


Safe Use of Corticosteroids in Non-Infectious Uveitis

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Abstract: Corticosteroids continue to represent the cornerstone of uveitis management, owing to their potent anti-inflammatory effects, which are pivotal for suppressing intraocular inflammation and mitigating the risk of irreversible visual impairment. This review focuses on the safety considerations associated with corticosteroid therapy across multiple administration routes, including topical, periocular, intravitreal, and systemic. Optimal corticosteroid therapy requires a personalized, stepwise approach, commencing with the least invasive modality at the lowest effective dose and escalating based on anatomical involvement, disease severity, and individual risk profiles, to balance efficacy with safety. Special attention is given to strategies for mitigating well-recognized local and systemic adverse effects, such as ocular hypertension, cataracts, osteoporosis, and increased cardiovascular risk. Beyond synthesizing current evidence, this review offers a novel perspective by integrating systemic and local therapy risks and by highlighting safety strategies that can guide individualized regimens. Finally, we identify persisting knowledge gaps, including the lack of long-term comparative safety data, limited evidence on risk stratification, and the need for biomarkers to guide therapy, which represent critical avenues for future research. Adjunctive use of immunosuppressive or biologic agents enables improved long-term control and facilitates corticosteroid tapering.

Keywords: uveitis, non-infectious uveitis, corticosteroids, glucocorticoids, safety

Introduction

Uveitis is a leading cause of vision loss.¹ Recurrent inflammatory episodes can result in cumulative ocular damage, progressively increasing the likelihood of visual impairment or blindness, with substantial personal, societal, and economic consequences.^{2,3} Despite the well-known and potentially severe side effects, corticosteroids are the mainstay for the management of non-infectious uveitis (NIU), but their use requires careful consideration of route, dose, duration, and risk of adverse effects.⁴ In fact, evidence from the VISUAL-1 and VISUAL-2 trials supports that chronic corticosteroid use in NIU is strongly associated with dose-dependent increases in adverse events, showing significantly higher incidence rates of corticosteroid-related adverse events during prednisone treatment compared to post-taper periods, highlighting the risks of higher dosing in both active and inactive noninfectious uveitis.⁵

Methods

This work was conducted as a narrative review. Studies were identified and selected based on the authors' expert knowledge of the field, with prioritization given to publications that have shaped current clinical practice in the management of non-infectious uveitis. No systematic database search or formal inclusion/exclusion criteria were applied. Instead, the selection process relied on expert choice, aiming to provide a balanced synthesis of key concepts and safety considerations across corticosteroid administration routes.

Results

Route and Dose

Topical

For noninfectious anterior uveitis, topical corticosteroids such as prednisolone acetate 1% are first-line, typically started at high frequency (eg, hourly during waking hours) and then tapered based on clinical response.^{4,6} Other topical steroids such as dexamethasone 0.1% are also frequently used in the treatment of anterior uveitis.⁷

There is one randomized trial, comparing prednisolone acetate 1% and rimexolone 1%, which demonstrates that both are effective, with no significant difference in reduction of anterior chamber inflammatory cells at 28 days.⁸ Additionally, a randomized trial found that non-preserved methylprednisolone 1% is non-inferior to preserved prednisolone acetate 1% in efficacy, with lower ocular surface toxicity and less subjective discomfort, but unfortunately this formulation is not commercially available.⁹

Furthermore, randomized controlled trials have demonstrated that difluprednate 0.05% (not commercially available in the EU) is non-inferior to prednisolone acetate 1% for the treatment of non-infectious anterior uveitis, with similar efficacy in reducing anterior chamber cell grade after 14 days of treatment and subsequent tapering. Notably, difluprednate achieves this effect with less frequent dosing (four times daily) compared to prednisolone acetate (eight times daily), which may improve adherence in some patients.^{10,11}

However, the risk profile of difluprednate requires careful consideration. Both adult and pediatric studies have consistently shown a higher incidence of clinically significant intraocular pressure (IOP) elevation with difluprednate compared to other topical corticosteroids.¹² In adults, IOP elevation (ie, ≥ 21 mmHg or ≥ 10 mmHg above baseline) occurred in approximately 31% of patients.¹² In pediatric populations, up to 50% of eyes experienced significant IOP elevation, and cataract formation or progression was observed in 39% of eyes, necessitating close monitoring.¹³ Most IOP elevations responded to cessation of difluprednate or addition of topical antihypertensive agents, but some pediatric cases required surgery to lower intraocular pressure.¹³

However, other topical steroids such as fluorometholone 0.1%, loteprednol 0.5% or hydrocortisone sodium phosphate 0.335% have a low penetrance intraocularly and therefore are not effective in treating anterior NIU.⁷

According to the SITE (Systemic Immunosuppressive Therapy for Eye Diseases) cohort study, the safe maintenance dose of topical corticosteroids to minimize the risk of adverse events such as cataract and ocular hypertension in the treatment of non-infectious anterior uveitis is ≤ 2 drops per day of prednisolone acetate 1% (or equivalent).¹⁴ Chronic use of higher doses, particularly >3 drops daily, is associated with a significantly increased risk of cataract formation and ocular hypertension, as demonstrated in both adult and pediatric populations.¹⁵ In the SITE study, topical corticosteroids were linked to an increased risk of cataract only when anterior chamber inflammation was absent or minimal, suggesting that when used to treat active inflammation (which is itself a risk factor for cataract) they do not result in a net increase in cataract incidence.¹⁴

In non-anterior (intermediate, posterior, panuveitis) forms of NIU, topical corticosteroids alone are generally inadequate because they do not reach therapeutic levels in the posterior segment due to limited penetration.⁷

Periocular or Intravitreal

Local corticosteroid therapies, including periocular injections, intravitreal injections, sustained-release implants, and suprachoroidal injections, are effective for controlling intraocular inflammation and macular edema.⁴

A recent Cochrane review, including four randomized controlled trials, evaluated the role of intravitreal corticosteroid implants (fluocinolone acetonide and dexamethasone) in non-anterior NIU (intermediate uveitis, posterior uveitis, and panuveitis). Comparing these implants to sham or standard-of-care therapies, it pointed out that corticosteroid implants reduced the risk of uveitis recurrence by 54–60%, though their impact on visual acuity and quality of life was limited or uncertain.¹⁶ The implants were consistently associated with increased risks of cataract progression and IOP elevation, often requiring medical or surgical intervention.¹⁶ Overall, the evidence supports a modest benefit in controlling inflammation, but highlights the need for careful monitoring and individualized risk–benefit assessment.¹⁶

The Multicenter Uveitis Steroid Treatment (MUST) trial was a randomized controlled trial comparing systemic corticosteroid therapy (with immunosuppression as per investigator's decision) to the surgically placed intravitreal

fluocinolone acetonide implant for patients with non-anterior NIU. The MUST trial demonstrated that, over the long term, systemic therapy was associated with slightly better visual acuity outcomes.¹⁷ Although no statistically significant difference in mean visual acuity improvement was observed between the groups at 2 and 4.5 years,^{18,19} by 7 years, systemic therapy was linked to a mean gain of 7.2 letters over the implant group (95% CI, 2.1–12).¹⁷ This difference reached clinical significance, although its interpretation is limited by loss to follow-up.

Control of intraocular inflammation was superior with the implant at all time points, but most patients on systemic therapy also achieved substantial improvement in inflammatory status.^{18,19} Furthermore, there was a rapid early improvement in macular edema in the implant group, but by 36 months, the rates of macular edema resolution were similar between groups.²⁰ On the contrary, the implant group had higher rates of ocular complications, including cataract surgery, elevated intraocular pressure, and glaucoma, while systemic therapy was associated with more systemic infections requiring antibiotics, but otherwise, serious systemic adverse events were uncommon and similar between groups.¹⁸ As a summary, cost-effectiveness and side-effect profiles suggest systemic therapy is generally preferred for bilateral disease, while implant therapy may be considered for unilateral disease or when systemic therapy is contraindicated or unsuccessful.^{18–22}

Nevertheless, the MUST trial used the surgically implanted 0.59 mg fluocinolone acetonide implant (not commercially available in the EU) as the comparator to systemic therapy. Since then, another 0.18/0.19 mg fluocinolone acetonide implant has been presented. The 0.59 mg fluocinolone acetonide implant is associated with the highest rates of adverse events.²³ Nearly all phakic eyes develop cataracts requiring surgery within 3 years, and approximately 77% require IOP-lowering medications and 37% require filtering surgery for IOP control.^{23,24} However, the security profile is more favorable in the case of the 0.18/0.19 mg implants. In pivotal trials, 80% of phakic eyes required cataract surgery over 3 years, and <5% required incisional IOP-lowering surgery; most IOP elevations were managed medically.²⁵

Randomized controlled trials of 0.18/0.19 mg implants, have also demonstrated a significant reduction in uveitis recurrence rates compared to sham (eg, 28% vs 86% recurrence at 12 months; $p < 0.01$), prolonged time to first recurrence, and improved visual outcomes, with approximately one-third of patients gaining ≥ 15 letters in BCVA at 36 months.²⁶ Although no head-to-head trials directly compare the 0.18/0.19 mg implants to the 0.59 mg implant, available data and systematic reviews indicate comparable efficacy in controlling inflammation and preserving vision.^{16,27}

In parallel, other trials have compared different corticosteroid delivery methods for uveitic macular edema. The Periocular and Intravitreal Corticosteroids for Uveitic Macular Edema (POINT) Trial was a multicenter randomized clinical trial comparing periocular triamcinolone acetonide, intravitreal triamcinolone acetonide, and the intravitreal dexamethasone implant for the treatment of uveitic macular edema in non-infectious uveitis. At 8 weeks, all three treatments led to significant reductions in central subfield thickness on optical coherence tomography (OCT), but intravitreal therapies were superior to periocular injection.²⁸ Specifically, the mean central subfield thickness reduction from baseline was 23% for periocular triamcinolone acetonide, 39% for intravitreal triamcinolone acetonide, and 46% for intravitreal dexamethasone implant. Both intravitreal triamcinolone acetonide and intravitreal dexamethasone implant were statistically superior to periocular triamcinolone acetonide in reducing central subfield thickness ($p < 0.0001$). Both intravitreal groups also achieved greater improvements in best-corrected visual acuity, with a mean gain of 5 letters more than the periocular triamcinolone acetonide group at 8 weeks ($p < 0.004$).²⁸ On the other hand, the risk of IOP elevation (≥ 24 mmHg) was higher in the intravitreal groups (hazard ratio [HR] 1.83 for intravitreal triamcinolone acetonide and 2.52 for intravitreal dexamethasone implant vs periocular triamcinolone acetonide), although no significant difference in IOP risk between the two intravitreal groups.²⁸

Even though intraocular steroids clearly reduce vitritis and macular edema, their effect on choroidal inflammation remains uncertain. Some studies suggest intraocular steroids may decrease choroidal inflammation and thickness in inflammatory eye disorders, while others, such as those on birdshot chorioretinopathy, indicate systemic therapy provides better control over choroidal inflammation.²⁹

Overall, the risk of glaucoma is dose- and duration-dependent, and is highest with the surgically implanted, higher-dose 0.59 mg fluocinolone acetonide implant. In long-term follow-up of the Multicenter Uveitis Steroid Treatment (MUST) trial, eyes treated with the fluocinolone acetonide implant had a significantly higher cumulative incidence of glaucoma compared to systemic therapy (40% vs 8% at median 6.9 years; HR 5.9), and this risk persisted even after

adjusting for IOP elevation during follow-up.^{21,24,30,31} Of particular concern is that, although most cases of steroid-induced glaucoma following intravitreal corticosteroid implants are indeed preceded by IOP elevation, which is the primary modifiable risk factor for glaucomatous optic neuropathy in this context, long-term prospective studies in uveitis has shown that some patients develop progressive glaucomatous optic nerve damage despite adequate IOP control, suggesting that corticosteroid exposure itself may contribute directly to optic nerve vulnerability or damage, independent of measured IOP.^{24,30,32} Importantly, while aggressive IOP management prevented progression in most cases, a subset of patients experienced worsening visual field or optic nerve cupping despite controlled IOP, underscoring the need for vigilant, indefinite monitoring for both IOP and structural/functional glaucomatous changes in patients receiving repeated or sustained intravitreal corticosteroid therapy for non-infectious uveitis.^{24,30,32,33}

In summary, repeated or sustained use of intravitreal corticosteroid implants for non-infectious uveitis is associated with a significantly increased risk of glaucoma, and this risk is highest with higher-dose, longer-acting implants and with repeated exposure. Close and indefinite monitoring for IOP elevation and structural glaucomatous damage is required in these patients.^{24,30,32,33}

Conversely, a novel delivery route for triamcinolone acetonide, the suprachoroidal administration, appears to carry a lower risk of developing glaucoma, similar to sham or control treatment.³⁴ In a randomized trial, the incidence of IOP elevation with suprachoroidal triamcinolone was 11.5%, not significantly different from the sham group (15.6%), and the rate of cataract formation was also similar (7.3% vs 6.3%).³⁴ In an open-label safety study, 15.8% of subjects experienced an IOP rise >10 mmHg, and only 5.3% had IOP >30 mmHg; no serious ocular adverse events or cases of glaucoma requiring surgery were reported over 24 weeks.³⁵ These findings suggest a low risk of clinically significant IOP elevation or glaucoma with suprachoroidal triamcinolone acetonide; however, further studies with longer follow-up are warranted to determine whether or not this route of administration is safer than others.

Systemic Steroids

Systemic corticosteroids (eg, oral prednisone) are effective for posterior segment or vision-threatening inflammation, although long-term use, especially at doses >7.5 mg/day, is associated with significant systemic risks, such as hyperglycemia and osteoporosis.¹ The addition of immunosuppressive agents is often necessary for steroid-sparing and to achieve long-term disease control.¹

The recommended initial dose of oral corticosteroids for the treatment of non-anterior NIU (based on clinical experience) is 1 mg/kg/day of oral prednisone (or equivalent), up to a maximum of 60–80 mg daily.^{4,36} The dose is then tapered over several weeks based on clinical response and the goal of minimizing long-term corticosteroid exposure.^{1,4,36} Doses much lower than 1 mg/kg/day are not recommended for induction of remission, as they are generally insufficient to control active intraocular inflammation.

In general, long-term maintenance with corticosteroids is not recommended due to the risk of adverse effects; instead, the goal is to taper prednisone to ≤7.5 mg/day within 3 months, at which point steroid-sparing immunosuppressive agents should be introduced if inflammation cannot be controlled at these lower doses.^{36,37} Furthermore, chronic use of low-dose corticosteroids (<7.5 mg/day) as monotherapy is considered ineffective for disease control and is discouraged in favor of immunosuppressive therapy.^{36,37}

Intravenous corticosteroids should be used in ocular inflammatory conditions that are severe, vision-threatening, or associated with rapid progression, where an immediate and robust anti-inflammatory effect is required. In such cases, promptly concomitant immunosuppressive therapy can also be started, either concurrently or shortly after corticosteroid pulse therapy. The most well-established indications include:

- Acute severe noninfectious posterior uveitis or panuveitis with threat to vision (eg, Behçet disease, Vogt-Koyanagi-Harada syndrome, or other fulminant posterior segment inflammation). In these cases, high-dose intravenous methylprednisolone (typically 500–1000 mg daily for 3 days) is recommended to achieve rapid control, followed by a transition to oral corticosteroids with a tapering regimen.^{36,38,39}
- Other situations where oral or local corticosteroid therapy is insufficient or contraindicated such as bilateral, rapidly progressive inflammation or when systemic disease activity requires immediate suppression.^{36,38,39}

Evidence from retrospective studies demonstrates that intravenous methylprednisolone induces rapid improvement in intraocular inflammation, including anterior chamber cells, vitritis, macular edema, and retinal vasculitis, with a favorable safety profile in the short term.^{38,40} In a retrospective multicenter cohort, 57% of patients achieved complete remission within 1 month after intravenous methylprednisolone, followed by oral prednisone taper.⁴⁰

Compared to oral corticosteroids at 1 mg/kg/day, intravenous corticosteroids provide more rapid suppression of inflammation but are not superior for long-term disease control. Oral prednisone at 1 mg/kg/day remains the standard initial therapy for most cases of severe non-infectious uveitis, with intravenous corticosteroids reserved for fulminant or refractory cases, or when immediate vision preservation is critical. Both approaches require transition to steroid-sparing immunosuppressive therapy for long-term management to minimize corticosteroid-related adverse effects.^{1,4,36}

The common side effects of systemic corticosteroids when used for the treatment of non-infectious uveitis include hyperglycemia, osteoporosis, hypertension, weight gain, cushingoid features, mood and psychiatric disturbances, increased risk of infection, adrenal suppression, myopathy, and gastrointestinal complications such as peptic ulcer disease.⁴¹ Ocular complications such as cataract and ocular hypertension/glaucoma can also occur, though the risk is more pronounced with local steroid administration; systemic steroids may contribute, especially with prolonged use, as explained above.⁴²

Risk factors for developing these side effects include higher corticosteroid dose, longer duration of therapy, older age, and pre-existing comorbidities (such as diabetes, hypertension, or osteoporosis). The risk of adverse events increases systematically with corticosteroid dose: each 10 mg increase in prednisone is associated with a 1.5- to 2.6-fold increase in overall adverse event rates.⁵ Chronic use of doses exceeding 7.5 mg/day of prednisone is particularly associated with metabolic and bone complications.^{43,44}

Regular monitoring for side effects and modification of risk factors (eg, bone protection, glucose monitoring) are essential components of care.^{43,44}

Before starting systemic corticosteroid therapy in a patient with non-infectious uveitis, it is recommended to perform baseline evaluations to identify comorbidities and risk factors for corticosteroid-related adverse effects (correcting them when possible), and to monitor for complications during therapy.⁴⁵ The following tests and analyses are commonly recommended (Table 1):

- Blood glucose (fasting or HbA1c): To screen for pre-existing or undiagnosed diabetes, as corticosteroids can induce hyperglycemia or worsen glycemic control.^{4,41}
- Serum electrolytes and renal function: To monitor for corticosteroid-induced electrolyte disturbances and to establish baseline renal function.⁴¹

Table 1 Recommended Baseline and Follow-up Assessments for Patients with Non-Infectious Uveitis Receiving Systemic Corticosteroid Therapy

ASSESSMENTS:	FREQUENCY:
Blood glucose (fasting or Hemoglobin A1c)	At baseline and every 3 to 6 months
Serum electrolytes and renal function	At baseline and every 3 to 6 months
Complete blood count	At baseline and every 3 to 6 months
Screening for latent infections	At baseline
Blood pressure measurement	At baseline and depending on initial findings and individual risk factors
Chest X-ray	At baseline
BMD (DXA scan)	At baseline in patients ≥ 40 years on treatment with glucocorticoid at ≥ 2.5 mg/day for >3 months and every 1–2 years depending on initial findings and individual risk factors
Weight and body mass index	Depending on patient's comorbidities.

Abbreviations: BMD, Bone mineral density; DXA, Dual-energy X-ray Absorptiometry.

- Complete blood count (CBC): To detect underlying infection or cytopenias.⁴¹
- Screening for latent infections: Tuberculosis (eg, interferon-gamma release assay or tuberculin skin test) and hepatitis B/C serologies, particularly if immunosuppressive therapy is anticipated.⁴⁴
- Blood pressure measurement: To assess for hypertension, which can be exacerbated by corticosteroids.^{4,41}
- Chest X-ray: It should be included if there is clinical suspicion for underlying infectious or granulomatous disease, such as tuberculosis or sarcoidosis, or if the etiology of uveitis is unclear. This is because systemic corticosteroids can exacerbate latent infections and may mask or worsen undiagnosed pulmonary disease.^{4,41}
- Bone mineral density (BMD) (Dual-energy X-ray absorptiometry (DXA) scan): Especially in patients at risk for osteoporosis, as corticosteroids increase fracture risk.^{4,41} This topic will be further explained in the next section.
- Weight and body mass index (BMI): To monitor for corticosteroid-induced weight gain.^{4,41}

Additional assessments may be indicated based on patient-specific risk factors, such as psychiatric history (for mood disorders), gastrointestinal history (for peptic ulcer risk), and cardiovascular risk profile. Patient education regarding infection risk, adrenal suppression, and the need for regular follow-up is also essential.⁴¹

However, recommended baseline assessments and tests should not delay the initiation of systemic corticosteroid therapy when urgent treatment is needed to prevent vision loss in a patient with NIU at risk of vision-threatening disease. In cases where there is imminent risk to vision, immediate initiation of high-dose systemic corticosteroids is recommended to rapidly control inflammation and prevent irreversible ocular damage, even if all baseline investigations have not yet been completed.^{4,41,44} Baseline assessments are important for identifying risk factors and guiding ongoing management, but they should be performed concurrently with, rather than prior to, urgent corticosteroid initiation in vision-threatening situations. This approach is consistent with expert opinion and clinical practice, which prioritize preservation of vision over the potential risks of corticosteroid therapy in the acute setting.^{4,36,41,44}

Bone Protection

Corticosteroids decrease bone formation and increase bone resorption, leading to bone loss and increased fracture risk. The primary mechanisms include direct inhibition of osteoblastogenesis, promotion of osteoblast and osteocyte apoptosis, and stimulation of osteoclast activity via increased Receptor Activator of Nuclear Factor Kappa- β Ligand (RANKL) expression.^{46–52} These effects result in rapid bone loss, particularly in the first 3 to 6 months of therapy, and a marked increase in vertebral and hip fracture risk, even at low to moderate doses (eg, 2.5–7.5 mg prednisolone daily).^{46–53}

Corticosteroids also have indirect effects on bone, such as reducing muscle mass (increasing fall risk), decreasing sex hormone levels, and altering calcium metabolism. The risk of bone loss and fracture is dose- and duration-dependent, but it can occur even with inhaled or intermittent high-dose regimens. Discontinuation of corticosteroids leads to partial recovery of bone mineral density and reduction in fracture risk.^{46,54}

Patients at high risk for corticosteroid-induced bone loss are those who are older (especially age >55 years), postmenopausal women, individuals receiving a daily dose of prednisone higher than 7.5 mg/day (or equivalent), those with prolonged or recent glucocorticoid exposure (≥ 3 months), an cumulative dose of prednisone > 5 g/year and patients with underlying conditions such as rheumatoid arthritis, inflammatory bowel disease (IBD), or other chronic inflammatory diseases. Additional risk factors include prior fragility fracture, low bone mineral density (T-score < -1.5), white race, low BMI (<18.5), hypogonadism, menopause, smoking, excessive alcohol use, and increased fall risk. The risk of rapid bone loss and fragility fractures is particularly pronounced in the first 3 to 6 months of therapy and increases with both dose and duration of corticosteroid use. Even low doses (as low as 2.5 mg/day) can contribute to bone loss, but fracture risk rises substantially at doses ≥ 5 –7.5 mg/day and with cumulative exposure.^{46,55–57}

Notably, the American College of Rheumatology recommend that all adults receiving ≥ 2.5 mg of prednisone daily for more than 3 months should be considered at risk of glucocorticoid induced osteoporosis, with higher risk thresholds for those on ≥ 7.5 mg/day or with additional risk factors. Although the risk of bone loss and fracture decreases after discontinuation of corticosteroids, it may not fully normalize, particularly after prolonged or high-dose exposure.^{46,53,54,56}

The most effective screening strategies for early detection of bone loss in high-risk groups for corticosteroid-induced bone loss are:

1. Early and systematic clinical risk assessment: This includes a detailed history of prior fractures (symptomatic and asymptomatic), glucocorticoid dose and duration, fall risk, low body weight, smoking, alcohol use, hypogonadism, and comorbidities such as rheumatoid arthritis or inflammatory bowel disease. The American College of Rheumatology recommends this assessment for all adults (≥ 18 years) initiating or continuing glucocorticoid therapy at ≥ 2.5 mg/day for >3 months, ideally within 6 months of starting therapy.⁵⁸

2. BMD assessment by DXA: DXA of the lumbar spine and hip is the gold standard for detecting bone loss and should be performed at baseline in patients ≥ 40 years on treatment with glucocorticoid at ≥ 2.5 mg/day for >3 months. Repeat DXA is typically advised every 1–2 years depending on initial findings and individual risk factors.⁵⁸

3. Vertebral fracture assessment (VFA) or lateral spine X-ray: The American College of Rheumatology strongly recommends VFA or spine X-ray at baseline to detect asymptomatic vertebral fractures, which are common and may influence management decisions. Reassessment is advised every 1–2 years if patients continue chronic glucocorticoid therapy at doses ≥ 2.5 mg/day.^{56,58}

4. Fracture risk estimation using FRAX: For adults ≥ 40 years, the FRAX tool (with BMD if available) should be used to estimate 10-year fracture risk, with dose adjustment for prednisone >7.5 mg/day (as this is associated with an increase on major osteoporotic fracture risk by 15% and hip fracture risk by 20%). FRAX is not validated for individuals under 40 years or for reassessment during ongoing therapy.⁵⁸

The most effective alternative medications for the prevention of bone loss in patients at high risk for corticosteroid-induced osteoporosis are oral bisphosphonates, intravenous bisphosphonates, denosumab, and anabolic agents, such as teriparatide or abaloparatide.

For prevention of glucocorticoid-induced osteoporosis in adults beginning long-term therapy, the American College of Rheumatology strongly recommends oral bisphosphonates (like alendronate or risedronate) as first-line therapy due to their efficacy, safety, and cost-effectiveness. Intravenous bisphosphonates (zoledronic acid, ibandronate) are appropriate for patients who cannot tolerate or adhere to oral therapy. Denosumab is a monoclonal antibody that is an alternative for those with contraindication or intolerance to bisphosphonates and has demonstrated superiority to risedronate in increasing spine bone mineral density in glucocorticoid-treated patients.

Anabolic agents are conditionally recommended as initial therapy over antiresorptive agents for patients at very high fracture risk, such as those with prior fragility fracture, very low BMD, or high dose/prolonged glucocorticoid exposure (>5 g/year), as they increase bone formation and reduce vertebral fracture risk more than bisphosphonates.

Raloxifene (for postmenopausal women intolerant to other agents) and romosozumab (a dual-acting agent that both stimulates bone formation and inhibits bone resorption, in select cases) are additional options but are generally reserved for those who cannot use other therapies due to safety concerns. It is also important to note that abaloparatide and romosozumab are not approved for the treatment of glucocorticoid-induced osteoporosis, and access to these medications for this indication may therefore be limited.⁵⁸ Furthermore, after discontinuation of anabolic therapy, transition to an antiresorptive agent is recommended to maintain gains in bone density. Similarly, discontinuation of denosumab must be followed by bisphosphonates, beginning at 6 to 7 months after the last dose to prevent rapid bone loss and multiple vertebral fractures.^{56,58–60}

All patients should also receive adequate calcium and vitamin D supplementation and lifestyle optimization. Dietary and supplemented elemental calcium intake of up to 1,000 to 1,200 mg daily is recommended for adults, and serum vitamin D levels should be monitored and vitamin D supplemented to maintain serum vitamin D levels ≥ 30 to 50 ng/mL (600 to 800 IU daily or more is typically required). Lifestyle modifications should include avoiding smoking, moderating alcohol intake to no more than two drinks per day, following a balanced diet, keeping a healthy body weight in the recommended range and engaging regularly in weight-bearing or resistance exercises.^{56,58–61}

Gastrointestinal Protection

Corticosteroids can affect the gastrointestinal (GI) tract, most notably increasing the risk of gastrointestinal bleeding and peptic ulcer disease. This risk is well established in hospitalized or critically ill patients, especially when used with non-steroidal anti-inflammatory drugs (NSAIDs), but remains controversial in ambulatory patients.^{62–64}

Recent case-control studies have shown that the use of NSAIDs, either alone or in combination with corticosteroids, is associated with a markedly increased risk of peptic ulcer bleeding compared with corticosteroid monotherapy. However, corticosteroids alone were linked to only a moderate increase in risk.^{65,66} Earlier clinical trials, by contrast, yielded conflicting results, with some suggesting a dose-dependent increase in peptic ulcer risk with corticosteroids,⁶⁷ while others found no significant difference between corticosteroid and placebo groups.⁶⁸

The recommended strategies to reduce gastrointestinal complications are currently restricted to high-risk patients on corticosteroids, which include concomitant use of NSAIDs, aspirin, or prior history of peptic ulcer disease or GI bleeding. In these cases, proton pump inhibitors (PPIs) are the preferred gastroprotective option.⁶⁹ *Helicobacter pylori* testing and eradication are recommended in patients with a history of peptic ulcers or GI bleeding, as eradication reduces the risk of recurrence. Nevertheless, maintenance PPI therapy remains advisable if concomitant NSAID or antiplatelet treatment is ongoing.⁷⁰

Altered gastrointestinal motility may also occur, with corticosteroids potentially accelerating gastric emptying and affecting small intestinal transit, though these effects are less clinically significant than bleeding or ulceration.^{71–73}

Adrenal Insufficiency

Glucocorticoid-induced adrenal insufficiency is the most common form of adrenal insufficiency, and the risk is primarily determined by the dose, duration, and route of glucocorticoid administration. According to the 2024 joint clinical guideline from the Endocrine Society and the European Society of Endocrinology, the pooled risk of biochemical adrenal insufficiency after oral glucocorticoid therapy is approximately 48.7% (95% CI, 36.9–60.6), with a higher risk associated with higher doses and longer treatment durations. For example, treatment exceeding one year can result in a risk of 27.4% (95% CI, 17.7–39.8) in asthma patients, and a similar risk is expected in other chronic inflammatory conditions such as NIU.^{74,75}

In the context of NIU, systemic corticosteroids are often used at doses exceeding 7.5 mg/day of prednisone for months, which is well within the range associated with hypothalamic-pituitary-adrenal axis suppression and subsequent adrenal insufficiency. The risk is not negligible even at lower doses or with shorter courses, as suppression can occur with as little as 5 mg/day of prednisone for 3–4 weeks or longer.⁷⁵

Patients at higher risk for developing adrenal insufficiency during systemic corticosteroid treatment for NIU include those receiving higher daily doses (prednisone ≥ 7.5 mg/day), those on prolonged courses (≥ 3 –4 weeks), older adults, and individuals with repeated or cumulative exposure to multiple glucocorticoid formulations (oral, inhaled, or injected). The risk is also increased in patients who undergo rapid tapering or abrupt discontinuation of steroids, and in those with comorbidities that increase susceptibility to infections, as intercurrent illness is a common trigger for adrenal crisis in this population.^{74,76}

Early symptoms that may indicate the development of adrenal insufficiency include fatigue, anorexia, weight loss, nausea, vomiting, abdominal pain, muscle or joint pain, and hypotension. These symptoms are often nonspecific and can overlap with the underlying disease or with glucocorticoid withdrawal syndrome, making clinical recognition challenging.^{76,77}

The European Society of Endocrinology emphasizes that hypotension (including postural hypotension), severe fatigue, gastrointestinal symptoms (nausea, vomiting, abdominal pain), and impaired consciousness (lethargy, confusion, somnolence) are key early clinical features, particularly during or after glucocorticoid tapering or abrupt cessation. Laboratory findings may include hyponatremia, hypoglycemia, and, less commonly, hyperkalemia. The risk of adrenal crisis is highest during periods of physiological stress (eg, infection, surgery) or rapid steroid dose reduction.⁷⁴ Therefore, the EULAR recommends adequate glucocorticoid replacement in acute situations for patients receiving chronic medium- or high-dose corticosteroid therapy, emphasizing that treatment should not be discontinued abruptly but tapered gradually. Currently, there is no evidence to support the superiority of any specific replacement or stress-dose regimen. In practice, clinicians may either increase the oral glucocorticoid dose for approximately three days or, depending on the clinical scenario, switch to intravenous hydrocortisone (eg, twice daily 25 mg for patients on 10 mg prednisone daily, or three times daily 50 mg for those on high-dose glucocorticoid therapy). Although higher stress-dose regimens have not been proven necessary, they may be considered in selected cases.⁷⁸

For the diagnosis of adrenal insufficiency in clinically suspected cases, the European Society of Endocrinology and the Endocrine Society recommend initial assessment with an early-morning (typically 8 am) serum cortisol measurement,

ideally at least 24 hours after the last glucocorticoid dose to avoid interference from exogenous steroids. A morning cortisol level $<5 \mu\text{g/dl}$ ($<138 \text{ nmol/l}$) is highly suggestive of adrenal insufficiency, while a level $>10 \mu\text{g/dl}$ ($>276 \text{ nmol/l}$) generally excludes the diagnosis and steroids can be stopped safely. Intermediate values ($5\text{--}10 \mu\text{g/dl}$) require further evaluation with a corticotropin (cosyntropin) stimulation test, measuring serum cortisol before and 30–60 minutes after intravenous administration of $250 \mu\text{g}$ cosyntropin. Failure to achieve a peak cortisol $>18 \mu\text{g/dL}$ (500 nmol/l) confirms adrenal insufficiency in this context.⁷⁴

Uncommon Side Effects

Less common side effects of the use of corticosteroids that the clinician needs to be aware of include:

- Corticosteroids-induced myopathy: Corticosteroids-induced myopathy typically presents as painless proximal muscle weakness, most often affecting the lower limbs, and is more likely with higher daily doses ($\geq 20\text{--}30 \text{ mg/day}$ prednisone or equivalent), prolonged therapy, and in older adults. The frequency of steroid myopathy in chronic glucocorticoid users has been estimated at up to 60% in some series, but this is more commonly reported with fluorinated glucocorticoids (eg, dexamethasone) than with non-fluorinated agents like prednisone, which is the standard for NIU.⁷⁹ Acute steroid myopathy is rare but can occur unpredictably, even after short courses or lower doses.⁸⁰
- Avascular necrosis of the hip: Meta-analyses and systematic reviews indicate that the incidence of avascular necrosis of the hip in patients receiving corticosteroid treatment at cumulative doses $>2 \text{ g}$ (prednisone-equivalent) is approximately 6.7% across various populations, with risk increasing in a dose-dependent manner.^{81,82} Each 10 mg/day increase in prednisone is associated with a 3.6% increase in avascular necrosis incidence, and daily doses $>20 \text{ mg}$ are associated with a higher risk.⁸¹ While most data are from populations with systemic autoimmune diseases, these findings are relevant to uveitis patients, as similar corticosteroid regimens are used. Patients at higher risk include those receiving high-dose or long-term corticosteroids, older adults, and those with additional risk factors such as underlying systemic disease or prior episodes of avascular necrosis.⁸¹ The risk is not negligible even with moderate doses if therapy is prolonged, and early detection is critical for joint preservation.⁸²
- Corticosteroid-induced psychosis: Large population-based data indicate that oral glucocorticoid treatment is associated with an increased risk of serious psychiatric outcomes, including new-onset or relapsed depressive, anxiety, and bipolar disorders, with hazard ratios ranging from 1.08 to 1.25 for these outcomes. The risk of acute psychosis is lower than for mood or anxiety disorders, but it is well recognized, especially at prednisone-equivalent doses $\geq 40 \text{ mg/day}$ and in the first weeks of treatment. The absolute prevalence of corticosteroid-induced psychosis in the general population receiving systemic steroids is estimated at 1–5%, with higher rates in those with prior psychiatric history or with high-dose regimens.⁸³

Use in Particular Populations

Pediatric Population

When using systemic corticosteroids to treat NIU in children, several caveats and considerations are critical due to the unique vulnerability of the pediatric population to adverse effects (Table 2). Growth retardation, weight gain, and cushingoid features are among the most common side effects, with growth suppression being particularly concerning due to the impact on final adult height. Osteoporosis and decreased bone density are also significant risks, with decreased bone density observed in over 20% of children on long-term corticosteroids and a smaller but real risk of osteoporosis and fractures.⁸⁴

Suppression of the hypothalamic-pituitary-adrenal axis is especially important in children, who are less resilient than adults, may show nonspecific symptoms, and face risks to growth and development. Gradual tapering after prolonged use ($>2\text{--}3$ weeks) and stress-dose steroids during illness or procedures are essential.⁸⁵

Hyperglycemia and new-onset diabetes mellitus are dose-dependent risks, with high-dose regimens increasing the risk substantially. Hypertension is also a well-documented complication, with a strong dose-response relationship.⁸⁶ Weight gain and central adiposity are also frequent and can contribute to metabolic syndrome. Skin changes (striae, acne, easy bruising) are

Table 2 Key Risks and Management Considerations of Systemic Corticosteroid Use in Special Populations with Non-Infectious Uveitis

Population	Key Risks	Management Considerations
Pediatric	<ul style="list-style-type: none"> • Growth retardation • Weight gain, cushingoid features • Decreased bone density • HPA axis suppression • Hyperglycemia, diabetes • Hypertension • Mood changes, infection risk (varicella zoster) • Higher risk of steroid-induced ocular complications 	<ul style="list-style-type: none"> • Use short courses, consider IV pulses • Gradual taper after use >2-3 weeks • Stress-dose steroids during illness • Review/update vaccinations • Multidisciplinary monitoring (pediatrics, ophthalmology)
Elderly	<ul style="list-style-type: none"> • Increased osteoporosis, fractures • Hyperglycemia, diabetes • Hypertension • Infection risk (opportunistic, respiratory) • GI bleeding risk • Skin atrophy • Ocular complications 	<ul style="list-style-type: none"> • Use lowest effective dose, shortest duration • Consider local steroids, early steroid-sparing agents • Bone density monitoring, calcium/vitamin D, bisphosphonates if needed • Monitor glucose and BP closely • Vaccination update

Abbreviations: HPA, Hypothalamic Pituitary Adrenal; GI, Gastrointestinal; BP, Blood Pressure.

common.⁸⁴ While mood changes (anxiety, agitation, sleep disturbance) are more commonly seen in pediatric steroid users, frank psychosis remains a rare and underreported event.⁸⁷

Increased susceptibility to infections is the most serious risk, with varicella zoster being particularly dangerous and responsible for mortality in this population; vaccination status should be reviewed and updated before initiating therapy.^{84,88}

Ocular hypertension, glaucoma, and cataract formation are particularly relevant in pediatric uveitis, with children at higher risk for steroid-induced glaucoma and cataracts than adults.⁸⁸⁻⁹⁰

The goal of corticosteroid treatment in children should be a brief, short course of steroids, including intravenous pulses of methylprednisolone (if that means a shorter use of systemic steroids).^{91,92}

Multidisciplinary care, including pediatric rheumatology and ophthalmology, is essential for optimal monitoring and management of these adverse effects.⁸⁸⁻⁹⁰

Elderly

For the safe use of corticosteroids in this population, the clinician should always keep in mind that in the elderly, there is a notable shift away from classic autoimmune causes toward infectious and neoplastic etiologies such as herpetic uveitis and intraocular lymphoma, where the use of steroids may be contraindicated.^{93,94}

When using systemic corticosteroids to treat NIU in elderly patients, special considerations are required due to increased vulnerability to adverse effects and comorbidities (Table 2). The elderly are at increased risk for osteoporosis, fractures, avascular necrosis, hyperglycemia/diabetes, hypertension, infections, gastrointestinal bleeding, skin atrophy, and ocular complications such as glaucoma and cataract. The risk of these complications is dose- and duration-dependent, and even short courses can precipitate significant morbidity in this population.^{43,44}

- Osteoporosis and fracture risk are particularly pronounced in the elderly, necessitating baseline and periodic bone mineral density assessment, calcium and vitamin D supplementation, and consideration of bisphosphonates for those at high risk.
- Hyperglycemia and new-onset diabetes are common, requiring regular glucose monitoring and adjustment of antidiabetic therapy as needed.
- Hypertension may be exacerbated, so blood pressure should be closely monitored and antihypertensive regimens adjusted accordingly.

- Infection risk is heightened, especially for opportunistic and respiratory infections; vaccination status should be reviewed and updated before initiating therapy.
- Gastrointestinal complications such as peptic ulcer disease and GI bleeding are more frequent, particularly with concomitant NSAID use; gastroprotection should be considered.
- Skin atrophy and impaired wound healing are also more problematic in the elderly.

To minimize these risks, corticosteroids should be used at the lowest effective dose for the shortest possible duration, and early transition to steroid-sparing immunosuppressive agents is recommended. Local corticosteroid delivery may be considered to reduce systemic exposure in selected cases. Elderly patients require vigilant monitoring and proactive management of corticosteroid-related adverse effects.^{43,44}

Conclusions

Corticosteroids remain the foundational therapy in the management of non-infectious uveitis due to their potent and rapid anti-inflammatory effects across all anatomical subtypes. However, their effectiveness must be balanced against the risks of both ocular and systemic adverse effects, which vary depending on the route of administration and duration of use. A strategic, individualized approach to corticosteroid therapy, tailored to the anatomical location, laterality, severity, and chronicity of inflammation, is essential to maximize therapeutic benefit while minimizing toxicity. Topical, periocular, intravitreal, and systemic corticosteroids each play a specific role in the stepwise management of uveitis, and their integration must be guided by clinical judgment and disease.

Given the limitations of prolonged corticosteroid exposure, early consideration of immunomodulatory therapies is warranted in many cases to achieve durable disease control and enable steroid tapering. Recent advances in sustained-release corticosteroid implants and novel drug delivery platforms hold promise for improving patient outcomes with reduced treatment burden. Continued research into personalized treatment algorithms, biomarker-driven approaches, and steroid-sparing strategies will be key to optimizing care for patients with uveitis.

In summary, while corticosteroids remain indispensable in the initial and adjunctive treatment of uveitis, their long-term success depends on thoughtful application within a comprehensive, multidisciplinary management framework.

Data Sharing Statement

No new data were generated or analyzed in support of this article. All data cited in this review are available in the public domain and referenced within the article.

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