatory diseases, such as rheumatoid arthritis, often receive glucocorticoids, but long-term use can produce adverse effects. Evidence from randomised controlled trials to guide tapering of oral glucocorticoids is scarce. We investigated a scheme for tapering oral glucocorticoids compared with continuing low-dose oral glucocorticoids in patients with rheumatoid arthritis.

Methods: The Steroid EliMination In Rheumatoid Arthritis (SEMIRA) trial was a double-blind, multicentre, two parallel-arm, randomised controlled trial done at 39 centres from six countries (France, Germany, Italy, Russia, Serbia, and Tunisia). Adult patients with rheumatoid arthritis receiving tocilizumab and glucocorticoids 5-15 mg per day for 24 weeks or more were eligible for inclusion if they had received prednisone 5 mg per day for 4 weeks or more and had stable low disease activity, confirmed by a Disease Activity Score for 28 joints-erythrocyte sedimentation rate (DAS28-ESR) of 3·2 or less 4-6 weeks before and on the day of randomization. Patients were randomly assigned 1:1 to either continue masked prednisone 5 mg per day for 24 weeks or to taper masked prednisone reaching 0 mg per day at week 16. All patients received tocilizumab (162 mg subcutaneously every week or 8 mg/kg intravenously every 4 weeks) with or without csDMARDs maintained at stable doses during the entire 24-week study. The primary outcome was the difference in mean DAS28-ESR change from baseline to week 24, with a difference of more than 0·6 defined as clinically relevant between the continued-prednisone group and the tapered-prednisone group. The trial is registered with ClinicalTrials.gov, NCT02573012.

Findings: Between Oct 21, 2015, and June 9, 2017, 421 patients were screened and 259 (200 [77%] women and 59 [23%] men) were recruited onto the trial. In all 128 patients assigned to the continued-prednisone regimen, disease activity control was superior to that in all 131 patients assigned to the tapered-prednisone regimen; the estimated mean change in DAS28-ESR from baseline to week 24 was 0·54 (95% CI 0·35-0·73) with tapered prednisone and -0·08 (-0·27 to 0·12) with continued prednisone (difference 0·61 [0·35-0·88]; p<0·0001), favoring continuing prednisone 5 mg per day for 24 weeks. Treatment was regarded as successful (defined as low disease activity at week 24, plus absence of rheumatoid arthritis flare for 24 weeks and no confirmed adrenal insufficiency) in 99 (77%) patients in the continued-prednisone group versus 85 (65%) patients in the tapered-prednisone group (relative risk 0·83; 95% CI 0·71-0·97). Serious adverse events occurred in seven (5%) patients in the tapered-prednisone group and four (3%) patients in the continued-prednisone group; no patients had symptomatic adrenal insufficiency.

Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial[52]

Objectives: To compare the efficacy to prevent flares of maintenance versus withdrawal of 5 mg/day prednisone in systemic lupus erythematosus (SLE) patients with clinically quiescent disease.

Methods: A monocentric, 12-month, superiority, open-label, randomised (1:1) controlled trial was conducted with 61 patients continuing 5 mg/day prednisone and 63 stopping it. Eligibility criteria were SLE patients who, during the year preceding the inclusion, had a clinically inactive disease and a stable SLE treatment including 5 mg/day prednisone. The primary endpoint was the proportion of patient experiencing a flare defined with the SELENA-SLEDAI flare index (SFI) at 52 weeks. Secondary endpoints included time to flare, flare severity according to SFI and British Isles Lupus Assessment Group (BILAG) index and increase in the Systemic Lupus International Collaborating Clinics (SLICC) damage index (SDI).

Results: Proportion of patients experiencing a flare was significantly lower in the maintenance group as compared with the withdrawal group (4 patients vs 17; RR 0.2 (95% CI 0.1 to 0.7), p=0.003). Maintenance of 5 mg prednisone was superior with respect to time to first flare (HR 0.2; 95% CI 0.1 to 0.6, p=0.002), occurrence of mild/moderate flares using the SFI (3 patients vs 12; RR 0.2 (95% CI 0.1 to 0.8), p=0.012) and occurrence of moderate/severe flares using the BILAG index (1 patient vs 8; RR 0.1 (95% CI 0.1 to 0.9), p=0.013). SDI increase and adverse events were similar in the two treatment groups. Subgroup analyses of the primary endpoint by predefined baseline characteristics did not show evidence of a different clinical response.

Conclusion: Maintenance of long term 5 mg prednisone in SLE patients with inactive disease prevents relapse.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 5 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to October 12, 2021

1.	exp Cortisone/tu [Therapeutic Use]	280
2.	exp Dexamethasone/tu [Therapeutic Use]	7229
3.	exp Hydrocortisone/tu [Therapeutic Use]	2364
4.	exp Methylprednisolone/tu [Therapeutic Use]	7136
5.	exp Prednisolone/tu [Therapeutic Use]	16744
6.	exp Prednisone/tu [Therapeutic Use]	11048
7.	1 or 2 or 3 or 4 or 5 or 6	36040
8.	limit 7 to (english language and humans)	29959
9.	limit 8 to (yr="2000 -Current" and (clinical trial, phase iii or guideline or meta-analysis or randomized controlled trial or "systematic review"))	2918
10.	Administration, Oral/	99903
11.	9 and 10	207