South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: Ophthalmology conditions

EVIDENCE SUMMARY

Title: Evidence review of the use of prednisone/prednisolone for severe bilateral posterior and panuveitis

Date: 15 September 2022

Reviewer: Zahiera Adam (ZA), Prof Linda Visser (LV), Dr Farah Moti (FM)

Affiliation and declaration of interests:

- ZA (Consultant Pharmacist, Right to Care). No interests to declare.
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- FM (Consultant Ophthalmologist in the private sector. Vice-President of the Ophthalmological Society of South Africa). No interests to declare.

Background:

The two key etiological categories of uveitis includes infectious and non-infectious uveitis. According to the Standardization of Uveitis Nomenclature (SUN) working group[1], depending on the primary site of inflammation, uveitis can be classified as anterior, intermediate or posterior uveitis. In anterior uveitis, the anterior chamber is the main site of inflammation and it includes iritis, iridocyctis and anterior cyclitis. In intermediate uveitis, the vitreous is the main site of inflammation and it includes posterior cyclitis, hyalitis and pars planitis. Posterior uveitis affects the retina and/or choroid. If all three eye segments are involved, the term panuveitis is used. Uveitis may be further classified as acute, recurrent or chronic depending on the type of presentation.

Uveitis is a major cause of blindness[2]. Posterior uveitis accounts for approximately 15% to 22% (1 in 4 to 6 cases) of uveitis cases and leads to approximately 10% (1 in 10 cases) of legal blindness in the United States.[3,4] In a prospective cross sectional study at a tertiary hospital in Cape Town[5], 80% of HIV positive cases had infectious uveitis with intraocular tuberculosis (IOTB), herpetic and syphilitic uveitis being the commonest infectious causes and sarcoidosis and HLA-B27-associated uveitis being most commonly associated with non-infectious uveitis. Although uveitis in South Africa is frequently of infectious aetiology, up to 50% of cases are either non-infectious or idiopathic.[6,7] Prevalence of non-infectious posterior and panuveitis amongst uveitis cases in general has not to our knowledge been quantified in South Africa.

[1] Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509–16. doi: http://dx.doi.org/10.1016/j.ajo.2005.03.057. PubMed.
[2] Nussenblatt RB. The natural history of uveitis. Int Ophthalmol 1990; 14: 303-8.
[3] Brady CJ, Villanti AC, Law HA, Rahimy E, Reddy R, Sieving PC, Garg SJ, Tang J. Corticosteroid implants for chronic non-infectious uveitis. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD010469. DOI: 10.1002/14651858.CD010469.pub2.
[4] Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. British Journal of Ophthalmology 1996;80(9):844-8.
[5] Smit DP, et al. The Etiology of Intraocular Inflammation in HIV Positive and HIV Negative Adults at a Tertiary Hospital in Cape Town, South Africa. Ocul Immunol Inflamm. 2019;27(2):203-210. doi: 10.1080/09273948.2018.1476555. Epub 2018 May 30. PMID: 29847196
[6] Rautenbach W, et al. Patterns of Uveitis at Two University-Based Referral Centres in Cape Town, South Africa. Ocul Immunol Inflamm. 2019;27(6):868-874. doi: 10.1080/09273948.2017.1391954. Epub 2017 Nov 9. PMID: 29120678 (ABSTRACT ONLY)
[7] Schaftenaar E, *et al*. Uveitis is predominantly of infectious origin in a high HIV and TB prevalence setting in rural South Africa. B*ritish Journal of Ophthalmology* 2016;100:1312-1316. (ABSTRACT ONLY)

To limit potentially sight-threatening complications, good control of the inflammation in the acute phase is necessary. Systemic corticosteroids are the recommended first line treatment for the management of non-infectious posterior or panuveitis, and have been so since the 1950s although not supported by good quality evidence.[8]

Chapter 18 of the Adult Hospital STG[9] includes the use of topical corticosteroids (e.g. dexamethasone 0.1% eye drops) for the management of uveitis. Topical corticosteroids are recommended as the first line standard of care for the management of anterior uveitis in international guidelines.[10,11] Based largely on in vivo pharmacokinetic data in rabbits[12], topical corticosteroids are thought to be less effective for disease affecting deeper layers of the eye due to poor absorption and/or penetration across the blood retinal barrier. As part of the 2022-23 STG review cycle, it was noted that the STG is not explicit in recommending topical corticosteroids for anterior disease only.

The PICO below was proposed with the intention of undertaking a literature review to assess the efficacy and safety of the use of oral corticosteroids for the management of non-infectious posterior uveitis or panuveitis.

Research question

ELIBILITY CRITERIA FOR REVIEW

Population	Adult patients with non-infectious posterior uveitis or panuveitis
Intervention	• Oral Prednisolone or prednisone
Comparators	• Placebo
Outcomes	**Efficacy** • Improved visual outcome and better resolution of disease **Safety** • Ocular and systemic side effects
Study designs	Clinical practice guidelines, systematic reviews of randomised controlled trials (RCTs), RCTs and, if the latter is unavailable, systematic reviews of non-randomised/ observational studies or observational studies.

Literature Review

Pubmed

A Pubmed search was conducted for published evidence on the use of corticosteroids for the management of uveitis. The search was limited to English language and included systematic, non-systematic reviews, and all clinical trials. Refer to addendum A for the search history. A title and abstract screen by a single reviewer yielded 225 results. Publications on the use of oral corticosteroids for the management of posterior and/or panuveitis included expert reviews, clinical practice guidelines and case reports with no primary randomised controlled trials (RCT) identified. Randomised controlled studies that were identified were limited to the use of corticosteroid-sparing agents and biological therapies and were compared either to placebo[13] or conventional therapy. Conventional therapy generally included the use of oral corticosteroids in combination with corticosteroid-sparing agents,[14] and therefore were not deemed relevant for the purposes of this evidence summary.

[8] The American Uveitis Society. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel AMERICAN JOURNAL OF OPHTHALMOLOGY OCTOBER 2000

[9] National Department of Health. Adult Hospital STG chapter 18 eye disorders (2019).

[10] The American Uveitis Society. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel AMERICAN JOURNAL OF OPHTHALMOLOGY OCTOBER 2000

[11] Scottish Uveitis National Managed Clinical Network Treatment Guidelines. Uveitis NMCN Treatment Guidelines Revised September 2010

[12] [12] Sigurdsson H et al. Topical and systemic absorption in delivery of dexamethasone to the anterior and posterior segments of the eye. Acta Ophthalmol. Scand. 2007: 85: 598–602

[13] Israel HL. The treatment of sarcoidosis. Postgrad Med J. 1970 Aug;46(538):537-40. doi: 10.1136/pgmj.46.538.537. PMID: 4921221; PMCID: PMC2467282.

[14] BenEzra D, Cohen E, Chajek T, Friedman G, Pizanti S, de Courten C, Harris W. Evaluation of conventional therapy versus cyclosporine A in Behçet's syndrome. Transplant Proc. 1988 Jun;20(3 Suppl 4):136-43. PMID: 3381269.

A search for relevant publications as cited in the literature reviewed was also undertaken. A consensus statement published by ophthalmology experts in Spain was identified (Espinosa et al)[15] which included a number of quality graded evidence-based recommendations.

Cochrane

A search of the Cochrane database of systematic reviews yielded 10 reviews with 'uveitis' matching in the title abstract key word. None of these reviews directly addressed the use of systemic corticosteroids versus placebo. Two Cochrane reviews that focused on the management of uveitis, were excluded due to incorrect therapeutic interventions (corticosteroids implants[16] and biologicals[17]).

Clinical Guidelines

The following organisations were identified by local experts as credible authorities for guideline development. Websites were reviewed to identify suitable guidelines for the management of uveitis.

- NICE guidance[18] – no relevant technology appraisals or clinical guidelines identified
- American Academy of Ophthalmologists (AAO)[19] - no relevant treatment guidelines identified
- International Council of Ophthalmologists (ICO)[20] - no relevant treatment guidelines identified

Additionally, a free text google search was undertaken to identify clinical guidelines/reviews from recognized clinical bodies/authorities within the ophthalmology specialty. The following clinical guidelines were identified.

- Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel[21]
- National Institute of Health review of Emerging drugs for Uveitis[22]
- Scottish Uveitis National Managed Clinical Network Treatment Guidelines[23]

In the absence of relevant systematic reviews and RCTs, this evidence summary presents a narrative overview of the literature to evaluate the effectiveness of the use of oral corticosteroids for the management of severe non-infectious posterior and panuveitis.

Summary of key evidence

A. EFFICACY

Systematic Reviews

While the two Cochrane reviews on the management of uveitis were excluded due to incorrect therapeutic interventions, in both of these reviews, systemic corticosteroids are acknowledged as a first line standard of care for the management of severe posterior and panuveitis.

Brady CJ et al. Corticosteroid implants for chronic non-infectious uveitis. Cochrane Database of Systematic Reviews 2016[24].

In this review on intravitreal corticosteroid implants, systemic corticosteroids were included as an example of the "standard of care" (examples listed*: as systemic steroids, intravitreal steroids, disease-modifying antirheumatic drugs*)

[15] Espinosa G, Herreras JM, Muñoz-Fernández S, García Ruiz de Morales JM, Cordero-Coma M. Recommendations statement on the immunosuppressive treatment of non-infectious, non-neoplastic, non-anterior uveitis. Med Clin (Barc). 2020 Sep 11;155(5):220.e1-220.e12. English, Spanish. doi: 10.1016/j.medcli.2019.10.023. Epub 2020 Mar 19. PMID: 32199631

[16] Brady CJ, Villanti AC, Law HA, Rahimy E, Reddy R, Sieving PC, Garg SJ, Tang J. Corticosteroid implants for chronic non-infectious uveitis. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD010469. DOI: 10.1002/14651858.CD010469.pub2.

[17] Barry RJ, Tallouzi MO, Bucknall N, Mathers JM, Murray PI, Calvert MJ, Moore DJ, Denniston AK. Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD012577. DOI: 10.1002/14651858.CD012577.pub2.

[18] NICE guidelines | NICE guidance | Our programmes | What we do | About | NICE

[19] American Academy of Ophthalmology: Protecting Sight. Empowering Lives - American Academy of Ophthalmology (aao.org)

[20] Main Page - International Council of Ophthalmology ICO-Exams ICO-Fellowship (icoph.org)

[21] Jabs D et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel AMERICAN JOURNAL OF OPHTHALMOLOGY OCTOBER 2000

[22] Lason T et al. Emerging drugs for uveitis. Expert Opin Emerg Drugs. 2011 June ; 16(2): 309–322. doi:10.1517/14728214.2011.537824.

[23] Scottish Uveitis National Managed Clinical Network Treatment Guidelines. Uveitis NMCN Treatment Guidelines Revised September 2010

[24] Brady CJ, Villanti AC, Law HA, Rahimy E, Reddy R, Sieving PC, Garg SJ, Tang J. Corticosteroid implants for chronic non-infectious uveitis. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD010469. DOI: 10.1002/14651858.CD010469.pub2.

for posterior uveitis and included as a comparator for the alternative treatments under review. Study authors noted the therapeutic challenge of topical corticosteroids not reaching therapeutic concentrations in the vitreous, thus necessitating the use of oral corticosteroids or local steroid injection.

Barry RJ, et al. Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis. Cochrane Database of Systematic Reviews 2018.[25]

The objective of this Cochrane review was to assess the efficacy of anti-tumour necrosis factor (TNF) therapy in treatment of Uveitic Macular Oedema (UMO). Of the two placebo-controlled RCTS cited in the review that investigated the effect of adalimumab in non-infectious intermediate, posterior or panuveitis, control of inflammation was first achieved with systemic corticosteroid treatment, before participants were randomised to receive either adalimumab by subcutaneous injection or placebo.[26,27]

Guidelines

Espinosa G, et al. Recommendations statement on the immunosuppressive treatment of non-infectious, non-neoplastic, non-anterior uveitis.[28]

A multidisciplinary group of five experts (2 ophthalmologists, an immunologist, a rheumatologist and an internist with recognized experience in treating the patient with non-infectious, non-neoplastic intermediate, posterior and panuveitis) undertook a systematic literature review to assess the efficacy and safety of immunomodulatory drugs in patients with non-infectious, non-neoplastic, non-anterior uveitis. Following the systematic review, an expert meeting was held during which 34 recommendations were generated and grade of evidence assessed. The level of agreement with the recommendations was subsequently tested with 25 additional experts following a Delphi process. The Delphi process involved an online questionnaire completed by 30 experts and used a Likert scale from 1 (totally disagree) to 10 (totally agree). Agreement was defined if at least 70% of the panelists voted ≥7 on the recommendation. Recommendations that did not meet the pre-defined score in the first round were re-evaluated and, if applicable, reissued and voted on in a second Delphi round. Results of the Delphi assessment (DA) of the 34 recommendations are tabulated below. This multidisciplinary project was promoted and endorsed by the Spanish Society of Ocular Inflammation, with scientific guarantees of the Spanish Society of Internal Medicine and the Spanish Society of Immunology.

Of the 34 recommendations, the following have specific relevance to the management of posterior and/or panuveitis with oral corticosteroids. The level of evidence (LoE) and degree of recommendation (DR) as included were assigned based on the Oxford Center for Evidence Based Medicine guidelines[29]:

Relevant recommendations	#LoE, DR and DA	Dose recommendations
R1. Not all patients with pars planitis require systemic immunomodulatory treatment. In severe cases, especially if they are bilateral, it is recommended to start treatment with systemic corticosteroids together with an immunomodulator such as AZA, MMF or MTX	(LoE 2a; DR B; DA 89%)	General guidance* Topical treatment**
R5. Not all sarcoidosis patients require systemic immunomodulatory treatment. In severe cases and especially if they are bilateral, it is recommended to start treatment with systemic corticosteroids together with an immunomodulator	(LoE 2a; DR B; DA 89%)	General guidance* Topical treatment**
R10. In patients with Behcet-associated panuveitis, it is recommended to start treatment with systemic corticosteroids and an immunomodulator	(LoE 2a; DR B; DA 100%)	General guidance*
R14. In patients with sarcoidosis-associated panuveitis, itis recommended to start treatment with systemic corticosteroids	(LoE 3a; DR BC; DA 86.7%)	General guidance* Topical treatment**

[25] Barry RJ, Tallouzi MO, Bucknall N, Mathers JM, Murray PI, Calvert MJ, Moore DJ, Denniston AK. Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema

[26] Jaffee GJ, Dick AD, Brezin AP, Nguyen QD, Thorne JE, Kestelyn P, et al. Adalimumab in patients with active noninfectious uveitis. New England Journal of Medicine 2016;375(10):932-43.

[27] Nguyen QD, Merrill PT, JaKe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet 2016;388(10050):1183-92.

[28] Espinosa G, Herreras JM, Muñoz-Fernández S, García Ruiz de Morales JM, Cordero-Coma M. Recommendations statement on the immunosuppressive treatment of non-infectious, non-neoplastic, non-anterior uveitis. Med Clin (Barc). 2020 Sep 11;155(5):220.e1-220.e12. English, Spanish. doi: 10.1016/j.medcli.2019.10.023. Epub 2020 Mar 19. PMID: 32199631

[29] Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009) — Centre for Evidence-Based Medicine (CEBM), University of Oxford

and an immunomodulator In these patients, topical treatment is adjuvant		
R17. In patients with idiopathic panuveitis, it is recommended to start treatment with systemic corticosteroids and an immunomodulator	(LoE 3a; DR C; DA 70.7%)	General guidance* The possibility that this type of PanU is of infectious or neoplastic origin is remarkably high, so it is essential to carry out a comprehensive etiological study. The topical route is part of the adjuvant treatment as in another uveitis.
R20. In patients with panuveitis secondary to sympathetic ophthalmia it is recommended to start treatment with systemic corticosteroids and an immunomodulator	(LoE 4; DR CD; DA 80%)	The initial treatment is systemic corticosteroids (high doses at least 6 months), and an immunomodulator must be associated in most cases.
R21. In especially severe cases of panuveitis secondary to sympathetic ophthalmia, the use of systemic corticosteroids can be considered with an immunomodulator and initial biological therapy	(LoE 5; DR D; DA 86.7%)	
R24. In patients with Vogt-Koyanagi-Harada (VKH) panuveitis, it is recommended to start treatment with systemic corticosteroids and an immunomodulator	(LoE 2a; DR B; DA 73.4%)	The goal of treatment in these patients is to suppress ocular inflammation, prevent relapse, and avoid visual complications. Systemic corticosteroid therapy will be initiated at high doses. But, in this case, unlike other types of uveitis, corticosteroid dose reduction should be slow Topical treatment**
R27. In patients with birdshot -type posterior uveitis it is recommended to start treatment with systemic corticosteroids and an immunomodulatory.	(LoE 2a; DR B; DA 86.7%).	General guidance* Topical treatment**
R30. In patients with posterior uveitis secondary to serpiginous choroiditis, it is recommended to start treatment with systemic corticosteroids and an immunomodulator	(LoE 3b; DR C; DA 86.7%)	General guidance* Topical treatment**
R33. In patients with posterior uveitis secondary to idiopathic retinal vasculitis, itis recommended to start treatment with systemic corticosteroids and an immunomodulator	(LoE 4; DR D; DA 80%)	General guidance* Topical treatment**

*General dose recommendations for corticosteroids: guideline authors have indicated adherence to the European Alliance of Associations for Rheumatology (EULAR) guidelines[30] on the use of corticosteroids i.e.

- *"As intravenous boluses of methylprednisolone (125–500 mg/day for 3 days), followed by prednisone 0.5 mg/kg/day (or equivalent) in a dose-reduction regimen."*
- *Or as oral corticosteroids at prednisone doses 0.5−1 mg/kg/day (or equivalent) in a dose-reduction regimen.*

The objective in both cases is the discontinuation of the steroid or maintenance with minimum doses (≤ 5 mg/day).

**Topical treatment: the use of topical, locoregional and/or intravitreal corticosteroids, as well as cycloplegics/mydriatics in certain cases of highly asymmetric and/or unilateral involvement, anterior chamber involvement, and if there is associated macular oedema

Level of evidence: 1a= Systematic reviews of RCTs, 1b=RCT, 2a= SR of cohort studies, 2b=cohort studies, 3a= SR of case-controls studies, 3b=case-control studies, 4=case series, 5=narrative (literature reviews, editorials

A=consistent kevel 1 studies, B=consistent level 2 or 3 studies or extrapolations from level 1 studies, C= level 4 studies or extrapolations from level 2 or 3 studies, D=level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Limitations noted by the authors of this publication include:

- The reliance on expert opinion to inform the recommendations put forward given the lack of published quality evidence

[30] Duru N, van der Goes MC, Jacobs JW, Andrews T, Boers M, Buttgereit F, et al. EULAR evidence-based and consensus-based recommendations on the management of mediumto high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis. 2013;72(12):1905–13. 14.

- Heterogeneity of the types of uveitis, both in terms of anatomical location and associated diseases, precluding the extrapolation of results

An AGREE II assessment of this guideline by two reviewers (ZA and FM) yielded an overall score of 50%.

Recommendations from three other guidelines[31,32,33] identified from a google search, similarly recommended the use of oral corticosteroids for the management on inflammation associated with posterior uveitis and panuveitis. Guideline recommendations on the use of oral corticosteroids for the management of posterior uveitis and panuveitis were informed by expert opinion without supporting evidence from the primary studies cited.

B. SAFETY

The Scottish Uveitis National Managed clinical Network Treatment Guidelines lists the following side effects with prednisolone: "acne, atherosclerosis, avascular necrosis of femoral head, cataract, delay in pubertal growth, diabetes *mellitus (up to 30%), dyslipidemia (up to 30%), heart failure, hypertension (up to 85%) , infection, osteoporosis, raised intraocular pressure (IOP), serious psychosis (up to 5%)), sleep disturbance".* Note that the supporting references cited in the guideline are not specific to the use of prednisolone for ophthalmic indications.

Aside from the well-recognised side effects of oral corticosteroids, diagnostic uncertainty relating to posterior or panuveitis presents a further challenge. Appropriate management of uveitis requires very careful consideration given the heterogenous diagnostic spectrum. Rapidly progressive conditions such as acute retinal necrosis and bacterial endophthalmitis can result in loss of vision if treatment is delayed. Similarly, empiric use of corticosteroids in some cases of infectious uveitis such as toxoplasmic chorioretinitis or fungal endophthalmitis can worsen the condition. The potential damage from high dose empiric corticosteroid therapy in undiagnosed infectious uveitis may be extreme and the following are recommended for risk mitigation[34]:

- Ensure documentation of a comprehensive patient history, including signs and symptoms
- Careful physical examination of the eye
- A complete blood count, chemistry panel, urinanalysis, C-reactive protein, herpes simplex, cytomegalovirus, Epstein-Barr virus, and toxoplasmosis infectious serologies can assist with the determination of prior exposures
- In the absence of a confirmed diagnosis, empiric anti-infective therapy is recommended with adjunctive corticosteroids to protect the eye against the secondary inflammatory reaction in infections.
- Systemic corticosteroids (oral or IV) are preferred to regional corticosteroid administration as systemic therapy is more easily reversible
- For empiric anti-infective therapy, establish a timeframe for response following initiation of anti-infective treatment i.e. viral retinitis should resolve within 4 to 6 weeks of treatment, bacterial infections should respond within 72 hours, syphilis within a week and tuberculosis within 3 to 6 weeks. Non-response to anti-infective therapy may warrant consideration of immunosuppressive therapy with systemic corticosteroids

Conclusion

Despite the lack of high quality evidence and the well documented risks of adverse effects with systemic corticosteroid therapy noting the long history of corticosteroid use from the 1950's), international ophthalmology experts consistently recommend the short term use of systemic corticosteroids as the first line treatment option for the management of severe non-infectious posterior and panuveitis. While there is a lack of expert consensus on the recommended dose and duration of corticosteroid therapy, treatment aims appear to be consistent in ensuring that the lowest possible dose be used for the shortest duration, with corticosteroid treatment being tailored based on individual patient response.

[31] The American Uveitis Society. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel AMERICAN JOURNAL OF OPHTHALMOLOGY OCTOBER 2000

[32] Lason T et al. Emerging drugs for uveitis. Expert Opin Emerg Drugs. 2011 June ; 16(2): 309–322. doi:10.1517/14728214.2011.537824.

[33] Scottish Uveitis National Managed Clinical Network Treatment Guidelines. Uveitis NMCN Treatment Guidelines Revised September 2010

[34] Davis JL. Diagnostic dilemmas in retinitis and endophthalmitis. Eye (Lond). 2012 Feb;26(2):194-201. doi: 10.1038/eye.2011.299. Epub 2011 Nov 25. PMID: 22116459; PMCID: PMC3272204.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: Oral prednisone/prednisolone is suggested as the first line standard of care for the management of non-infectious posterior or panuveitis in adults. Prescribing should be limited to specialists or ophthalmology medical officers in consultation with a specialist, where diagnosis of non-infectious uveitis is confirmed.

Rationale: Posterior uveiits and panuveitis are potentially sight-limiting conditions. International guidelines informed by expert opinion recommend oral corticosteroids as a first line treatment for posterior uveitis and panuveitis due to their perceived efficacy and well-established safety profile.

Level of Evidence: Very low certainty of evidence

Review indicator: Published evidence of benefit or harm.

NEMLC RECOMMENDATION 20 OCTOBER 2022:

The NEMLC supported the addition of oral prednisone/prednisolone to the EML as the first line standard of care for the management of non-infectious posterior or panuveitis in adults, pending editorial adjustments to the review document and the development of a new STG for the management of posterior uveitis and panuveitis.

Monitoring and evaluation considerations

Research priorities

Refer to Addendum B: Evidence to decision framework

Addendum A: Pubmed search history

Search number	Query	Filters	Search Details	Results
9	uveitis AND corticosteroids	Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review, English	(("uveitis"[MeSH Terms] OR "uveitis"[All Fields] OR "uveitides"[All Fields]) AND ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields])) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (english[Filter]))	957
4	uveitis AND corticosteroids	English	(("uveitis"[MeSH Terms] OR "uveitis"[All Fields] OR "uveitides"[All Fields]) AND ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields])) AND (english[Filter])	4,421
3	uveitis AND corticosteroids		(("uveitis"[MeSH Terms] OR "uveitis"[All Fields] OR "uveitides"[All Fields]) AND ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields])	5,313
2	corticosteroids		"adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields] OR "corticosteroids"[All Fields] OR "corticosteroidal"[All Fields] OR "corticosteroide"[All Fields] OR "corticosteroides"[All Fields]	373,474
1	uveitis		"uveitis"[MeSH Terms] OR "uveitis"[All Fields] OR "uveitides"[All Fields]	41,424

List of excluded publications as follows:

- Studies with a therapeutic focus on the following: biologicals, injections intended for intra-ocular or peri-orbital administration (e.g. intravitreal corticosteroids), mechanistic target of rapamycin (mTOR) inhibitors (e.g. sirolimus), fingolimod, simvastatin, lens implants, zinc , colchicine, dapsone, diltiazem, NSAIDS, steroid-sparing agents, combination therapy with corticosteroids (e.g. interferon in combination with corticosteroids).
- Studies on the management of the following conditions: multiple sclerosis, cataract management in patients with uveitis, pre and post-surgical management of inflammation, glaucoma, neoplastic-related ocular inflammation, diabetic macular oedema
- Studies on the management of uveitis other than non-infectious posterior and/or panuveitis: e.g. anterior and intermediate uveitis, infection-related uveitis, HLAB27, Fuchs heterochromic uveitis, spondyloarthropathy uveitis
- Studies in paediatric patients

Addendum B : Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ X *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	No RCT evidence identified to support the use of oral corticosteroids in the management of posterior and/or panuveitis. Clinical guideline recommendations for oral corticosteroids in the management of posterior and/or panuveitis is limited to expert opinion that dates back to the 1970s.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☐	UNCERTAIN Unable to assess the effect size for evidence of benefit In the absence of clinical trial evidence the size of effect cannot be determined. Severe posterior and panuveitis is however a sight limiting condition which often presents with concomitant auto-immune diseases. Based on expert opinion included in international clinical guideline recommendations, it would be unethical to withhold treatment with oral corticosteroids.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ X *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	No RCT evidence identified to support the use of oral corticosteroids in the management of posterior and/or panuveitis. Clinical guideline recommendations for oral corticosteroids in the management of posterior and/or panuveitis is limited to expert opinion that dates back to the 1970s.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☐	UNCERTAIN Unable to assess the effect size for evidence of harm
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒ X	While the long term side effects of high dose systemic corticosteroid therapy is well recognised, no RCT evidence has been identified to support the risk of harm with the use of oral corticosteroids in the management of posterior and/or panuveitis. Despite the lack of high quality evidence, expert opinion included in international clinical guidelines support a favourable clinical benefit:risk assessment for the use of oral corticosteroids for the management of posterior and panuveitis.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available:	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ X No ☐ Uncertain ☐	Oral prednisone is readily accessible at secondary care level for multiple indications.

RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☐	Prescribing limited to specialists or medical officers under the supervision of a specialist, in facilities with access to slit lamps. Access to oral prednisolone may already be available for the management of concomitant auto-immune conditions being managed by a rheumatologist or other specialists. **Comparative costs:** Topical corticosteroids are not regarded as a therapeutic alternative to oral corticosteroids for posterior or panuveitis – costs included below are for comparative budgetary consideration only <u>Oral corticosteroids:</u> Dose: 1mg/kg/day (max 80mg/day) for no longer than one month[35] Contract Price Trolic® 100s = R18.75 (19cents/tablet) 80mg/day for 30 days =480 tablets Treatment cost= R91.20* **Based on maximum dose and duration* *(Excludes cost of any maintenance treatment with steroid-sparing agents)* <u>Topical dexamethasone 0.1% eye drops:</u> Maxidex® 5mL eye drops = R12.32
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☒ **Is the option acceptable to key stakeholders?** Yes ☒ No ☐ Uncertain ☐	As posterior and panuveitis are potentially sight-limiting conditions, lack of access to a low cost, first line treatment option based on international guideline recommendations would be challenging to defend. Prednisone is an inexpensive treatment and is already routinely available in state facilities for multiple indications. Based on anecdotal reports from Tygerberg (WC) and McCord (KZN) Hospitals, prescribing of oral corticosteroids by ophthalmologists is routine for the management of uveitis in State facilities and inclusion in the STG is not anticipated to result in significant incremental budget impact.
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☒ Uncertain ☐	No impact with access to the medicine. There may be potential inequity based on facilities with access to slit lamps.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	9 February 2023	ZA, LV, FM	

[35] Jabs D et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel AMERICAN JOURNAL OF OPHTHALMOLOGY OCTOBER 2000