CHAPTER 18

EYE DISORDERS

For many eye conditions early specialist consultation and advice is required. To mitigate delays in referral it is recommended that electronic consultation methods are utilised with transmission of appropriate images so that appropriate treatment can be initiated before referral.

18.1 CONJUNCTIVITIS

H10.9

DESCRIPTION

Inflammation of the conjunctiva, usually due to allergy or infection (viral or bacterial).
Conjunctivitis is usually bilateral. Other causes of a red eye are often unilateral.
The condition is self-limiting and usually resolves within 14 days.

GENERAL MEASURES

If it is due to an infection, counsel on the importance of:
» frequent hand washing,
» using separate linen, towels and washcloths, and
» avoiding direct contact with infected material or individuals.

Contact lenses should not be worn if conjunctivitis is present or during a course of topical therapy. Soft lenses should not be worn within 24 hours of instilling eye drops containing the preservative benzalkonium chloride.

18.1.1 CONJUNCTIVITIS, VIRAL

B30.1+ (H13.1*)

DESCRIPTION

Viral conjunctivitis is the commonest cause of infective conjunctivitis. It may be unilateral but often progresses to bilateral. Adenovirus is the commonest viral conjunctivitis, however other viral causes of conjunctivitis present in the same way.

Clinical features:
» Viral conjunctivitis may be associated with an upper respiratory tract infection.
» A burning, sandy, or gritty feeling in the eyes.
» Morning crusting followed by watery discharge.
» Preauricular lymphadenopathy may be present.
» The cornea, iris, and pupil are completely normal with normal visual acuity.

The condition is self-limiting but eye irritation and discharge may get worse for the first week depending on the specific virus. Duration varies from 3-5 days to 2-3 weeks before resolution.

MEDICINE TREATMENT

- Sodium chloride 0.9%, eye washes or irrigation.

If sodium chloride 0.9% is not available, use cooled boiled water/sterile water.

- Oxymetazoline 0.025%, ophthalmic drops, instil 1 drop 6 hourly for a maximum of 7 days to reduce redness of eyes.

18.1.2 CONJUNCTIVITIS, ALLERGIC

See Primary Health Care Standard Treatment Guidelines and Essential Medicine List; section 18.1.1 Conjunctivitis, allergic.

18.1.3 CONJUNCTIVITIS, BACTERIAL (NON-GONOCOCCAL)

H10.0

DESCRIPTION

Clinical features:

» It may be either unilateral or bilateral.
» There is matting of lashes in the morning with the eyelids stuck shut.
» There is a mucopurulent discharge throughout the day.
» The eyelids may be swollen.

MEDICINE TREATMENT

- Immediate irrigation of the eyes with sodium chloride 0.9%.

During the day:

- Chloramphenicol 1%, ophthalmic ointment 6 hourly for 7 days.

LoE: IVb[i]

OR

- Fluoroquinolone ophthalmic drops as second-line treatment (i.e. poor response to chloramphenicol or contra-indication/drug interactions with chloramphenicol) e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop 2 hourly for 2 days.
  - Then reduce frequency to 1 drop 4 hourly during waking hours, for 5 days.

LoE: IIb[ii]

REFERRAL

No response to treatment.

18.1.4 CONJUNCTIVITIS, BACTERIAL (GONOCOCCAL)

H10.0

Hyperacute bacterial conjunctivitis involves rapid onset and progression of conjunctivitis and is often caused by *N.gonorrhoeae*. **Gonococcal conjunctivitis requires immediate referral to an ophthalmologist to prevent corneal involvement and potential perforation.**

Clinical features:

» Hyperpurulent discharge
» Diminished visual acuity
» Eye tenderness
» Swollen lymph nodes

For conjunctivitis of the newborn, See Primary Health Care Standard Treatment Guidelines and Essential Medicine List; section 18.1.3.

MEDICINE TREATMENT

- Ceftriaxone, IM, 250 mg as a single dose.
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g as a single dose.

For persistent infection, refer to Section 25.1 Male urethral syndrome or section 25.2 Vaginal discharge syndrome.

REFERRAL

Refer all cases to an ophthalmologist immediately.

18.2 ENDOPHTHALMITIS, BACTERIAL

S05.4-6 + (Y43.99), H44.0

DESCRIPTION

Infection of the ocular cavity is an emergency as it can cause blindness. This may occur secondary to bacteraemia (endogenous infection) or, more commonly, after penetrating ocular injury or surgery.

In patients with endogenous endophthalmitis blood cultures should be done and the source of infection identified and treated.

In patients with endophthalmitis after penetrating injury/surgery culture should be done on specimens of aqueous or vitreous humour.

MEDICINE TREATMENT

Refer immediately to an ophthalmologist.

Endogenous endophthalmitis

Specialist initiated, vitrectomy often required:

- Ceftriaxone, IV, 2 g daily for 7 days.

Adjust antibiotics according to culture and sensitivity results.

AND

- Ceftazidime, intravitreal, 2.25 mg. *LoE:IIIb[iii]*

AND

- Vancomycin, intravitreal, 1 mg. *LoE:IIIb[iv]*
  - Administer antibiotics using separate tuberculin syringes.
  - Antibiotic doses may be repeated after 48 hours depending on culture results or clinical response. *LoE:IIIb[v]*

Post-surgical endophthalmitis

Specialist initiated, vitrectomy often required:

- Ceftazidime, intravitreal, 2.25 mg.

AND

- Vancomycin, intravitreal, 1 mg.
  - Administer antibiotics using separate tuberculin syringes.
  - Antibiotic doses may be repeated after 48 hours depending on culture results or clinical response. *LoE:IIIb[vi]*

In addition, if there is soft tissue involvement or as prophylaxis after a penetrating eye injury:

- Ciprofloxacin, oral, 750 mg 12 hourly for 7 days.

18.3 GLAUCOMA

H40.0-6/H40.8-9

DESCRIPTION

Glaucoma is characterised by damage to the optic nerve with associated visual field loss, for which raised intra-ocular pressure (IOP) is a primary risk factor. Glaucoma is classified as open-angle or angle-closure. Glaucoma may occur as a primary condition or secondary to other ocular conditions. The condition is usually bilateral, but may be unilateral or asymmetrical (especially with secondary causes).

18.3.1 OPEN-ANGLE GLAUCOMA

H40.1

DESCRIPTION

» Mostly asymptomatic.
» History of gradual loss of vision in the affected eye or loss of visual field.
» Often suspected after seeing cupping of optic disc on routine fundoscopy or finding elevated intra-ocular pressure on screening.

MEDICINE TREATMENT

Refer to an ophthalmology unit for diagnosis and initiation of treatment.

First line

ß-blocker monotherapy:

- Non-selective β-blocker, e.g.: *LoE:IIb*[vii]
- Timolol 0.25%, ophthalmic drops, instil 1 drop 12 hourly.

OR

Selective β-blocker: *LoE:IVb*

- Betaxolol 0.25–0.5%, ophthalmic drops, instil 1 drop 12 hourly.

Second line *LoE:IIb*[viii]

- Prostaglandin analogue monotherapy, e.g.:
  - Latanoprost 0.005%, ophthalmic drops, instil 1 drop daily.
  - Use as first line if patient has contra-indication to ß-blocker.
  - Use in place of ß-blocker if patient has intolerable side effects with ß-blocker or if there is no significant reduction in IOP with ß-blocker.

OR

- Prostaglandin analogue in combination with non-selective ß-blocker if there is insufficient reduction in IOP with ß-blocker monotherapy, e.g.
  - Bimatoprost 0.03% + Timolol 0.5% *LoE:Ib*[ix]

OR

- Prostaglandin analogue in combination with selective ß-blocker if there a contraindication to a non-selective ß-blocker e.g.
  - Latanoprost 0,005% with betaxolol 0.25-0.5%

Third line

Intolerance to prostaglandin analogue, or poor response:

- Alpha-agonist, e.g.: *LoE:IIIb*[x]
  - Brimonidine 0.15–0.2%, ophthalmic drops, instil 1 drop 12 hourly.
  - Use as second line if patient is allergic to prostaglandin analogue.
  - Use in place of prostaglandin analogue if there is no significant further reduction in IOP when adding prostaglandin analogue to ß-blocker.
  - Use in combination with ß-blocker and prostaglandin analogue if the patient still has progression of disease or target IOP is not reached.

Failure to respond: *LoE:IVb*

Alternatives in consultation with a specialist:

Parasympathomimetic agent:

- Pilocarpine 1%, ophthalmic drops, instil 1 drop 6 hourly.

In severe cases, as a temporary measure before ocular surgery, in consultation with a specialist: *LoE:IIIb*[xi]

Carbonic anhydrase inhibitor:

- Acetazolamide, oral, 250 mg 6 hourly.

REFERRAL
All to an ophthalmology unit.

18.3.2 ACUTE ANGLE-CLOSURE GLAUCOMA
H40.2

DESCRIPTION

» Usually presents acutely with sudden onset of severe eye pain and redness, associated with nausea, vomiting and hemicranial headache.
» Loss of vision in the affected eye.
» Coloured haloes or bright rings around lights.
» Hazy-looking cornea.
» Fixed, semi-dilated pupil.
» Shallow anterior chamber.
» Severely elevated intra-ocular pressure. When measured with finger palpation, the affected eye feels hard, compared to the other eye.
» If intraocular pressure rises more slowly, the patients may be asymptomatic with gradual loss of vision.

MEDICINE TREATMENT
Institute initial therapy and then refer IMMEDIATELY to an ophthalmology unit.

Try to achieve immediate reduction in IOP:

- Acetazolamide, oral, 500 mg immediately as a single dose.
  - Followed by 250 mg 6 hourly.

AND

- Timolol 0.25–0.5%, ophthalmic drops, instil 1 drop 12 hourly.

Also treat patient for associated pain and nausea. See sections 12.4.1: Perioperative analgesics and 12.6.5.2: Treatment of PONV.

Where those measures fail, for short-term use only:

- Mannitol, IV, 1.5–2 g/kg as a 20% solution over 30–60 minutes.

OR

Glycerol, oral, 1 g/kg of 50% solution as a single dose immediately.

REFERRAL
All to an ophthalmology unit.

18.4 HERPES ZOSTER OPHTHALMICUS

B02.3,G53.0

DESCRIPTION

Herpes zoster ophthalmicus (HZO) occurs when the varicella-zoster virus reactivates in the trigeminal ganglion and passes down the ophthalmic division of the trigeminal nerve. Patients present with a painful vesicular rash in the trigeminal V1 area – vesicles on the tip of the nose indicate nasociliary branch involvement, which indicates the risk of ocular involvement. A minority of patients may develop conjunctivitis, keratitis, uveitis, retinitis, and cranial nerve involvement (oculomotor or optic nerves). Permanent sequelae of ophthalmic zoster infection may include chronic ocular inflammation, loss of vision, and debilitating post-herpetic neuralgia. All patients should be offered HIV testing.

MEDICINE TREATMENT

- Acyclovir, oral, 800 mg 5 doses per day (4 hourly while awake) for 7–10 days.
    - Treatment should be initiated within the first three days of onset of symptoms, except in HIV-infected patients who should be treated if there are active skin lesions. *LoE:IVb*

<u>For patients unable to take oral medication, severely immunocompromised patients and for patients with complicated HZO e.g. acute retinal necrosis (ARN), optic neuropathy or orbitopathy:</u>

- Acyclovir, IV infusion over one hour, 10 mg/kg 8 hourly for 7-14 days.
    - Seek specialist advice for duration of treatment and for switching to oral acyclovir therapy.
    - Adjust dose based on renal clearance (See Appendix II for guidance on prescribing and monitoring). *LoE:IIIb*[xii]

Post-herpetic neuralgia:

Initiate treatment with adjuvant therapy (i.e. amitriptyline) early.
See section 26.1.4: Management of neuropathic pain (Post-herpetic neuralgia). *LoE:IIIb*[xiii]

REFERRAL

» Vesicles on the tip of the nose.
» Fluorescein staining of cornea shows corneal/ulceration.
» Decreased vision.
» Red eye (uveitis or keratitis).
» Cranial nerve palsies.

18.5 KERATITIS

18.5.1 KERATITIS, HERPES SIMPLEX

B00.5† + (H19.1*)

DESCRIPTION

Acute unilateral painful red eye with visual blurring and decreased corneal sensation. Characteristic dendritic corneal ulcer seen on staining with fluorescein.

MEDICINE TREATMENT

- Acyclovir, oral, 400 mg five times daily for 10–14 days. *LoE:Ib*[xiv]

Note: Topical corticosteroids are contraindicated for treating dendritic ulcers.

18.5.2 KERATITIS, SUPPURATIVE

H16.8

DESCRIPTION

Painful red eye with corneal lesion that stains with fluorescein and has creamy white appearance. Contact lenses are a major risk factor, especially for bacterial infections. Have a high index of suspicion for fungal infection in PLHIV, or there is a history of injury to eye with plant matter.

MEDICINE TREATMENT

Empiric therapy until culture results become available:

Bacterial infection:

- Fluoroquinolone ophthalmic drops, e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop hourly for 3 days.
  - Then reduce frequency to 1 drop 3–4 hourly until the ulcer is completely healed.
  - Patients requiring treatment for longer than 2 weeks should be on the advice of an ophthalmologist.

LoE: IVb[xv]

Fungal infection:

- Natamycin 5%, ophthalmic drops, instil 1 drop 1–2 hourly for 3–4 days. (Specialist prescribed).
  - Then reduce frequency to 1 drop 3–4 hourly.
  - Continue for 14–21 days until resolution of infection.

LoE: Ib[xvi]

REFERRAL

» All patients to be managed in consultation with an ophthalmologist.

18.6 RETINITIS, HIV CMV

H30.9 + (B20.2)

DESCRIPTION

Cytomegalovirus (CMV) retinitis is seen in advanced HIV infection, with CD4 count <100 cells/mm^3. The characteristic retinal appearance is that of necrosis, i.e. white exudates, and hemorrhages at the edges of the exudates. Visual loss is irreversible – the goal of therapy is to limit further loss.

MEDICINE TREATMENT

Limited CMV retinitis:

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks, then 900 mg daily until immune recovery (CD4 >100) and a minimum of 3 months of therapy with valganciclovir (if available). *LoE:IIIb*[xvii]
  - Monitor FBC weekly during induction, then monthly, as valganciclovir can cause bone marrow suppression. Avoid concomitant zidovudine use.
  - Initiate ART 2 weeks after starting induction therapy.

If valganciclovir is not available:

- Ganciclovir, intravitreal, 2 mg twice a week for three weeks then once a week (specialist)
  - Once immune function has been restored with antiretroviral therapy (CD4 >100) and the features of active retinitis has cleared, maintenance ganciclovir can be stopped but monitor for recurrence.

REFERRAL

To ophthalmologist for confirmation of diagnosis.
Patients with extensive or wide-spread CMV infection to be managed by an infectious disease specialist.

18.7 UVEITIS

H20.0

Uveitis can be associated with systemic diseases or infection, necessitating a careful history and review of presenting symptoms. Physical examination of the eye and pertinent organ systems should be performed to characterise the type of inflammation present and any concomitant systemic disease. Multimodal ophthalmic imaging has an important role in characterising certain types of intraocular inflammation. Determining the specific type of uveitis guides the selection of treatment. The goal of treatment is to control the disease activity and eliminate or reduce the risk of loss of vision. Uveitis is often classified anatomically based on the primary site of inflammation: anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (retina or choroid) and panuveitis (whole eye), with posterior segments of the eye generally associated with more severe disease.

18.7.1 INFECTIOUS UVEITIS

H20.0

Infectious uveitis may be caused by:

» Bacteria - (syphilis (refer to Section 6.8 syphilis, section 14.6.3 meningovascular syphilis), tuberculosis (refer to Section 16.9 pulmonary TB , Section 16.10 Pleural TB), bartonellosis),
» Viruses - (herpes (refer to Section 4.11.2 Herpes zoster, Section 14.6.2 Herpes simplex encephalitis, Section 18.4 Herpes Zoster ophthalmicus, Section 18.5 Herpes simplex keratitis, Section 25.3 recurrent herpes simplex), cytomegalovirus (refer to Section 10.2.6 CMV, Section 18.6 retinitis, HIV CMV),
» Fungi - (histoplasmosis) and
» Protozoa - (toxoplasmosis (refer to Section 10.2.10 Cerebral toxoplasmosis), toxocariasis, and cysticercosis (refer to Section 14.6.6 neurocysticercosis)).

Patients must be investigated for infectious causes. Further screening should be performed which should be informed by obtaining a full clinical history along with presenting signs and symptoms. Consider the following for further investigation:

» TB - Chest XR or TB ,
» Syphilis – VDRL test
» Toxoplasmosis - toxoplasma PCR
» Herpes simplex and Herpes zoster: HSV or HZV PCR
» Cat-scratch disease (bartonella): bartonella PCR

If an infectious cause is found, treatment of the ocular disease is as for the systemic disease. Once the infection has been addressed, residual inflammation can be treated with adjuvant anti-inflammatory therapy.

18.7.2 NON-INFECTIOUS UVEITIS, ANTERIOR

H20.0

DESCRIPTION

The commonest form of non-infectious uveitis is acute anterior uveitis, which presents with pain and photophobia, variable loss of vision, circumcilliary injection, and a miotic pupil. Chronic anterior uveitis may lead to cystoid macular oedema with decreased central acuity, cataract formation, and secondary glaucoma.

MEDICINE TREATMENT

- Cycloplegic agent, e.g.:
- Atropine 1%, ophthalmic drops, instil 1 drop 12 hourly.

AND

- Corticosteroids, e.g.:
- Dexamethasone 0.1%, ophthalmic drops, instil 1–2 drops 4–6 hourly.

LoE:Ib[xviii]

REFERRAL

All, for management at an ophthalmology unit.

18.7.3 NON-INFECTIOUS POSTERIOR UVEITIS AND PANUVEITIS

H20.0

DESCRIPTION

Non-infectious posterior and panuveitis may be sight limiting if inflammation is not controlled. Both auto-inflammatory and autoimmune processes may be implicated. Posterior uveitis and panuvetis both present similarly with loss of vision, pain and photophobia, floaters and a red eye and are treated similarly as outlined below.

Indicators of severe inflammation include:

» Impairment of visual function
» Bilateral disease
» Vitreous haze
» Macular or optic nerve disease
» Retinal vascular inflammation
» Exudative detachment
» Ocular structural complications that threaten visual function

LoE:IVb[xix]

MEDICINE TREATMENT

- Cycloplegic agent, e.g.:
- Atropine 1%, ophthalmic drops, instil 1 drop 12 hourly.

- Corticosteroids, e.g.:

<u>Acute inflammation/flare</u>

- Prednisone, oral 1 mg/kg/day (max 80 mg/day) for one week
  - Use lowest possible dose for shortest possible duration to control inflammation.
  - Apply a dose tapering regimen over 3-6 weeks typically reducing doses every 1-2 days based on treatment response.

LoE:IIb[xx]

<u>Chronic inflammation</u>

- Prednisone, oral 1 mg/kg/day (max 80 mg/day) for no longer than one month
  - Use lowest possible dose for shortest possible duration to control inflammation.
  - Apply a dose tapering regimen typically reducing doses every 1-2 weeks based on treatment response.

- Monitor for infection, hypertension, fluid retention, diabetes mellitus, hyperlipidaemia, atherosclerosis, osteoporosis, glaucoma, and cataracts.

Patients requiring corticosteroid-sparing control or for persistent severe inflammation refractory to corticosteroid therapy:

Initiation of immunosuppressant therapy should be considered under the following conditions: *LoE:IVb*[xxi]

» Worsening of disease while on high dose corticosteroids
» No response to high dose corticosteroids after 2 to 4 weeks
» Lack of control of inflammation following treatment with high dose corticosteroids for 4 weeks.
» Patients requiring maintenance corticosteroid doses ≥7.5 mg/day for three or more consecutive months.
» Contra-indication or intolerance to corticosteroids. *LoE:IVb*[xxii]

- DMARDs (Disease-modifying antirheumatic drugs)
- Methotrexate, oral, 7.5 mg once weekly *LoE:IIb*[xxiii]
  - Dose titration should be based on individual patient response using increments of 2.5 mg weekly to a maximum dose of 25 mg weekly.
  - As the onset of action is slow with a delayed time to full effect, commence dose tapering of concomitant corticosteroid therapy 2 weeks after initiating methotrexate therapy, based on treatment response.
  - Pre-treatment screening: exclude any infectious diseases that may be exacerbated by immunosuppression.
  - Monitoring: FBC and LFTs at baseline, 4 weeks after initiating treatment and 8 weekly thereafter.
  - Methotrexate is teratogenic - ensure women of childbearing potential are counselled.

AND

- Folic acid, oral 5 mg daily

Patients presenting with concomitant anterior uveitis should also be managed with topical treatment (See Section 18.7.1).

REFERRAL

All, for management at an ophthalmology unit.
If there is concomitant systemic disease refer to appropriate specialist.

18.8 SURGICAL AND DIAGNOSTIC PRODUCTS

Ocular peri-operative pharmaceutical products

- Sodium hyaluronate 10 mg/mL
- Acetylcholine chloride (for intra-ocular irrigation)
- Sterile intraocular irrigating solution
- Hyaluronidase 1500 IU injection (adjunct to anaesthesia for cataract surgery) *LoE:IIb*[xxiv]
- Mitomycin C 2 mg injection (for sponge application during trabeculectomy for glaucoma management) *LoE:IIb*[xxv]

Ocular diagnostic products

- Fluorescein 2%, ophthalmic drops
- Fluorescein ophthalmic strips
- Tropicamide 1%, ophthalmic drops
- Cyclopentolate 2 mg/mL ophthalmic drops (for cycloplegic refraction)
- Cyclopentolate 2 mg/mL and phenylephrine 10 mg/mL (for fundoscopic examination)
- Polyacrylic acid 2 mg/g ophthalmic gel (as coupling liquid for diagnostic contact lenses)

▪ **Local anesthetics used on the eye**

- Oxybuprocaine hydrochloride 0.4% *LoE:IIIb*[xxvi]

▪ **Preparations for tear deficiency**

- Hydroxypropyl methylcellulose 0.3–0.5%

18.9 DRY EYE DISEASE

H04.1

DESCRIPTION

Dry eye occurs when there is inadequate tear volume or function. It is a multifactorial disease of the ocular surface.

The common symptoms include feelings of dryness, grittiness, burning and foreign body sensation, usually worse during the day. A stringy discharge, redness and transient blurring of vision are also common.
Allergic conjunctivitis should be excluded.

GENERAL MEASURES

The management of dry eye involves controlling the symptoms, since the disease is generally not curable.
Management encompasses both pharmacologic and non-pharmacologic approaches.

Relieve symptoms with warm compresses, i.e. a clean moistened cloth over the eyes for at least 1 minute two to three times per day.
Patients should be educated to avoid over the counter topical medications, many of which exacerbate dryness, and control their environmental factors (e.g. encourage frequent blinking during visually attentive tasks, avoid air conditioners or heating, use humidifiers).

MEDICINE TREATMENT

Tear substitutes:

- Hydroxypropyl methylcellulose, ophthalmic drops, 1 drop, 6 hourly.

OR *LoE:IVb*[xxvii]

Lanolin, anhydrous liquid, ophthalmic ointment, at night.

LoE:IVb[xxviii]

18.10 MEDICAL MANAGEMENT OF EYE INJURY

18.10.1 CHEMICAL BURN

This is a medical emergency.
See Primary Health Care Standard Treatment Guidelines section 18.3.1: Eye injury, chemical burn.

18.10.2 EYE INJURY: BLUNT/PENETRATING/ FOREIGN BODY

See Primary Health Care Standard Treatment Guidelines sections 18.3.2 Eye injury/foreign bodies and 18.3.3: Eye injury (blunt or penetrating).

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SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
AH CHAPTER 18: EYE CONDITIONS
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).
All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/
Note that the associated EML chapter has been subjected to subsequent clinical editing. These editorial amendments may not be reflected in the report below.

A: NEW STGs

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
18.1.4 Conjunctivitis, bacterial (gonococcal)	Ceftriaxone	New STG – *aligned to PHC Chp 12 STIs*
	Azithromycin	New STG– *aligned to PHC Chp 12 STIs*
18.7 Uveitis		
18.7.1 Non-infectious uveitis, anterior	STG guidance for non-infectious anterior uveitis separated from non-infectious posterior and panuveitis (new)	AMENDED
	Medicine treatment - homatropine:	DELETED - discontinued
	Medicine treatment – prednisolone acetate eye drops	NOT ADDED
18.7.2 Non-infectious uveitis, posterior uveitis and panuveitis	Medicine Treatment – Cycloplegic eye drops:	RETAINED
	Medicine treatment – prednisone oral	ADDED
	Medicine treatment – methotrexate oral	ADDED
	Medicine treatment – folic acid oral	ADDED
	Medicine treatment – azathioprine	Added to the therapeutic interchange database

B: MEDICINE AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
Eye chapter	Consultation with specialists	Referral guidance - ADDED
18.1.1 Conjunctivitis, viral	Description	Amended
	Medicine treatment, oxymetazoline	Indication - CLARIFIED
18.1.2 Conjunctivitis, allergic	Medicine treatment– Epinastine hydrochloride 0.5mg/mL eye drops:	NOT ADDED
18.1.3 Conjunctivitis, bacterial (non-gonococcal)	Medicine treatment - Sodium chloride 0.9% irrigation	- ADDED
	Medicine treatment – fluoroquinolone ophthalmic drops:	Guidance CLARIFIED
18.3.1 Open-angle glaucoma	STG guidance separated for open-angle and angle closure glaucoma	Amended -Guidance separated
	Medicine treatment – bimatoprost:	DELETED - as example within therapeutic class
	Medicine treatment – Latanoprost:	ADDED – as example within therapeutic class
	Medicine treatment – Bimatoprost 0.03% + Timolol 0.5%:	ADDED - as example within therapeutic class
18.2 Endophthalmitis, bacterial	Endophthalmitis – vancomycin, intravitreal	Guidance AMENDED
18.3.2 Acute angle-closure glaucoma	STG guidance separated for open-angle and angle closure glaucoma	Amended -Guidance separated
18.4 Herpes zoster ophthalmicus	Description	Editorial amendment
	Aciclovir, IV	ADDED
	Valaciclovir, oral	NOT ADDED
18.5.1 Keratitis, herpes simplex	Medicine treatment – acyclovir 3% ophthalmic ointment	DELETED – *discontinued*
18.5.2 Keratitis, suppurative	Description	Editorial amendment
	Medicine treatment – chloramphenicol eye ointment:	NOT ADDED
	Medicine treatment – fluoroquinolone ophthalmic drops	Guidance CLARIFIED

	Referral	Amended
18.6 Retinitis, HIV CMV	Medicine treatment – ganciclovir, intravitreal	Dose CLARIFIED
	Referral	Guidance ADDED
18.8 Surgical and diagnostic products	Hyaluronidase 1500IU injection	ADDED
	Mitomycin C 2mg injection	ADDED
18.9 Dry Eye Disease	Description	Amended
	General measures	Amended

A. NEW STGs

18.1.4 CONJUNCTIVITIS, BACTERIAL (GONOCOCCAL)

Medicine treatment – ceftriaxone: *Added*

Medicine treatment – azithromycin: *Added*

The following guidance for the management of gonococcal conjunctivitis has been added to the chapter and is in alignment with the PHC Chp 12 STIs, Section 12.1 Vaginal discharge syndrome (VDS) and Section 12.3 Male urethritis syndrome (MUS)

8.1.4 CONJUNCTIVITIS, BACTERIAL (GONOCOCCAL)

H10.0

Hyperacute bacterial conjunctivitis involves rapid onset and progression of conjunctivitis and is often caused by N.gonorrhoeae. Gonococcal conjunctivitis requires immediate referral to an ophthalmologist to prevent corneal involvement and potential perforation.

Clinical features:
» Hyperpurulent discharge
» Diminished visual acuity
» Eye tenderness
» Swollen lymph nodes

For conjunctivitis of the newborn, See Primary Health Care Standard Treatment Guidelines and Essential Medicine List; section 18.1.3.

MEDICINE TREATMENT

- Ceftriaxone, IM, 250 mg as a single dose.
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g as a single dose.

For persistent infection, refer to Section 25.1 Male urethral syndrome or section 25.2 Vaginal discharge syndrome.

REFERRAL

Immediate referral to an ophthalmologist.

18.7 UVEITIS

The STG for the management of uveitis has undergone extensive revision. Guidance has been added on the screening of infectious uveitis. Furthermore, guidance for the management of non-infectious uveitis has been separated into Section 18.7.1 Infectious uveitis, 18.7.2 Non-infectious uveitis, anterior which is primarily managed with topical ophthalmic treatments and Section 18.7.2 Non-infectious uveitis, posterior and panuveitis which is managed with oral immunosuppressant therapies. STG guidance amended as follows:

AMENDED FROM:

18.7 UVEITIS

H20.0

DESCRIPTION

Inflammation of the uveal tract and adjacent structures. The commonest form is acute anterior uveitis, which presents with pain and photophobia, variable loss of vision, circumcilliary injection, and a miotic pupil. Chronic uveitis may lead to cystoid macular oedema with decreased central acuity, cataract formation, and secondary glaucoma. Numerous systemic diseases can cause uveitis.

MEDICINE TREATMENT

- Cycloplegic agent, e.g.:
- Homatropine 2 %, ophthalmic drops, instil 1–2 drops 3–4 hourly.

OR

Atropine 1%, ophthalmic drops, instil 1 drop 12 hourly.

AND

- Corticosteroids, e.g.:
- Dexamethasone 0.1%, ophthalmic drops, instil 1–2 drops 4–6 hourly.

REFERRAL

All, for management at an ophthalmology unit.

AMENDED TO:

18.7 UVEITIS

H20.0

Uveitis can be associated with systemic diseases or infection, necessitating a careful history and review of presenting symptoms. Physical examination of the eye and pertinent organ systems should be performed to characterise the type of inflammation present and any concomitant systemic disease. Multimodal ophthalmic imaging has an important role in characterising certain types of intraocular inflammation. Determining the specific type of uveitis guides the selection of treatment. The goal of treatment is to control the disease activity and eliminate or reduce the risk of loss of vision. Uveitis is often classified anatomically based on the primary site of inflammation: anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (retina or choroid) and panuveitis (whole eye), with posterior segments of the eye generally associated with more severe disease.

18.7.1 INFECTIOUS UVEITIS

H20.0

Infectious uveitis may be caused by:

» Bacteria - (syphilis (refer to Section 6.8 syphilis, section 14.6.3 meningovascular syphilis), tuberculosis (refer to Section 16.9 pulmonary TB , Section 16.10 Pleural TB), bartonellosis),
» Viruses - (herpes (refer to Section 4.11.2 Herpes zoster, Section 14.6.2 Herpes simplex encephalitis, Section 18.4 Herpes Zoster ophthalmicus, Section 18.5 Herpes simplex keratitis, Section 25.3 recurrent herpes simplex), cytomegalovirus (refer to Section 10.2.6 CMV, Section 18.6 retinitis, HIV CMV),
» Fungi - (histoplasmosis) and
» Protozoa - (toxoplasmosis (refer to Section 10.2.10 Cerebral toxoplasmosis), toxocariasis, and cysticercosis (refer to Section 14.6.6 neurocysticercosis)).

Patients must be investigated for infectious causes. Further screening should be performed which should be informed by obtaining a full clinical history along with presenting signs and symptoms. Consider the following for further investigation:

» TB - Chest XR or TB ,
» Syphilis – VDRL test
» Toxoplasmosis - toxoplasma PCR
» Herpes simplex and Herpes zoster: HSV or HZV PCR
» Cat-scratch disease (bartonella): bartonella PCR

If an infectious cause is found, treatment of the ocular disease is as for the systemic disease. Once the infection has been addressed, residual inflammation can be treated with adjuvant anti-inflammatory therapy.

18.7.2 NON-INFECTIOUS UVEITIS, ANTERIOR

STG Guidance: *Amended*

Guidance for the management of uveitis has been separated for non-infectious anterior uveitis which is primarily managed with topical ophthalmic treatments.

Medicine treatment - homatropine: *Deleted*

Homatropine 2% as an example of a cycloplegic agent has been removed from the EML as it is no longer available locally. Atropine 1% ophthalmic drops is retained in the EML as the recommended alternative.

Medicine treatment – prednisolone acetate eye drops: *Not added*

External comment to include prednisolone acetate eye drops as an alternative to dexamethasone eye drops was not supported by the Committee in accordance with a previous NEMLC decision[1] that there is no good evidence of

[1] NDoH Evidence Review. Prednisolone acetate versus dexamethasone 0.1% eye drops for uveitis. October 2017_v4.0

superiority to justify the price difference over dexamethasone. Refer to the Knowledge Hub or NHI webpage for the complete evidence review.

NDoH Evidence review: Prednisolone_Uveitis_October 2017_v4.0

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	X	☐	☐

Recommendation: Dexamethasone 0.1% ophthalmic drops be retained in the Adult Hospital Level EML for uveitis.

Rationale: Much as corticosteroids are the main stay in the management of uveitis, there are no robust comparative studies to qualify the use of either prednisolone acetate or dexamethasone. However, prednisolone is widely used and it would be appropriate to consider as a second agent for treatment of acute non infectious uveitis, where the cheaper option dexamethasone is not available.

Level of Evidence: III Expert opinion, Guidelines

Other Factors and Considerations:

- Cost implication
- Efficacy in non-acute uveitis

,Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x		X

VEN status:

Vital	Essential	Necessary
	X	

NEMLC MEETING OF 26 SEPTEMBER 2019
NEMLC accepted the medicine review and the proposed recommendations proposed by the Adult Hospital Level Committee.

Monitoring and evaluation considerations

Research priorities: Controlled head to head studies for topical steroids need to be prioritised especially prednisolone and dexamethasone

The STG has been amended as tabulated below:

18.7.2 NON-INFECTIOUS UVEITIS, ANTERIOR

H20.0

DESCRIPTION

~~Inflammation of the uveal tract and adjacent structures.~~ The commonest form of non-infectious uveitis is acute anterior uveitis, which presents with pain and photophobia, variable loss of vision, circumcilliary injection, and a miotic pupil. Chronic anterior uveitis may lead to cystoid macular oedema with decreased central acuity, cataract formation, and secondary glaucoma. ~~Numerous systemic diseases can cause uveitis.~~

MEDICINE TREATMENT

- Cycloplegic agent, e.g.:

~~• Homatropine 2 %, ophthalmic drops, instil 1–2 drops 3–4 hourly.~~

~~OR~~

Atropine 1%, ophthalmic drops, instil 1 drop 12 hourly.

AND

- Corticosteroids, e.g.:
- Dexamethasone 0.1%, ophthalmic drops, instil 1–2 drops 4–6 hourly.

REFERRAL

All, for management at an ophthalmology unit.

18.7.3 NON-INFECTIOUS POSTERIOR UVEITIS AND PANUVEITIS

Medicine Treatment – Cycloplegic eye drops: *Retained*
Medicine Treatment- Prednisone oral: *Added*
Medicine Treatment- Methotrexate oral: *Added*
Medicine Treatment- Folic acid oral: *Added*

Prednisone oral has been added to the STG for the acute management of ocular inflammation and flare ups associated with non-infectious uveitis as well as short term treatment of chronic inflammation. Refer to the evidence summary included at the end of this report or alternatively, accessible on the Knowledge Hub or NHI webpage.

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

Methotrexate has been added to the AH EML for the management of non-infectious posterior and panuveitis for patients requiring corticosteroid-sparing control or for persistent severe inflammation refractory to corticosteroid therapy. Refer to the evidence summary included at the end of this report or alternatively, accessible on the Knowledge Hub or NHI webpage.

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: The PHC/ Adult Hospital Level Committee suggests using methotrexate for the management of non-infectious posterior uveitis or panuveitis in patients who are refractory to corticosteroids or who require ongoing corticosteroids to maintain inflammation control. The recommendation is based on the limited observational data supporting the use of methotrexate for the management of non-infectious posterior uveitis or panuveitis.

Rationale: The potential harms with long term corticosteroid exposure is a concern as well as the risks of progression to blindness if inflammation is not controlled. Methotrexate is the cheapest of the DMARDs reviewed and is widely used for multiple indications already approved on the EML.

Level of Evidence: Low certainty

Review indicator: New RCT data for efficacy or safety.

NEMLC RECOMMENDATION (30 NOVEMBER 2023): NEMLC supports the recommendation by the ERC as above.

Monitoring and evaluation considerations

Therapeutic Interchange database

The following updates to the therapeutic interchange database were supported by the Committee:

Section - Heading	Indication	INN	strength	unit	formulation
Uveitis	Ocular inflammation	Methotrexate	2.5	mg	oral
Uveitis	Ocular inflammation	Azathioprine	50	mg	oral

Methotrexate oral
Dose: 7.5 mg to 25 mg per week
Azathioprine oral
Dose: 1mg – 4mg/kg/day

New guidance for the management of posterior and panuveitis has been added as tabulated below:

18.7.3 NON-INFECTIOUS UVEITIS, POSTERIOR UVEITIS AND PANUVEITIS

H20.0

DESCRIPTION

Non-infectious posterior and panuveitis may be sight limiting if inflammation is not controlled. Both auto-inflammatory and autoimmune processes may be implicated. Posterior uveitis and panuvetis both present similarly with loss of vision, pain and photophobia, floaters and a red eye and are treated similarly as outlined below.

Indicators of severe inflammation include:

- » Impairment of visual function
- » Bilateral disease
- » Vitreous haze
- » Macular or optic nerve disease
- » Retinal vascular inflammation
- » Exudative detachment
- » Ocular structural complications that threaten visual function

MEDICINE TREATMENT

- Cycloplegic agent, e.g.:
- Atropine 1%, ophthalmic drops, instil 1 drop 12 hourly.

- Corticosteroids, e.g.:

Acute inflammation/flare

- Prednisone, oral 1mg/kg/day (max 80mg/day) for one week
  - Use lowest possible dose for shortest possible duration to control inflammation.
  - Apply a dose tapering regimen over 3-6 weeks typically reducing doses every 1-2 days based on treatment response.

Chronic inflammation

- Prednisone, oral 1mg/kg/day (max 80mg/day) for no longer than one month
  - Use lowest possible dose for shortest possible duration to control inflammation.
  - Apply a dose tapering regimen typically reducing doses every 1-2 weeks based on treatment response.
  - Monitor for infection, hypertension, fluid retention, diabetes mellitus, hyperlipidemia, atherosclerosis, osteoporosis, glaucoma, and cataracts.

Patients requiring corticosteroid-sparing control or for persistent severe inflammation refractory to corticosteroid therapy:

Initiation of immunosuppressant therapy should be considered under the following conditions:

- Worsening of disease while on high dose corticosteroids
- No response to high dose corticosteroids after 2 to 4 weeks
- Lack of control of inflammation following treatment with high dose corticosteroids for 4 weeks.
- Patients requiring maintenance corticosteroid doses ≥7.5mg/day for three or more consecutive months
- Contra-indication or intolerance to corticosteroids

- DMARDs (Disease-modifying antirheumatic drugs)
- Methotrexate, oral 7.5 mg once weekly
  - Dose titration should be based on individual patient response using increments of 2.5 mg weekly to a maximum dose of 25mg weekly.
  - As the onset of action is slow with a delayed time to full effect, commence dose tapering of concomitant corticosteroid therapy 2 weeks after initiating methotrexate therapy, based on treatment response.
  - Pre-treatment screening: exclude any infectious diseases that may be exacerbated by immunosuppression.
  - Monitoring: FBC and LFTs at baseline, 4 weeks after initiating treatment and 8 weekly thereafter.
  - Methotrexate is teratogenic - ensure women of childbearing potential are counselled.

AND
- Folic acid, oral 5mg daily

Patients presenting with concomitant anterior uveitis should also be managed with topical treatment (See Section 18.7.1).

REFERRAL
All, for management at an ophthalmology unit.
If there is concomitant systemic disease refer to appropriate specialist

B. MEDICINE AMENDMENTS

18. EYE CHAPTER

Consultation with specialists: *Guidance added*

The following guidance has been added to the chapter to mitigate delays with referring patients for specialist care:

For many eye conditions early specialist consultation and advice is required.
To mitigate delays in referral it is recommended that electronic consultation methods are utilised with transmission of appropriate images so that appropiate treament can be initiated before referral.

18.1.1 CONJUNCTIVITIS, VIRAL

Description: A*mended*

Medicine treatment - oxymetazoline: *Guidance clarified*

The following amendments were made to the description of viral conjunctivitis which may be caused by a number of viruses, of which, adenovirus is the most common cause:

DESCRIPTION
~~Adenovirus is a~~ Viral conjunctivitis is the commonest cause of infective conjunctivitis. It may be unilateral but ~~is usually~~ often progresses to bilateral. Adenovirus is the commonest viral conjunctivitis, however other viral causes of conjunctivitis present in the same way.

Clinical features:
» Viral conjunctivitis may be associated with an upper respiratory tract infection.
» A burning, sandy, or gritty feeling in the eyes.
» Morning crusting followed by watery discharge.
» Preauricular lymphadenopathy may be present.
» The cornea, iris and pupil are completely normal with normal visual acuity.

The condition is self-limiting but eye irritation and discharge may get worse~~ for 3-5 days before getting better and symptoms can persist~~ for the first week depending on the specific virus. Duration varies from 3-5 days to 2-3 weeks before resolution.

The following statement was amended to clarify that the use of oxymetazoline (a vasoconstrictor), is intended as symptomatic management of redness of the eye only: *"Oxymetazoline 0.025%, eye drops, instil 1–2 drops 6 hourly for a maximum of 7 days to reduce redness of eyes.'*

Long term use of vasoconstrictors may cause rebound congestion and should be avoided.

18.1.2 CONJUNCTIVITIS, ALLERGIC

Medicine treatment– Epinastine hydrochloride 0.5mg/mL eye drops: *Not added*

External comment received for the inclusion of epinastine hydrochloride 0.5mg/mL eye drops for the management of allergic conjunctivitis. Epinastine eye drops is already included on the therapeutic interchange database and has therefore not been added to the EML. Guidance on the management of allergic conjunctivitis is included in the PHC Chp 18 Eye chapter Section 18.1.1 and is cross referenced in the Adult Hospital EML.

NEMLC report 2019

Medicine	Directions for use	Price (ZAR)*	ml	Daily dose (ml)**	Price for 30 days (ZAR)
cromoglicic acid 2%,	1 drop 6 hourly	75.59	13	0.2	34.89
lodoxamide 0.01%	1 drop 6 hourly	288.63	10	0.2	173.18
olopatadine 0.1%	1 drop 12 hourly	251.74	5	0.1	151.04
epinastine 0.05%	1 drop 12 hourly	225.61	5	0.1	135.37
ketotifen 0.025%,	1 drop 12 hourly	253.74	5	0.1	152.24
azelastine 0.05%	1 drop 12 hourly	88.70	10	0.1	39.92

* Cheapest product listed on SEP database, accessed 26 June 2019
** 1 drop = 0.05mL

Level of Evidence: II Systematic review and meta-analysis of low to moderate quality RCTs, Guidelines

18.1.3 CONJUNCTIVITIS, BACTERIAL (NON-GONOCOCCAL)

Medicine treatment - Irrigation with sodium chloride 0.9%*: Added*

The use of sodium chloride 0.9% for irrigation of the eyes has been added to the list of topical therapies for the management of non-gonococcal bacterial conjunctivitis. Furthermore, the management of bacterial conjunctivitis has been separated into non-gonococcal and gonococcal (refer to section 18.1.4) conjunctivitis.

Medicine treatment – fluoroquinolone ophthalmic drops: *Guidance clarified*

Guidance has been clarified as to when the use of fluoroquinolone ophthalmic drops as a second line option would be applicable i.e. contraindications to chloramphenicol or where drug interactions may be a concern. Chloramphenicol ophthalmic ointment is inactivated in the liver and may interact with medicines that are metabolised by hepatic microsomal enzymes[2]. Amendments to the STG are as tabulated below:

AMENDED FROM:
MEDICINE TREATMENT

During the day:

- Chloramphenicol 1%, ophthalmic ointment 6 hourly for 7 days.

OR

- Fluoroquinolone ophthalmic drops as second-line treatment, e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop 2 hourly for 2 days.
  - Then reduce frequency to 1 drop 4 hourly during waking hours, for 5 days.

AMENDED TO:
MEDICINE TREATMENT

- Immediate irrigation of the eyes with sodium chloride 0.9%.

During the day:

- Chloramphenicol 1%, ophthalmic ointment 6 hourly for 7 days.

OR

- Fluoroquinolone ophthalmic drops as second-line treatment (i.e. poor response to chloramphenicol or contra-indication/drug interactions with chloramphenicol) e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop 2 hourly for 2 days.
  - Then reduce frequency to 1 drop 4 hourly during waking hours, for 5 days.

18.2 ENDOPHTHALMITIS, BACTERIAL

Endophthalmitis – vancomycin, intravitreal: *Guidance amended*

[2] Product information. Chloramex® Ophthalmic Ointment. PHARMACARE LIMITED. Date of the most recent amendment to the professional information as approved by the Authority: 29 September 2017

Doses on intravitreal vancomycin when used for endogenous or post-surgical endophthalmitis, may be repeated after 48 hours depending on culture results or clinical response[3]. Amendments to the STG are as tabulated below:

AMENDED FROM:

Endogenous endophthalmitis

Specialist initiated, vitrectomy often required:

- Ceftriaxone, IV, 2 g daily for 7 days.
  - Adjust antibiotics according to culture and sensitivity results.

AND

- Ceftazidime, intravitreal, 2.25 mg.

AND

- Vancomycin, intravitreal, 1 mg.
  - Administer using separate tuberculin syringes.

Post-surgical endophthalmitis

Specialist initiated, vitrectomy often required:

- Ceftazidime, intravitreal, 2.25 mg.

AND

- Vancomycin, intravitreal, 1 mg.
  - Administer using separate tuberculin syringes.

AMENDED TO:

Endogenous endophthalmitis

Specialist initiated, vitrectomy often required:

- Ceftriaxone, IV, 2 g daily for 7 days.
  - Adjust antibiotics according to culture and sensitivity results.

AND

- Ceftazidime, intravitreal, 2.25 mg.

AND

- Vancomycin, intravitreal, 1 mg.
  - Administer antibiotics using separate tuberculin syringes.
  - Antibiotic doses may be repeated after 48 hours depending on culture results or clinical response.

Post-surgical endophthalmitis

Specialist initiated, vitrectomy often required:

- Ceftazidime, intravitreal, 2.25 mg.

AND

- Vancomycin, intravitreal, 1 mg.
  - Administer antibiotics using separate tuberculin syringes.
  - Antibiotic doses may be repeated after 48 hours depending on culture results or clinical response.

18.3.1 OPEN-ANGLE GLAUCOMA

STG Guidance: *Amended -Guidance separated*
Medicine treatment – bimatoprost: *Deleted*
Medicine treatment – Latanoprost: *Added*
Medicine treatment – Bimatoprost 0.03% + Timolol 0.5%: *Added*

Guidance on the management of glaucoma has been separated into two subsections, namely 18.3.1 Open-angle glaucoma and 18.3.2 Angle-closure glaucoma.

The EML has been updated to reflect the latest prostaglandin analogues allocated on tender including latanoprost 0.005% and the combination eye drop, Bimatoprost 0.03% + Timolol 0.5%. Updates are as tabulated below. The Committee acknowledged the availability of multiple generic formulations of prostaglandin analogues which does warrant prioritisation of this STG during the next review cycle.

AMENDED FROM:	AMENDED TO:
18.3.1OPEN-ANGLE GLAUCOMA	**18.3.1 OPEN-ANGLE GLAUCOMA** H40.1

[3] Durand ML.Endophthalmitis. Clinical Microbiology and Infection 2013;19(3):227-34. As cited in Cochrane review Emami S, Kitayama K, Coleman AL. Adjunctive steroid therapy versus antibiotics alone for acute endophthalmitis a#er intraocular procedure. Cochrane Database of Systematic Reviews 2022, Issue 6. Art. No.: CD012131. DOI: 10.1002/14651858.CD012131.pub3

MEDICINE TREATMENT

Open-angle glaucoma

Refer to an ophthalmology unit for diagnosis and initiation of treatment.

First line

ß-blocker:

- Non-selective β-blocker, e.g.:
- Timolol 0.25%, ophthalmic drops, instil 1 drop 12 hourly.

OR

Selective β-blocker:

- Betaxolol 0.25–0.5%, ophthalmic drops, instil 1 drop 12 hourly.

Poor response despite adequate adherence:

ADD

- Prostaglandin analogues, e.g.:
- Bimatoprost 0.01%, ophthalmic drops, instil 1 drop daily.
  - As first line if patient has contra-indication to ß-blocker.
  - In place of ß-blocker if patient has intolerable side effects with ß-blocker or if there is no significant reduction in IOP with other medicines.
  - In combination with ß-blocker if there is significant reduction in IOP with ß-blocker.

Intolerance to prostaglandin analogue, or poor response:

- Alpha-agonist, e.g.:
- Brimonidine 0.15–0.2%, ophthalmic drops, instil 1 drop 12 hourly.
  - Second line if patient allergic to prostaglandin analogue.
  - In place of prostaglandin analogue if there is no significant further reduction in IOP when adding prostaglandin analogue to ß-blocker.
  - In combination with ß-blocker and prostaglandin analogue if the patient still has progression of disease or target IOP is not reached.

Failure to respond:

Alternatives in consultation with a specialist:

Parasympathomimetic agent:

- Pilocarpine 1%, ophthalmic drops, instil 1 drop 6 hourly.

In severe cases, as a temporary measure before ocular surgery in consultation with a specialist:

Carbonic anhydrase inhibitor:

- Acetazolamide, oral, 250 mg 6 hourly.

MEDICINE TREATMENT

Refer to an ophthalmology unit for diagnosis and initiation of treatment.

First line

ß-blocker monotherapy:

- Non-selective β-blocker, e.g.:
- Timolol 0.25%, ophthalmic drops, instil 1 drop 12 hourly.

OR

Selective β-blocker:

- Betaxolol 0.25–0.5%, ophthalmic drops, instil 1 drop 12 hourly.

Second line

- Prostaglandin analogue monotherapy, e.g.:
  - Latanoprost 0.005%, ophthalmic drops, instill 1 drop daily.
  - Use as first line if patient has contra-indication to ß-blocker.
  - Use in place of ß-blocker if patient has intolerable side effects with ß-blocker or if there is no significant reduction in IOP with ß-blocker.

OR

- Prostaglandin analogue in combination with non-selective ß-blocker if there insufficient reduction in IOP with ß-blocker monotherapy, e.g.
  - Bimatoprost 0.03% + Timolol 0.5%

OR

- Prostaglandin analogue in combination with selective ß-blocker if there a contraindication to a non-selective ß-blocker e.g.
  - Latanoprost 0,005% with betaxolol 0.25-0.5%

Third line

Intolerance to prostaglandin analogue, or poor response:

- Alpha-agonist, e.g.:
  - Brimonidine 0.15–0.2%, ophthalmic drops, instil 1 drop 12 hourly.
  - Use as second line if patient is allergic to prostaglandin analogue.
  - Use in place of prostaglandin analogue if there is no significant further reduction in IOP when adding prostaglandin analogue to ß-blocker.
  - Use in combination with ß-blocker and prostaglandin analogue if the patient still has progression of disease or target IOP is not reached.

Failure to respond:

Alternatives in consultation with a specialist:

Parasympathomimetic agent:

- Pilocarpine 1%, ophthalmic drops, instil 1 drop 6 hourly.

In severe cases, as a temporary measure before ocular surgery, in consultation with a specialist:

Carbonic anhydrase inhibitor:

- Acetazolamide, oral, 250 mg 6 hourly.

REFERRAL

All to an ophthalmology unit.

18.3.2 ACUTE ANGLE-CLOSURE GLAUCOMA

STG Guidance: *Amended - Guidance separated*

Guidance on the management of glaucoma has been separated into two subsections, namely 18.3.1 Open-angle glaucoma and 18.3.2 Angle-closure glaucoma. For angle-closure glaucoma, initial therapy should be instituted with immediate referral to an ophthalmology unit.
As for Section 18.3.1 Open-angle glaucoma, the Committee supported that this STG be prioritized for review during the next review cycle.

18.4 HERPES ZOSTER OPHTHALMICUS

Description: *Editorial amendment*
The following statement as included in the description was amended: '*Patients present with a painful vesicular rash in the trigeminal V1 area – vesicles on the tip of the nose indicate nasociliary branch involvement, which i~~ncreases~~ indicates the risk of ocular involvement*

Medicine treatment – Acyclovir, IV: Added
Medicine treatment – Valacyclovir, oral: Not added
Aciclovir IV was added to the AH chp 18 Section 18.4 herpes zoster ophthalmicus (HZO) for patients unable to take oral medication, severely immunocompromised patients and for patients with complicated HZO e.g. acute retinal necrosis (ARN), optic neuropathy or orbitopathy. This addition has been aligned to guidance in the AH Chp 9 Infections Section 9.13: Zoster (shingles).

While oral valacyclovir does offer a theoretical advantage of improved compliance with its TDS dosing regimen relative to oral acyclovir's 4 hourly dosing regimen, the Committee did not support the inclusion of valacyclovir on the EML. Authors of a Cochrane review[4] comparing valacyclovir versus acyclovir for the treatment of herpes zoster ophthalmicus in immunocompetent patients concluded that there is uncertainty of the relative benefits and harms of valacyclovir over acyclovir in HZO. The certainty of evidence was rated by the study authors as low to very low which was downgraded for both imprecision and study limitations. Valacyclovir is also significantly more expensive than oral acyclovir. Note that studies comparing oral antiviral therapies for the management of HZO in immunocompromised patients are lacking and a Cochrane protocol by Olusanya et al published in 2010[5], specifically in PLHIV was subsequently withdrawn in 2018 due to insufficient progress having been made with the review.
Updates to the STG are as tabulated below:

AMENDED FROM:
MEDICINE TREATMENT
- Acyclovir, oral, 800 mg 4 hourly (4 hourly while awake for 7–10 days).
    - Treatment should be initiated within the first three days of onset of symptoms, except in HIV-infected patients who should be treated if there are active skin lesions.

AMENDED TO:
MEDICINE TREATMENT
- Acyclovir, oral, 800 mg 5 doses per day (4 hourly while awake) for 7–10 days.
    - Treatment should be initiated within the first three days of onset of symptoms, except in HIV-infected patients who should be treated if there are active skin lesions.

For patients unable to take oral medication, severely immunocompromised patients and for patients with complicated HZO e.g. acute retinal necrosis (ARN), optic neuropathy or orbitopathy:
- Acyclovir, IV infusion over one hour, 10 mg/kg 8 hourly for 7-14 days.
    - Seek specialist advice for duration of treatment and for switching to oral acyclovir therapy.
    - Adjust dose based on renal clearance (See Appendix II for guidance on prescribing and monitoring).

18.5.1 KERATITIS, HERPES SIMPLEX

Medicine treatment – acyclovir 3% topical eye ointment: *deleted*

[4] Schuster AK, et al. (2016). Valacyclovir versus acyclovir for the treatment of herpes zoster ophthalmicus in immunocompetent patients. Cochrane Database of Systematic Reviews.

[5] Olusanya BA, Oshun PO. Management of herpes zoster ophthalmicus in people with HIV infection. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD008770

The recommendation for the use of acyclovir 3% topical eye ointment for the management of herpes simplex keratitis has been removed as the eye ointment has been discontinued locally. Oral acyclovir 400mg five times daily for 10-14 days has been retained in the STG for the management of herpes simplex keratitis.

18.5.2 KERATITIS, SUPPURATIVE

Description: *Editorial amendment*

The description has been amended to include bacterial infections as a major risk factor for contact lens wearers. Fungal infections as a risk factor for PLHIV has been retained with editorial amendments as tabulated below:

AMENDED FROM:

DESCRIPTION

Painful red eye with corneal lesion that stains with fluorescein and has creamy white appearance. Contact lenses are a major risk factor, especially for fungal infections. Have a high index of suspicion for fungal infection if HIV positive or there is a history of injury to eye with plant matter.

AMENDED TO:

DESCRIPTION

Painful red eye with corneal lesion that stains with fluorescein and has creamy white appearance. Contact lenses are a major risk factor, especially for bacterial infections. Have a high index of suspicion for fungal infection in PLHIV, or there is a history of injury to eye with plant matter.

Medicine treatment – chloramphenicol eye ointment: *Not added*

External comment received to include chloramphenicol eye ointment in addition to ciprofloxacin 03% eye drops for the management of bacterial keratitis to cover for gram positive organisms. Based on a small retrospective study in a tertiary hospital in the KZN province, the susceptibility patterns for most patients with culture-positive keratitis suggests that empiric therapy with ciprofloxacin monotherapy is appropriate for local consideration[6]. The Committee did not support the addition of chloramphenicol eye ointment for empiric therapy, but suggested that a review on the empiric treatment of bacterial keratitis be considered for the next review cycle.

Medicine treatment – fluoroquinolone ophthalmic drops: *Guidance clarified*

Guidance on the use of empiric fluoroquinolone ophthalmic drops has bene clarified as tabulated below:

AMENDED FROM:

MEDICINE TREATMENT

Empiric therapy until culture results become available:

Bacterial infection:

- Fluoroquinolone ophthalmic drops, e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop hourly for 3 days.
  - Then reduce frequency to 1 drop 3–4 hourly.

AMENDED TO:

MEDICINE TREATMENT

Empiric therapy until culture results become available:

Bacterial infection:

- Fluoroquinolone ophthalmic drops, e.g.:
- Ciprofloxacin 0.3%, ophthalmic drops, instil 1 drop hourly for 3 days.
  - Then reduce frequency to 1 drop 3–4 hourly until the ulcer is completely healed.
  - Patients requiring treatment for longer than 2 weeks should be on the advice of an ophthalmologist.

Referral: *Amended*

[6] Proxenos CJ et al. Bacterial keratitis at a tertiary hospital in KwaZulu-Natal: a retrospective study. **South African Ophthalmology JournalVol. 16, No. 4**. 26 Jan 2022. https://hdl.handle.net/10520/ejc-nm_saoj_v16_n4_a5

The criteria for referral has been removed as tabulated below. The Committee noted that there is a risk of blindness if patients are not managed appropriately hence the recommendation to seek expert advice for all patients diagnosed with suppurative keratitis.

AMENDED FROM:

REFERRAL

» Hypopyon (pus in the anterior chamber)
» No facilities for microscopy, culture and sensitivity.

AMENDED TO:

REFERRAL

» All patients to be managed in consultation with an ophthalmologist.

18.6 RETINITIS, HIV CMV

Medicine treatment – ganciclovir, intravitreal: Dose clarified

The dose of intravitreal ganciclovir has been clarified and is aligned to dosing guidance included in the SAMF, as tabulated below:

AMENDED FROM:

If valganciclovir is not available:

- Ganciclovir, intravitreal, 2 mg once a week (specialist)
  - Once immune function has been restored with antiretroviral therapy (CD4 >100) and the features of active retinitis has cleared, maintenance ganciclovir can be stopped but monitor for recurrence.

AMENDED TO:

If valganciclovir is not available:

- Ganciclovir, intravitreal, 2 mg twice a week for three weeks then once a week (specialist)
  - Once immune function has been restored with antiretroviral therapy (CD4 >100) and the features of active retinitis has cleared, maintenance ganciclovir can be stopped but monitor for recurrence.

Referral: *Guidance added*

Guidance to refer patients with extensive or widespread CMV infection for management by an infectious disease specialist, has been added to the STG.

18.8 SURGICAL AND DIAGNOSTIC PRODUCTS

Ocular peri-operative pharmaceutical products – hyaluronidase 1500 IU injection: *ADDED*
Mitomycin C 2mg injection: *ADDED*

Hyaluronidase 1500IU injection has been added to the EML as an adjunct to anaesthesia for cataract surgery. Refer to the evidence summary included at the end of this report or alternatively, accessible on the Knowledge Hub or NHI webpage.

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: The Committee suggests a conditional recommendation for the use of hyaluronidase as an adjunct to anaesthesia for peri-orbital block. Its potential for improved akinesia may be beneficial in certain clinical settings, (extracapsular cataract surgery or manual small incision cataract surgery is still the predominant method used at many sites locally). As the technique uses larger incisions and it is difficult to stabilize the eye with one

instrument, movement of the eye increases the risk of posterior capsule rupture with vitreous loss resulting in poor visual outcomes.

Rationale: Operating with good akinesia is of utmost importance for trainee and inexperienced surgeons performing extracapsular surgery which is of lesser importance when phacoemulsification is used with smaller incisions and two hands available to stabilize the eye. Hyaluronidase also assists with spreading fluid in the tissues, which reduces the risk of elevated intraocular pressure. A high coincidence rate exists between sharp rise of IOP and undesirable intraoperative complications such as: shallowing of anterior chamber, herniation of iris through incision site and stromal corneal oedema. Javrishvili (2021)).

Level of Evidence: Low quality evidence

Review indicator:

NEMLC RECOMMENDATION (MEETING OF 23 FEBRUARY 2023):

NEMLC supports the recommendation of the Expert Review Committee as detailed above.

Monitoring and evaluation considerations

Research priorities

Mitomycin C 2mg injection

Mitomycin 2mg injection has been added to the EML for the management of glaucoma, as a sponge application during trabeculectomy. Refer to the evidence summary included at the end of this report or alternatively, accessible on the Knowledge Hub or NHI webpage.

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: The committee suggests that adult patients with glaucoma undergoing filtration surgery (trabeculectomy) should receive intraoperative mitomycin compared to No mitomycin-C, No 5-fluorouracil, placebo or sham *(conditional, low certainty of evidence).*

Rationale: Intraoperative sponge application of MMC results in fewer surgical failures at 12 months compared to No mitomycin-C, No 5-fluorouracil, placebo or sham. The benefits of 5-FU versus placebo or control is limited to low risk patients only. Furthermore, while the cost per unit of MMC is greater than 5-FU, utilizing an ARR 5%, (NNT 20) for MMC versus 5-FU, the cost of treating 20 patients with intraoperative sponge application of MMC is R5000 to prevent 1 additional surgical failure that would result in a cost of R5500-7200 being averted for an Ahmed valve which is used in follow up surgery, as the current standard of care for patients with failed trabeculectomies.

Level of Evidence: MMC vs placebo or no antimetabolite (moderate certainty evidence) and MMC v 5-FU (low certainty of evidence

Review indicator: New evidence on efficacy or safety of MMC

NEMLC RECOMMENDATION (MEETING OF 30 November 2023): NEMLC supports the ERC's recommendation as stated above.

Monitoring and evaluation considerations

Research priorities

Additions to the STG are as tabulated below:

18.8 SURGICAL AND DIAGNOSTIC PRODUCTS

Ocular peri-operative pharmaceutical products

- Sodium hyaluronate 10 mg/mL
- Acetylcholine chloride (for intra-ocular irrigation)
- Sterile intraocular irrigating solution
- Hyaluronidase 1500IU injection (adjunct to anaesthesia for cataract surgery)
- Mitomycin C 2mg injection (for sponge application during trabeculectomy for glaucoma management)

18.9 DRY EYE DISEASE

Description: *Amended*
General measures: *Amended*
The description of dry eye disease has been amended as follows: '*Dry eye occurs when there is inadequate tear volume or function. It is a multifactorial disease of the ocular surface.'*

The section on general measures for the management of dry eye disease has been amended with additions as tabulated below:

GENERAL MEASURES
The management of dry eye involves controlling the symptoms, since the disease is generally not curable. Management encompasses both pharmacologic and non-pharmacologic approaches. Relieve symptoms with warm compresses, i.e. a clean moistened cloth over the eyes for at least 1 minute two to three times per day. Patients should be educated to avoid over the counter topical medications, many of which exacerbate dryness, and control their environmental factors (e.g. encourage frequent blinking during visually attentive tasks, avoid air conditioners or heating, use humidifiers

REQUEST FOR NEW STGs

External comments have been received motivating for the development of new STGs for both the PHC and AH Eye chapters. The Eye chapters have been identified for priority review in the next review cycle. The following will be considered for prioritization in the PHC Eye chapter:

- Vernal Keratoconjunctivitis (VKC)
- Keratoconus
- Ocular Surface squamous neoplasia
- Peripheral ulcerative keratitis
- Stevens-Johnson syndrome (with ocular involvement)

Existing STGs to be considered for prioritization include:

- Section 18.2 Prevention of post-surgical endopthalmitis
- Section 18.3 Glaucoma management
- Section 18.5.2 Bacterial keratitis – empiric antibiotic therapy
- Section 18.8 Surgical and diagnostic products such as:
  - Viscoelastics
  - Local anaesthetics
  - Phenylephrine hydrochloride 10% minims to dilate the pupil in floppy iris syndrome (for intra-ocular injection)
  - Tropicamide 1% minims for intra-ocular use (to dilate the pupil during surgery)
  - Cyclopentolate hydrochloride 1% minims for intra-ocular use (to dilate pupil during surgery)
  - Preservative free moxifloxacin 0.5%, 0.1ml injected intra-ocular at the end of intra-ocular surgery (for prophylaxis of endophthalmitis)
  - Riboflavin 0.1% for use during collagen cross linking for keratoconus (isotonic and hypotonic)
  - Trypan blue 0.06 - 0.15% for staining the anterior capsule during cataract surgery
  - Preservative free triamcinolone for staining the vitreous during cataract and retinal surgery
  - MMC or 5FU as adjuvant treatment for conjunctival carcinoma.

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.
- LV (Associate Professor/Head of Division of Ophthalmology, Department of Surgical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University). No interests to declare.
- 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

South African National Essential Medicine List
Primary Healthcare/ Adult Hospital Level of Care Medication Review Process
Component: Eye conditions

MEDICINE REVIEW

1. Executive Summary

Date: July 2023
Medicine (INN): Non-biologic corticosteroid-sparing agents: methotrexate, azathioprine, cyclosporine
Medicine (ATC): L01BA01 (methotrexate), L04AX01 (azathioprine) , L04AD01 (cyclosporine)
Indication (ICD10 code): H30.23
Patient population: Adult patients with non-infectious severe bilateral posterior uveitis and panuveitis.
Level of Care: Adult Hospital Level of care
Prescriber Level: Doctor prescribed
Motivator/reviewer name(s): Zahiera Adam, Prof Linda Visser, Dr Farah Moti

Key findings

- Inflammatory eye disease may be infectious or non-infectious in aetiology which could be restricted to the eye or associated with systemic disease. Uveitis is often classified anatomically based on the primary site of inflammation: anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (retina or choroid) and panuveitis (whole eye), with posterior segments of the eye generally associated with more severe disease.
- Corticosteroids are the mainstay of treatment for patients with non-infectious uveitis, although the optimal dose and/or duration of corticosteroid therapy is not clear. **However, the systemic and ocular side effects associated with prolonged use of corticosteroids is well-documented. Immunomodulatory drugs may be required to prevent complications from long-term corticosteroid use, or to manage steroid resistant disease.**
- The aim of this review is to compare the safety and efficacy of three non-biologic, disease-modifying anti-rheumatic drugs (DMARDs), namely methotrexate, azathioprine and cyclosporine for the management of non-infectious, severe posterior uveitis and panuveitis in patients who are refractory to corticosteroids or who require ongoing corticosteroids to maintain inflammation control.
- We identified three clinical guidelines (CG), of which, only one (Dick AD et al, 2018) was deemed to be of sufficient quality to report on (AGREE II score= 83%). A search of Pubmed, the Cochrane Library and Epistemonikos identified 3 systematic reviews (SRs), one of which has not been included (Karam M et al, 2022) as a full text reference could not be sourced. The pre-specified PICO included the use of 3 DMARDs as monotherapy (methotrexate, azathioprine and cyclosporine) as the intervention in adult patients with non-infectious posterior and panuveitis. However, following a review of the published literature, it was noted that no direct evidence that addressed the pre-specified PICO could be identified, and it was agreed that the PICO would be amended to better reflect trends in clinical practice i.e. the intervention was amended to include DMARDs in combination with corticosteroids.
- The CGs and SRs identified all recommend the use DMARDs for the management of non-infectious posterior and panuveitis – recommendations are informed primarily by observational studies and expert opinion.
- In the absence of robust RCT evidence, we summarised key efficacy and safety outcomes from cohort studies and case series as referenced in the guideline by (Dick AD et al, 2018).
- **Methotrexate:** has demonstrated efficacy with control of inflammation, steroid-sparing ability as well as the maintenance and improvement of visual acuity (Evidence level 2B, *Cohort studies)* (Dick AD et al, 2018).
- **Azathioprine:** is described as having moderate efficacy for control of inflammation and corticosteroid-sparing effects in patients with intermediate, posterior and panuveitis (Evidence level 2B, *Cohort studies)*. Evidence for

improvements in visual outcomes is noted as lacking. Azathioprine demonstrated moderate efficacy in inflammation control and a significant steroid-sparing effect in patients with severe uveitis secondary to Behçet's disease. Results from a SR (E Mayhew RG, 2022) suggests that corticosteroids with or without azathioprine results in little to no difference when compared to cyclosporine in the control of inflammation (RR 0.84, where < 1 favors cyclosporine A, 95% CI 0.70 to 1.02; I^2 = 0%), but is very uncertain.

- **Cyclosporine:** RCTs published between 1986 and 1993 generally used higher doses of cyclosporine (8 mg to 15 mg/kg/day) than is currently used in clinical practice. The more recently published studies between 2010 and 2021 used lower doses of cyclosporine which ranged from 3 mg to 5 mg/kg/day. Cyclosporine A plus oral steroid was not found to be superior to IV pulse of steroid plus steroid taper (Ono 2021) or azathioprine plus oral steroid (Cuchacovich 2010) for both efficacy and safety outcomes (low- or very low-certainty evidence).
- Overall, there is a paucity of data to recommend the use of one non-biologic DMARD over another in the management of non-infectious uveitis, based on either safety or efficacy. The few RCTs that were identified, included relatively small numbers of study participants in select patient groups. The heterogeneity in study design and reported outcomes do not readily support combined review through meta-analysis. Furthermore, application to the local setting is limited due to an under-representation of the African continent based on the geographic location of the included studies and the significant proportion of participants with Vogt-Koyanagi-Harada [VKH] disease in the key systematic review (SR) by (E Mayhew RG, 2022), as well as exclusion of HIV positive individuals in the SITE cohort study (Kempen JH et al, 2008).

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: The PHC/ Adult Hospital Level Committee suggests using methotrexate for the management of non-infectious posterior uveitis or panuveitis in patients who are refractory to corticosteroids or who require ongoing corticosteroids to maintain inflammation control. The recommendation is based on the limited observational data supporting the use of methotrexate for the management of non-infectious posterior uveitis or panuveitis.

Rationale: The potential harms with long term corticosteroid exposure is a concern as well as the risks of progression to blindness if inflammation is not controlled. Methotrexate is the cheapest of the DMARDs reviewed and is widely used for multiple indications already approved on the EML.

Level of Evidence: Low certainty

Review indicator: New RCT data for efficacy or safety.

NEMLC RECOMMENDATION (30 NOVEMBER 2023): NEMLC supports the recommendation by the ERC as above.

Monitoring and evaluation considerations

Research priorities

Name of author(s)/motivator(s)

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BACKGROUND

Uveitis encompasses a broad spectrum of conditions which could range from relatively benign to sight threatening. The annual incidence of uveitis is estimated at 14–50 per 100 000 with a prevalence of around 38–200 per 100 000 general population (Durrani OM et al, 2004). To our knowledge, accurate local prevalence data is not available, however uveitis is stated to account for up to 25% of total blindness in the developing world (Rao, 2013).

Inflammatory eye disease may be infectious or non-infectious in aetiology which could be restricted to the eye or associated with systemic disease. Infectious uveitis may be caused by viruses including HSV and VZV (after ophthalmic shingles), syphilis and tuberculosis (TB) and antimicrobial therapy is guided by the underlying cause of the inflammation.

Non-infectious uveitis may be associated with systemic disease and could include the following aetiologies: sarcoidosis, Behçet's disease, ankylosing spondylitis, inflammatory bowel disease, juvenile idiopathic arthritis, seronegative arthropathy, reactive arthritis, multiple sclerosis and Vogt-Koyanagi-Harada syndrome. Uveitis may be further classified as follows (The Standardization of Uveitis Nomenclature (SUN) Working Group , 2005)

- Anatomically based on the primary site of inflammation: anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (retina or choroid) and panuveitis (whole eye)
- Onset of inflammation: sudden or insidious
- Duration of inflammation: Limited (</= 3 months duration) or Persistent (>3 months duration)
- Course of disease: Acute (Episode characterized by sudden onset and limited duration), Recurrent (Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration), Chronic (Persistent uveitis with relapse in <3months after discontinuing treatment)

Non-infectious intermediate, posterior and panuveitis (NIIPPU) may be sight limiting if inflammation is not controlled. The pathophysiology of NIIPPU is not well understood and it is believed that both auto-inflammatory and autoimmune processes may be involved which often presents as a chronic course of disease (E Mayhew RG, 2022). NIPPU are generally managed with similar systemic therapies and are often grouped together in clinical studies even though the aetiologies are wide ranging. This does present significant heterogeneity challenges when reviewing published data.

Prompt therapy and rapid control of ocular inflammation are the key to maintaining good visual acuity. Corticosteroids are the mainstay of treatment for patients with non-infectious uveitis. However, the systemic and ocular side effects associated with prolonged use of corticosteroids is well-documented. Common systemic complications associated with long term corticosteroid use includes diabetes, systemic hypertension, osteoporosis and mood disorders, with cataracts and raised intraocular pressure noted as ocular complications. Lens opacity rarely improves following drug withdrawal and a persistently raised intraocular pressure may lead to open-angle glaucoma (Rossi DC et al, 2019).

It is not clear what the optimal dose and/or duration of corticosteroid use is to minimise the risk of ocular side effects. Based on a review conducted by (Dammacco R et al, 2022), daily corticosteroid use (equivalent to prednisolone 10mg daily) for longer than one year leads to the onset of cataracts in approximately 75% of patients but even low doses of 5mg daily for 2 months in susceptible individuals may lead to the onset of posterior subcapsular cataracts.

Immunomodulatory drugs may be required to prevent complications from long-term corticosteroid use or to manage steroid resistant disease. In order to limit steroid side-effects, classic immunosuppressant agents have been widely used as steroid-sparing agents, particularly with steroid doses still over 10mg/day after six months of therapy (Jabs D et al, 2000).

RESEARCH QUESTION

How do the corticosteroid-sparing agents (methotrexate, azathioprine and cyclosporine) compare in terms of efficacy and safety for the management of non-infectious, severe posterior uveitis and panuveitis?

ELIBILITY CRITERIA FOR REVIEW

Population	Adult patients with non-infectious posterior uveitis or panuveitis
Intervention	Oral corticosteroids in combination with any one of the following DMARDs • Methotrexate (MTX), OR • Azathioprine (AZA), OR • Cyclosporine (CS)
Comparator	• Oral corticosteroids
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.

Note: While in the process of undertaking the literature screen and summary, a decision was taken to amend the pre-specified PICO (see Appendix 1) to better reflect clinical practice. More specifically, the intervention was amended to include the use of DMARDs (methotrexate, azathioprine and cyclosporine) in combination with oral corticosteroids for the management of severe posterior and panuveitis. As the original literature search was sufficiently broad, we did not deem it necessary to revise the literature search. Furthermore, the inclusion and exclusion criteria as stated in the pre-specified PICO were also retained.

METHODS

a. Data sources:

The websites of organisations identified by local experts as credible authorities for guideline development (European Society of Ophthalmology, Royal College of Ophthalmologists, American Uveitis Society) were searched for relevant guidelines. Additionally, a free text google search was undertaken to identify clinical guidelines/reviews from recognized clinical bodies/authorities within the ophthalmology specialty. Systematic reviews (SRs) and randomised controlled trials (RCTs) were sought in PubMed, the Cochrane Library, and Epistemonikos.

b. Search strategy:

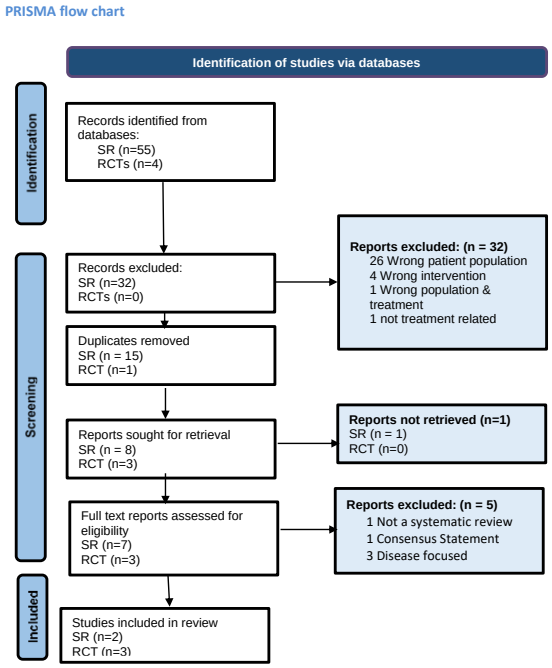
A search for systematic reviews and meta-analyses was conducted on the 9 November 2022 from the following databases: Pubmed, the Cochrane Library and Epistemonikos. Details of the Pubmed search strategy and search terms are included Appendix 2.

Screening, data extraction and analysis, evidence synthesis: Titles and abstracts were screened independently (ZA) and a spot check conducted by (FM). Full text screening was by (ZA) with spot checks by (FM). Eligible clinical guidelines were appraised with the AGREE II tool and eligible systematic reviews were appraised using the AMSTAR II Checklist independently by two reviewers (ZA and VN), with discrepancies resolved following discussion.

RESULTS

Search results:

The literature search yielded 55 records – refer to the PRISMA diagram below for details on the screening process (see Appendix 2 for the list of excluded studies). Of the three SRs considered for inclusion, an AMSTAR II rating was completed for two studies, as a full text article by (Karam M et al, 2022), could not be sourced. The SR by (E Mayhew RG, 2022) was assessed as a high quality review and the (Gomez-Gomez A , 2020) SR was assessed as low quality based on the AMSTAR II assessment.



DESCRIPTION OF CLINICAL GUIDELINES, SYSTEMATIC REVIEWS AND RCTs IDENTIFIED

a. Guidelines

Search results from the list of organisations reviewed as follows:

- NICE guidance[1] – no relevant technology appraisals or clinical guidelines identified
- American Academy of Ophthalmologists (AAO)[2] - see table 1 below for guideline summary

Following a free text google search, the following clinical guidelines were identified.

- Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel (Jabs D et al, 2000)
- Scottish Uveitis National Managed Clinical Network Treatment Guidelines (Scottish Uveitis National Managed Clinical Network, Revised September 2010)

[1] NICE guidelines | NICE guidance | Our programmes | What we do | About | NICE
[2] American Academy of Ophthalmology: Protecting Sight. Empowering Lives - American Academy of Ophthalmology (aao.org)

The guidelines that were identified and appraised were of variable quality, with AGREE II scores ranging from 8%-83% (Table 1). With the exception of the guideline by (Espinosa G et al, 2020) which specifically refers to non-anterior uveitis, the guidelines listed below have not excluded reference to anterior uveitis. The original scope of the guideline by (Dick AD et al, 2018) included only non-anterior uveitis, however, the guideline authors indicated that limited information was available when the searches were restricted to non-anterior uveitis. As the evidence assessed by the authors was deemed to be more broadly applicable, the guideline applies to the general management of non-infectious uveitis with reference to specific types of uveitis where relevant.

Table 1: Guidelines and recommendations for management of uveitis

Citation	Recommendation	AGREE II score
(Dick AD et al, 2018)* **American Academy of Ophthalmology Fundamentals of Care (FOCUS) Initiative**	<u>Determining factors for initiating DMARDs:</u> • To control persistent or severe inflammation (*impairment of visual function, bilateral disease, vitreous haze, macular or optic nerve disease, retinal vascular inflammation, macular oedema, exudative detachment, or ocular structural complications that threaten visual function)* • To prevent ocular structural complications that present a risk to visual function • Contra-indications or intolerance to other therapies • Need for corticosteroid-sparing effect to maintain disease remission (grade C recommendation) <u>Clinical criteria to adjust systemic therapy:</u> • Deterioration (or lack of response) in measures of visual function, anterior chamber cells, anterior chamber flare, vitreous haze, chorioretinal lesions, retinal vascular lesions, or macular or optic nerve involvement (grade B/C recommendation) <u>If the DMARD is not adequately effective:</u> • Before a change in therapy is considered, ensure medication adherence and exclude infectious uveitis and masquerade syndromes (grade B recommendation) • Dose escalation to the maximum tolerated therapeutic dose before considering an alternative (grade B recommendation) • If the initial DMARD is not effective transition to an alternative or additional agent. (grade A recommendation) • Choice of therapy to be individualised based on patient's history, aetiology and other systemic comorbidities (grade C recommendation) <u>Withdrawal of treatment:</u> • Treatment withdrawal should be individualised and informed by: patient preference, tolerance and risk to treatment, duration of disease control, aetiology (grade C recommendation) <u>Evidence to guide the selection of DMARDs:</u> • Data for the most commonly used non-biologic DMARDs are included in Appendix 7, although many studies did not distinguish between different aetiologies and subtypes of uveitis	83%
(Espinosa G et al, 2020)** **Recommendations statement on the immunosuppressive treatment of non-infectious, non-neoplastic, non-anterior uveitis**	• See Appendix 8 for a list of the 34 guideline recommendations	50%
(Jabs D et al, 2000)*** **Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel**	• Recommendations not listed due to low scoring on AGREE II assessment *Guideline authors support the use of DMARDs if there is no response after 2 to 4 weeks of high dose corticosteroids or if the patient's disease worsens while on high dose corticosteroids. DMARDs are also recommended where chronic suppression of disease requires more than 10mg/day of prednisone.*	33%
(Scottish Uveitis National Managed Clinical Network, Revised September 2010) **Uveitis NMCN Treatment Guidelines**	• Recommendations not listed due to low scoring on AGREE II assessment. *Guideline authors support the use of DMARDS for chronic immunosuppression (prednisone >7.5mg/day), lack of response to adequate doses of corticosteroids, reactivation during steroid dose tapering.*	8%

*Quality of evidence was defined using the Oxford Centre for Evidence-Based Medicine levels of evidence criteria grading:

- 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.

** The Jadad scale was used for clinical trials and the Oxford scale for the rest of the designs to assess the methodological quality of the included studies

***Recommendations were rated according to the strength and quality of available evidence. The categories have been adapted from Gross and associates[3]

American Academy of Ophthalmology Fundamentals of Care (FOCUS) Initiative (Dick AD et al, 2018)

The Fundamentals of Care for Uveitis (FOCUS) initiative, was a global initiative organized to achieve consensus through evidence synthesis on optimal systemic treatment of patients with non-infectious uveitis. The initiative involved an international steering committee (ISC) comprising 9 international experts in uveitis, including 7 ophthalmologists and 2 rheumatologists. A further 130 uveitis specialists across 28 countries were included to provide input at a local level. The initiative was convened by AbbVie who are reported to have no involvement in the methodology, data collection, analysis or completion of the report.

The initiative included a literature search spanning January 1996 to August 2016 for relevant publications in English. The literature search included RCTs, prospective and retrospective studies, case series with >/=1 patients, peer reviewed articles, and conference abstracts. A systematic review was undertaken to support the final consensus statement. The authors noted that while the original scope of the analysis included only non-anterior uveitis, much of the evidence applied to a broader anatomical scope. As a result, most of the guideline statements apply generally to non-anterior uveitis unless explicitly stated otherwise.

While cohort studies were not included in our pre-specified PICO, a number of the recommendations in the Fundamentals of Care for Uveitis (FOCUS) initiative, were informed by cohort studies. In view of the lack of suitable RCT evidence identified from our literature search, we have reported on some of the key cohort studies that informed recommendations in the FOCUS initiative as detailed further below.

b. Systematic reviews

We identified two SRs for inclusion. A full text reference for the third SR (Karam M et al, 2022) could not be sourced.

- (E Mayhew RG, 2022)
- (Gomez-Gomez A , 2020)

Based on the AMSTAR II quality assessment of the two SRs identified**,** we focussed on the outcomes of the more recently published and high quality Cochrane review (E Mayhew RG, 2022). However, as significant overlap in RCTs was noted between the (E Mayhew RG, 2022) and (Gomez-Gomez A , 2020) SRs, a high level overview of the (Gomez-Gomez A , 2020) review is included even though the AMSTAR II assessment identified this as a low quality review. Furthermore, a gap analysis was conducted to assess for RCTs that were excluded from the Cochrane review (E Mayhew RG, 2022), which also cited the (Gomez-Gomez A , 2020) publication.

Edwards Mayhew *et al* (2022)

This recently published Cochrane review compared the effectiveness and safety of selected DMARDs (methotrexate, mycophenolate mofetil, tacrolimus and azathioprine) in the treatment of non-infectious intermediate, posterior and panuveitis (NIIPPU) in adults. The review included 11 RCTS (in which 7 studies n<50) and a total of 601 participants, which included a mix of adults, adolescents, and children (7 RCTs were in adults only). While our PICO is focussed on adult patients, the Cochrane reviewers (E Mayhew RG, 2022), acknowledge that they planned on including trials with adult participants only (age 18 and over), which was subsequently changed to include trials with a mix of adults, adolescents, and children but excluded trials where all participants were under 18 years old. As the majority of RCTs included in (E Mayhew RG, 2022) involved adults, we did not exclude this SR.

The reviewers compared each of the DMARDS under review with placebo or with standard of care (e.g. topical steroids with or without systemic steroids), or with each other. DMARDs with overlapping mechanisms of action (e.g. tacrolimus

[3] Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. Infectious Diseases Society of America. Clin Infect Dis 1994;18:421.

versus cyclosporine) were not compared. The review focussed on 4 critical outcomes which were assessed at 6 and 12 months follow-up: Proportion of participants achieving control of inflammation, Change in best corrected visual acuity (BCVA), Proportion of participants achieving a 2-line improvement in visual acuity and Proportion of participants with macular oedema, confirmed by optical coherence tomography (OCT). Other important efficacy, safety and cost effectiveness outcomes were also assessed at 6 and 12 months follow up. (Refer to Appendix 3 for types of outcome measures and how they were assessed by the Cochrane reviewers).

Note that this SR included the use of mycophenolate mofetil and tacrolimus which are outside the scope of our pre-defined PICO.

Gomez-Gomez (Gomez-Gomez A , 2020)

This systematic review was undertaken to evaluate the published evidence regarding the use of immunomodulatory drugs (including biologicals) in adult patients with non-infectious non-anterior (NINA) uveitis. NINA uveitis included intermediate (IU) and posterior uveitis (PU), panuveitis (PanU) and macular oedema (ME). This SR included a wider range of DMARDs compared to our stated PICO, including: methotrexate (MTX), cyclosporine A and G (CsA, CsG), azathioprine (AZA), cyclophosphamide (CYC), mycophenolate mofetil (MMF), tacrolimus, sirolimus, chlorambucil, interferon b (IFN-b), IFN-a and biologic therapies such as infliximab (IFX), adalimumab (ADA), golimumab, certolizumab), rituximab (RTX), secukinumab, sarilumab and daclizumab. Outcomes that were considered, included control of inflammation, steroid-sparing effects, visual acuity (VA), best corrected visual acuity (BCVA), and reduction of the number of uveitis flares and adverse events (AEs). Nineteen RCTs were included in the SR and the Jadad score was used to grade the quality of evidence.

This SR (Gomez-Gomez A , 2020) which is also cited in the more recently published Cochrane review by Mayhew (E Mayhew RG, 2022) discusses the evidence for each of the immunosuppressant drugs listed above. With specific reference to the DMARDs included in our PICO, we noted an overlap of five RCTS between the (Gomez-Gomez A , 2020) and (E Mayhew RG, 2022) SRs (refer to Appendix 4). Of the five overlapping studies, Gomez et al assessed 3 studies to be of good quality and 2 studies of low quality evidence (assessed based on the Jadad scale). Furthermore, a gap analysis identified three small RCTs (n < 30 in each study) that were included in the (Gomez-Gomez A , 2020) SR that were not included in the Cochrane review. Two of the three RCTS were assessed as not relevant to our PICO, due to wrong comparators, and the third study was a VKH only sub-analysis of the (Rathinam SR et al, 2014) study which was included in the Cochrane review (Refer to Appendix 5 for study details).

The authors of (Gomez-Gomez A , 2020) conclude that classical immunomodulatory drugs such as methotrexate, azathioprine and cyclosporine are effective in intermediate and posterior uveitis. The authors, however noted that although azathioprine is widely used for ocular inflammation (Pasadhika, S et al, 2009), no direct evidence could be extracted from the literature reviewed. Cyclosporine A was noted to improve visual acuity with enhanced efficacy when combined with prednisolone or ketoconazole. Furthermore, the authors state that while there is sufficient evidence for recommending the use of immunomodulatory drugs for the treatment of uveitis and/or as corticosteroid-sparing agents, no reliable conclusions can be drawn regarding the optimum treatment guideline.

c. <u>Randomised Controlled Trials (RCTs)</u>

Four RCTs were identified that were published subsequent to the literature search undertaken by the Cochrane reviewers (E Mayhew RG, 2022).

- (Kelly NK et al., 2021): Health- and Vision-Related Quality of Life in a Randomized Controlled Trial Comparing Methotrexate and Mycophenolate Mofetil for Uveitis.
- (Tsui E et al, 2022): Outcomes of Uveitic Macular Edema in the First-line Antimetabolites as Steroid-Sparing Treatment Uveitis Trial.
- (Kong CL et al, 2022): Comparison of CD4 Counts with Mycophenolate Mofetil versus Methotrexate from the First-line Antimetabolites as Steroid-sparing Treatment (FAST) Uveitis Trial.

- (Ono T et al., 2022): Comparison of combination therapy of prednisolone and cyclosporine with corticosteroid pulse therapy in Vogt-Koyanagi-Harada disease.

Three [(Kelly NK et al., 2021), (Tsui E et al, 2022), (Kong CL et al, 2022)] of the four RCTS identified are a secondary analysis of the original FAST trial (Rathinam SR et al, 2019). The original FAST trial has been included in the Cochrane SR and involved the randomisation of either methotrexate 25mg weekly (MTX) or mycophenolate mofetil 1.5g twice daily (MMF), orally in patients with with non-infectious intermediate, posteriori and pan-uveitis. As MMF is outside the scope of our pre-specified PICO, the FAST trial and the associated secondary analysis were excluded from this review.

The pre-print publication by (Ono T et al, 2021) has been included in the Cochrane review. Final publication of the study (Ono T et al., 2022) was subsequently available which we have not duplicated in our review. Furthermore, VKH is very infrequent among persons of African descent and applicability of these results to the local population is limited.

A subsequent Pubmed search for RCTs conducted on the 25th January 2023 (Appendix 2), was undertaken to identify any newly published studies since the literature search undertaken by the Cochrane reviewers (E Mayhew RG, 2022) in April 2021. The search yielded four RCTS, one of which was excluded as a duplicate as a pre-print of the article was included in the Cochrane review.

EFFECTIVENESS OF THE INTERVENTIONS

a. Guidelines

We have limited our reporting to the guideline by (Dick AD et al, 2018) in view of the relatively higher AGREE II score. With specific reference to the supporting evidence for methotrextate, azathioprine and cyclosporine, these were informed primarily by cohort studies as detailed below, with a more detailed summary of the reported efficacy and safety outcomes included in Appendix 6.

American Academy of Ophthalmology Fundamentals of Care (FOCUS) Initiative (Dick AD et al, 2018)

Evidence for Individual Systemic Non-corticosteroid Immunomodulatory Therapy Agents and Disease-Specific Recommendations

The quality of evidence was defined using the Oxford Centre for Evidence-Based Medicine levels of evidence criteria grading.

Drug	No. of Studies*	Disease Anatomic Locations†	Disease Entities or Cause	Outcomes: *Inflammation Control*	Outcomes: *Visual Acuity Stability or Improvement*	Outcomes: *Steroid Sparing*	Evidence Level	Recommendation Level
Mycophenolate preparations‡	13	Anterior uveitis,	NIU	Yes	Yes	Yes	2B§	B§
		intermediate uveitis,	BCR	Yes	No	Yes‖	2B/3	C
		posterior uveitis, and panuveitis	VKH disease	Yes	Yes	Yes¶	2B/3	C
Azathioprine**	4	Anterior uveitis,	NIU	Yes	No	Yes	2B	C
		intermediate uveitis,	BD	Yes	Yes	Yes	2B	B
		posterior uveitis, and panuveitis	VKH disease	Yes	No	Yes	4	C
Methotrexate††	5	Anterior uveitis,	NIU	Yes	Yes	Yes	2B	B
		intermediate uveitis, posterior uveitis, and panuveitis	VKH disease	Yes	Yes	Yes	2B/3	C
Cyclophosphamide	2	Anterior, intermediate, and posterior uveitis	NIU	Yes‡‡	No	Yes‡‡	4	C
Calcineurin inhibitors: tacrolimus/ cyclosporine	4	Anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis	NIU	Yes	Yes	Yes	2B	B
Chlorambucil	1	Panuveitis	Sympathetic ophthalmia	Yes	Yes	Yes	4	C
Evidence for noncorticosteroid local therapy								
Methotrexate	1	Anterior uveitis, intermediate uveitis, and panuveitis	NIU	Yes		No	4	C
Sirolimus	4	Intermediate uveitis, posterior uveitis, and panuveitis	NIU	Yes	Yes	Yes	2B	C

BCR = birdshot chorioretinopathy; BD = Behçet's disease; NIU = noninfectious uveitis; VKH = Vogt-Koyanagi-Harada.
*Some older studies identified in the literature search were excluded based on quality of reporting, consistency in reporting steroid-sparing effect (prednisone ≤10 mg), use of Standardization of Uveitis Nomenclature criteria, and adherence to Standardization of Uveitis Nomenclature criteria for reporting improvement or failure to improve.
†Data are consolidation of all anatomic locations covered in the associated publications. Some publications may cover some anatomic locations and some may cover others.
‡Seven studies with mycophenolate mofetil, 1 study with mycophenolate sodium, and 1 study in combination with cyclosporine; 2 studies in BCR; and 2 in VKH disease, including 1 study with methotrexate as comparator (no evidence of superiority of either drug) and 1 with methotrexate and azathioprine as comparators.
§Evidence level 4 and grade C recommendation for mycophenolate sodium.
‖Data not available for combination with cyclosporine.
¶One hundred percent steroid-sparing control of inflammation with mycophenolate mofetil alone.
**Includes study with mycophenolate mofetil and methotrexate as comparators.
††Includes 1 study with methotrexate and mycophenolate mofetil as comparators and 1 study in VKH disease with mycophenolate mofetil as comparator.
‡‡One study reported only on the entire cohort and not on uveitis patients within the cohort.

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Efficacy

Methotrexate (MTX)

The AAO guideline cites two studies (Samson CM et al., 2001) (Gangaputra S et al. , 2009) in support of the efficacy of methotrexate for the management of uveitis with a grade B recommendation). According to the guideline authors, methotrexate has demonstrated efficacy with control of inflammation, steroid-sparing ability as well as the maintenance and improvement of visual acuity (Evidence level 2B, *Cohort studies)*. In the (Gangaputra S et al. , 2009) study, a discontinuation rate of 13% (50 out of 384 patients) due to ineffectiveness, was reported within 1 year of commencing methotrexate.

Azathioprine (AZA)

The AAO guideline team recommend a moderate efficacy rating for azathioprine (grade B recommendation) for control of inflammation and corticosteroid-sparing effects in patients with intermediate, posterior and panuveitis, based on the outcomes of two studies (Pacheco PA et al. , 2008) (Pasadhika, S et al, 2009)(Evidence level 2B, *Cohort studies*. Evidence for improvements in visual outcomes is noted as lacking. A third cohort study by (Saadoun et al, 2010) was cited in support of the reviewers comments that azathioprine demonstrated moderate efficacy in inflammation control and a significant steroid-sparing effect in patients with severe uveitis secondary to Behçet's disease (Evidence level 2B, *Cohort studies)*. A small cohort study (n=16) limited to patients with VKH by (Kim et al, 2007), included by the guidelines reviewers demonstrated control of inflammation and a steroid sparing effect with azathioprine (low-level evidence (EL 4)).

Cyclosporine (CS)

The AAO guideline stipulates a grade B recommendation for the calcineurin Inhibitors (tacrolimus and cyclosporine). Guideline authors indicate that the efficacy of cyclosporine for control of inflammation and improvements in visual acuity is supported by evidence level 2B (cohort studies with consistent level 2 or 3 studies or extrapolations from level 1 studies). Only the cohort study by (Kacmaz et al, 2010) reported on the safety and efficacy of cyclosporine (i.e. the other 3 studies cited by the reviewers included tacrolimus which is outside the scope of our PICO).

Safety

Overall mortality and cancer mortality

Although mortality is not included as a pre-specified outcome in the PICO, three of the cohort studies cited above, involving methotrexate (Gangaputra S et al. , 2009), azathioprine (Pasadhika, S et al, 2009) and cyclosporine (Kacmaz et al, 2010) were sub-studies of the larger SITE study (Kempen JH et al, 2008) which assessed overall mortality and cancer mortality.

The SITE study (Kempen JH et al, 2008), was a large retrospective cohort study involving 7957 US residents treated at five tertiary ocular clinics with non-infectious ocular inflammation to assess whether immunosuppressive drugs increase mortality (overall mortality and cancer mortality). The study period ran from 1979-2005 spanning over 66 802 person years. Patients with HIV infection were ineligible to participate in the SITE study. The primary outcomes included mortality and fatal malignancy, while secondary outcomes such as ophthalmological response and short-term toxicities of immunosuppressive therapy were reported in sub-studies over a shorter reporting period (Appendix 6).

For the primary outcomes, among the 2340 patients who received immunosuppressive drugs, 323 deaths were reported out of a total of 936 deaths. The overall mortality risk (adjusted for age, sex and race) in patients unexposed to immunosuppressive therapy was reported as a standardised mortality ratio of 1.02 95% confidence interval [CI] 0.94 to 1.11 with a cancer specific mortality ratio of 1.10, 95% CI 0.93 to 1.29). After adjusting for confounding, the antimetabolite immunosuppressive drugs were not associated with a substantial increase in overall mortality (fully adjusted hazard ratio 1.08, 95% CI 0.86 to 1.37) or cancer mortality (0.89, 0.54 to 1.48). Individually, azathioprine and methotrexate which were among the more commonly used antimetabolites were not associated with increased risk of overall or cancer mortality either. Similarly, the T cell inhibitor class of immunosuppressants did not demonstrate an increase in mortality risk i.e. (fully adjusted hazard ratio 0.81, 95% CI 0.59 to 1.11), and cancer mortality (0.78, 0.38 to 1.59). Individually, cyclosporine had overall and cancer-related mortality similar to that of the overall T cell class of drugs. Systemic corticosteroid therapy

was not associated with increased overall (hazard ratio 1.13, 95% CI 0.96 to 1.33) or cancer mortality (1.02, 0.72 to 1.45) after adjusting for confounding.

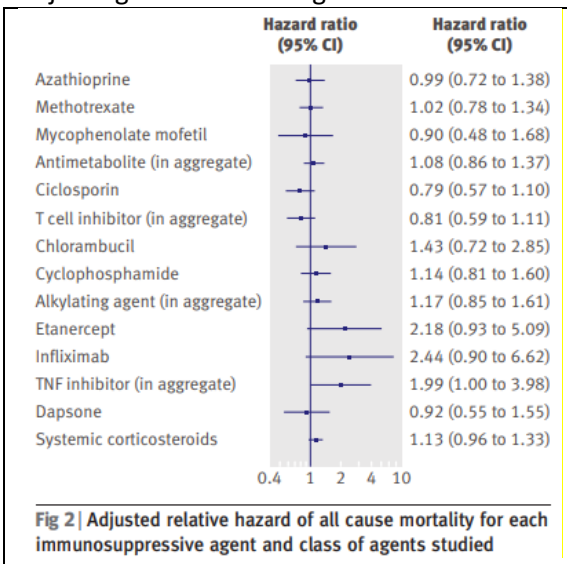


Fig 2 | Adjusted relative hazard of all cause mortality for each immunosuppressive agent and class of agents studied

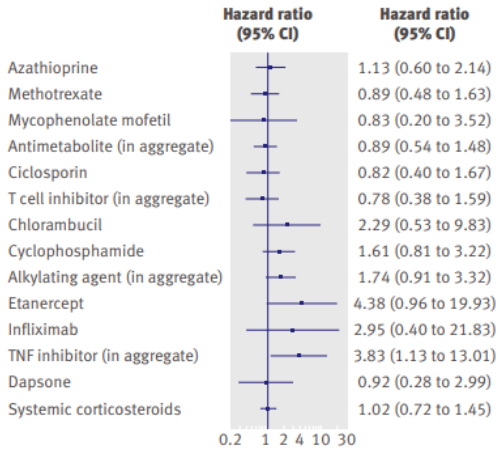


Fig 3 | Adjusted relative hazard of mortality attributed to cancer for each immunosuppressive agent and class of agents studied

According to the study authors, the tendency towards increased crude and demographic adjusted hazard ratios observed with antimetabolite therapy corresponded to greater use of these drugs in patients who had systemic inflammatory comorbidities and were older, as can be noted in the tables below:

Table 3 | Use of immunosuppressive drugs and risk of overall mortality*

Agent	Crude HR (95% CI)	P	HR adjusted for age, race, sex (95% CI)	P	HR fully adjusted model (95% CI)	P
No immunosuppressive agent	1.00		1.00		1.00	
Antimetabolite (any)	1.60 (1.33 to 1.91)	<0.0001	1.23 (1.02 to 1.47)	0.029	1.08 (0.86 to 1.37)	0.50
Azathioprine	1.73 (1.35 to 2.21)	<0.0001	1.13 (0.88 to 1.46)	0.33	0.99 (0.72 to 1.38)	0.97
Methotrexate	1.56 (1.25 to 1.95)	<0.0001	1.19 (0.95 to 1.49)	0.129	1.02 (0.78 to 1.34)	0.87
Mycophenolate mofetil	0.94 (0.53 to 1.67)	0.82	1.00 (0.56 to 1.78)	0.99	0.90 (0.48 to 1.68)	0.73
T cell inhibitor (any)	0.89 (0.69 to 1.14)	0.35	1.22 (0.95 to 1.56)	0.121	0.81 (0.59 to 1.11)	0.18
Ciclosporin	0.81 (0.63 to 1.05)	0.118	1.17 (0.90 to 1.52)	0.25	0.79 (0.57 to 1.10)	0.16
Alkylating agent (any)	2.36 (1.92 to 2.90)	<0.0001	1.26 (1.02 to 1.56)	0.031	1.17 (0.85 to 1.61)	0.34
Chlorambucil	1.33 (0.73 to 2.41)	0.35	1.97 (1.08 to 3.59)	0.027	1.43 (0.72 to 2.85)	0.30
Cyclophosphamide	2.54 (2.05 to 3.14)	<0.0001	1.19 (0.96 to 1.49)	0.116	1.14 (0.81 to 1.60)	0.45
TNF inhibitor (any)	1.45 (0.75 to 2.82)	0.27	1.96 (1.01 to 3.81)	0.048	1.99 (1.00 to 3.98)	0.050
Etanercept	1.78 (0.79 to 3.99)	0.16	2.04 (0.91 to 4.59)	0.085	2.18 (0.93 to 5.09)	0.072
Infliximab	1.31 (0.49 to 3.51)	0.59	2.25 (0.83 to 6.05)	0.110	2.44 (0.90 to 6.62)	0.080
Dapsone	3.45 (2.76 to 4.30)	<0.0001	0.98 (0.77 to 1.24)	0.85	0.92 (0.55 to 1.55)	0.77
No systemic corticosteroids	1.00		1.00		1.00	
Systemic corticosteroids	1.03 (0.90 to 1.19)	0.63	1.24 (1.08 to 1.43)	0.003	1.13 (0.96 to 1.33)	0.15

HR=hazard ratio; CI=confidence interval; TNF=tumour necrosis factor.
*For immunosuppressive agents, each comparison is of person time after exposure to the agent indicated compared with patients never exposed to any of the agents listed. For corticosteroids, the comparison is of person time after use of systemic corticosteroids versus person time before use of systemic corticosteroids. Fully adjusted models adjust for age, race, sex, smoking status, site of ocular inflammation, bilaterality of ocular inflammation, Charlson index score, and indicator variables for those systemic inflammatory diseases that were significantly associated with mortality in Cox regression. In addition to the agents listed, small numbers of patients taking leflunomide, tacrolimus, sirolimus, and adalimumab were included in the antimetabolite, T cell inhibitor, and TNF inhibitor groups, respectively.

Table 4 | Use of immunosuppressive drugs and risk of mortality caused by cancer*

Agent	Crude HR (95% CI)	P	HR adjusted for age, race, sex (95% CI)	P	HR fully adjusted model (95% CI)	P
No immunosuppressive drug	1.00		1.00		1.00	
Antimetabolite (any)	1.16 (0.76 to 1.76)	0.49	0.87 (0.57 to 1.32)	0.50	0.89 (0.54 to 1.48)	0.66
Azathioprine	1.73 (1.04 to 2.87)	0.034	1.06 (0.63 to 1.77)	0.83	1.13 (0.60 to 2.14)	0.70
Methotrexate	1.03 (0.60 to 1.76)	0.93	0.76 (0.44 to 1.32)	0.33	0.89 (0.48 to 1.63)	0.70
Mycophenolate mofetil	0.65 (0.16 to 2.66)	0.55	0.67 (0.16 to 2.76)	0.58	0.83 (0.20 to 3.52)	0.80
T cell inhibitor (any)	0.85 (0.51 to 1.44)	0.55	1.15 (0.68 to 1.95)	0.60	0.78 (0.38 to 1.59)	0.50
Ciclosporin	0.88 (0.52 to 1.48)	0.63	1.24 (0.73 to 2.10)	0.42	0.82 (0.40 to 1.67)	0.59
Alkylating agent (any)	2.36 (1.54 to 3.60)	<0.0001	1.21 (0.78 to 1.88)	0.39	1.74 (0.91 to 3.32)	0.092
Chlorambucil	1.02 (0.25 to 4.14)	0.97	1.54 (0.38 to 6.27)	0.55	2.29 (0.53 to 9.83)	0.26
Cyclophosphamide	2.54 (1.64 to 3.93)	<0.0001	1.14 (0.72 to 1.79)	0.58	1.61 (0.81 to 3.22)	0.17
TNF inhibitor (any)	2.06 (0.65 to 6.55)	0.22	2.44 (0.77 to 7.75)	0.132	3.83 (1.13 to 13.01)	0.031
Etanercept	2.47 (0.60 to 10.06)	0.21	2.51 (0.61 to 10.24)	0.20	4.38 (0.96 to 19.93)	0.056
Infliximab	1.42 (0.20 to 10.26)	0.73	2.13 (0.29 to 15.51)	0.45	2.95 (0.40 to 21.83)	0.29
Dapsone	1.92 (1.06 to 3.47)	0.031	0.55 (0.29 to 1.02)	0.056	0.92 (0.28 to 2.99)	0.89
No systemic corticosteroids	1.00		1.00		1.00	
Systemic corticosteroids	0.95 (0.70 to 1.28)	0.72	1.10 (0.81 to 1.49)	0.55	1.02 (0.72 to 1.45)	0.89

HR=hazard ratio; CI=confidence interval; TNF=tumour necrosis factor.
*For immunosuppressive drugs, each comparison is of person time after exposure to the agent compared with patients never exposed to any of the agents listed. For corticosteroids, the comparison is of person time after use of systemic corticosteroids versus person time before use of systemic corticosteroids. Fully adjusted models adjust for age, race, sex, smoking status, site of ocular inflammation, bilaterality of ocular inflammation, Charlson index score, and indicator variables for those systemic inflammatory diseases that were significantly associated with mortality in Cox regression. In addition to the agents listed, small numbers of patients taking leflunomide, tacrolimus, sirolimus, and adalimumab were included in the antimetabolite, T cell inhibitor, and TNF inhibitor groups, respectively.

Adverse reactions and discontinuation (Appendix 6)

Methotrexate (MTX)

In the study by (Samson CM et al., 2001), 18% (n=29) of the 160 participants discontinued therapy due to adverse effects. Potentially serious reactions were reported for 8 patients with persistent elevated liver enzymes and 3 with leukopenia. In the (Gangaputra S et al. , 2009) study, side effects were reported in 16% of participants (60 of 384 participants) which were generally reversible with dose reduction or discontinuation.

Azathioprine (AZA)

A discontinuation rate of 24% due to adverse effects in the first year of treatment, was reported in the (Pasadhika, S et al, 2009) study. Key reported side effects included (GI upset, bone marrow suppression, elevated LFTs, infection and allergic reactions. A further 15% discontinued therapy at one year but the reason was not specified. A similar side effect profile was noted in the study by (Saadoun et al, 2010) which included 157 patients with Behcet's disease i.e. side effects noted in 67 patients (42.6%) and mainly included gastrointestinal events (19.1%), cytopenia (18.4%), and infections (17.8%). There were 3 withdrawals due to toxicity during azathioprine therapy, 2 for hepatotoxicity and 1 for septicaemia.

Cyclosporine (CS)

In the study by (Kacmaz et al, 2010), a discontinuation rate of 10.7% (95% CI, 7.6–15.1) due to toxicity was reported (renal toxicity and hypertension most commonly reported) with a further 12.4% of participants discontinuing therapy where the reasons were reported as unknown. Discontinuation for toxicity was progressively more frequent with increasing age, particularly among patients aged between 55 and 64 years (adjusted RR = 3.25; CI, 1.54– 6.88) and patients aged more than 65 years (adjusted RR = 5.66; CI, 2.14–14.98, P =0.0005).

Comparative Studies of Antimetabolites (Mycophenolate Mofetil, Azathioprine, and Methotrexate)

The guideline authors also reported on comparative studies of antimetabolites which they state demonstrates moderate support of methotrexate and mycophenolate mofetil in steroid-sparing control (overall grade C recommendation), with no significant differences in uveitis control among these drugs. Azathioprine was reported to be associated with higher rates of side effects, laboratory test complications, and discontinuation of therapy relative to methotrexate and mycophenolate.

b. Systematic reviews

Edwards Mayhew *et al* (2022)

Refer to Appendix 7 for the summary of findings tables from the Cochrane review - 6 of the 15 outcomes measures included in Appendix 3 were assessed at 6 and 12 months and have been reported in the SoF table.

Methotrexate (MTX)
Nothing reported

Azathioprine (AZA)
Nothing reported.

Cyclosporine (CS)
The De Vries 1990 study compared cyclosporine with placebo, both in combination with oral steroid (0.3 mg/kg/ day). The Cochrane reviewers, however noted that the dose of cyclosporine A used in De Vries 1990 (10 mg/kg/day) is higher than that used in current clinical practice, indicating that the results of this study provide only indirect evidence on the effectiveness of cyclosporine A.

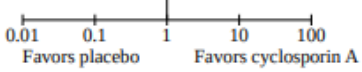
Indirect evidence

A. *Cyclosporine* (De Vries J et al, 1990)*:*

- Control of inflammatory activity: This was defined using a modified Hogan-Thygeson-Kimura scale which scored congestion, keratic precipitates, anterior chamber cells and flare, vitreous opacity, macular edema, optic disc edema, vasculitis, infiltrates, 'snowballs' and 'snowbanks', exudates, and hemorrhages.

Analysis 1.2. Comparison 1: DMARDs plus steroid versus steroid monotherapy, Outcome 2: Control of inflammation: high-dose cyclosporine A

Study or Subgroup	Cyclosporine A plus steroid Events	Total	Placebo plus steroid Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
De Vries 1990 (1)	1	14	1	13	0.93 [0.06 , 13.37]		? + + + ? ?



Footnotes
(1) At 12 month, CsA 10 mg/kg/day plus steroid 0-3 mg/kg/day

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

The effect of cyclosporine plus oral steroid versus placebo plus oral steroid on the control of inflammation (RR 0.93, where > 1 favors cyclosporine plus steroid, 95% CI 0.06 to 13.37;) is described by the Cochrane reviewers to be based on very uncertain evidence (Analysis 1.2 above).

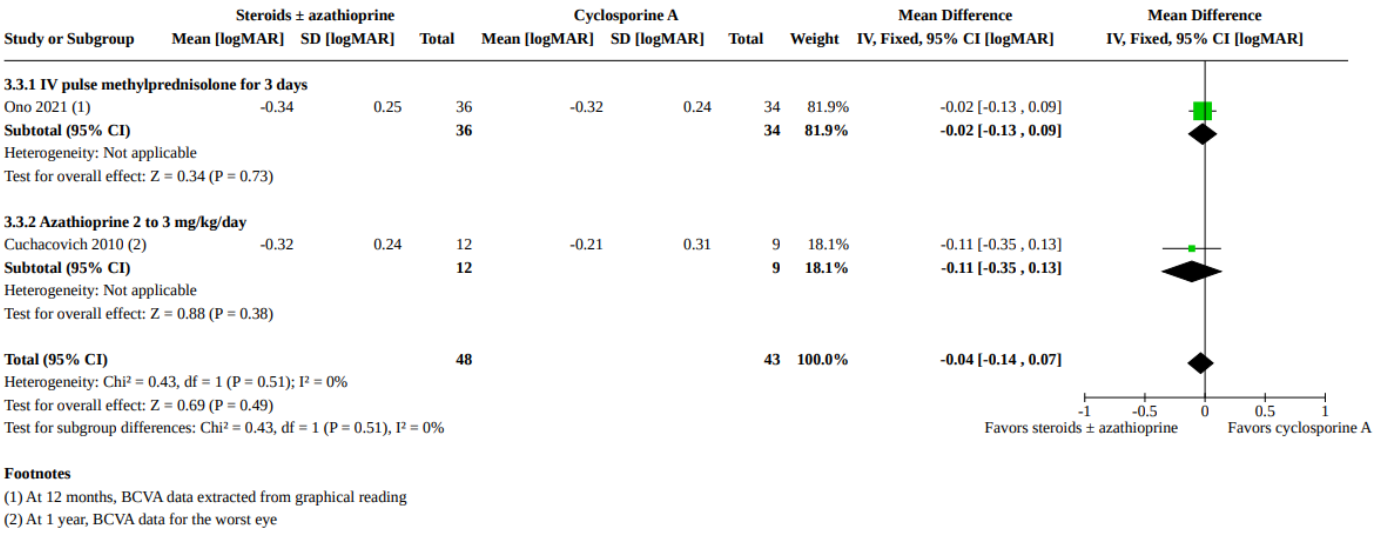
- Proportion of participants to achieve steroid-sparing control or to achieve reduction in oral steroid dose: The dose of oral steroid (0.3mg/kg/day) used by De Vries did not meet the Cochrane reviewers definition of steroid sparing control which was (</= 10mg/day).
- Proportion of participants experiencing complications requiring cessation of medication: As no events were reported for cyclosporine A (0 of 14 participants) or placebo (0 of 13 participants) a risk ratio was not estimatable.

B. Steroids with or without azathioprine versus cyclosporine A

This comparison by the Cochrane reviewers comparing steroids with or without azathioprine to cyclosporine A included 145 participants across four studies ((Cuchacovich M et al, 2010), (Nussenblatt RB, et al, 1991), (Ono T et al, 2021), (Wiederholt M et al, 1986), with Cuchacovich and Ono including only VKH patients. Note that the Nussenblatt (1991) and Wiederholt (1986) studies used high dose cyclosporine.

- Control of inflammation: Based on the analysis of two studies (Cuchacovich 2010; Ono 2021), the evidence may suggest the steroids with or without azathioprine results in little to no difference in control of inflammation at 12 months over cyclosporine, but is very uncertain (RR 0.84, where < 1 favors cyclosporine A, 95% CI 0.70 to 1.02; I2 = 0% (very low certainty). Note that all 112 participants had VKH.
- Change in BVCA: From the analysis of two trials (Cuchacovich 2010; Ono 2021), the evidence is very uncertain whether the steroids with or without azathioprine improve vision over cyclosporine (RR -0.04, where < 0 favours comparators, 95% CI -0.14 to 0.07; I2 = 0%.

Figure 5: analysis 3.3. comparison 3: Steroids with or without azathiprine vs cyclosporin A, outcome 3: change in BVCA



- Proportion of participants achieving steroid-sparing control: The reviewers report that the evidence is very uncertain as to whether there is a difference in the proportion of participants achieving steroid-sparing control between AZA and CsA (RR 0.64, where < 1 favors cyclosporine, 95% CI 0.33 to 1.25), very low certainty. This analysis was based on the (Cuchacovich M et al, 2010) study involving only VKH patients with evidence downgraded one level due to data imprecision and two levels due to risk of bias.
- Proportion of participants experiencing any adverse effects: Over the course of 12 months, 6 out of 9 patients on cyclosporine and 8 of 12 patients on azathioprine experienced any adverse event resulting in a RR=1 (95% CI 0.54 to 1.84), as reported in the (Cuchacovich M et al, 2010) study.

In view of the paucity of both efficacy and safety data, the Cochrane reviewers were unable to formulate any recommendations on which DMARD/s should be considered for the management of NIPPU. The authors noted the heterogeneity of studies (both in design and outcome measures*) and small sizes of the trials. While data on head to head comparisons of different DMARDs is lacking, the authors concluded that methotrexate is probably slightly more efficacious than mycophenolate *(not included in our PICO)* in achieving control of inflammation, including steroid-sparing control (moderate-certainty evidence), except for the VKH subgroup where there is insufficient evidence to preferentially consider one drug over another (very low-certainty evidence). No significant differences in safety outcomes were noted between

methotrexate and mycophenolate. The Cochrane reviewer's (E Mayhew RG, 2022) further concluded that the findings from their review was similar to that from (Gomez-Gomez A , 2020) cited below, as well as the SR by (Pato E, et al, 2011), identified in our literature search and for which for which a full text of the reference could not be sourced.

*Example: The use of topical and systemic corticosteroids varied considerably across included studies. Regimens for oral corticosteroids also varied considerably with doses ranging from 10-100mg daily with variable dose tapering regimens. Steroid tapers were generally aimed to achieve a dose of 5 to 10mg daily.

Furthermore, the authors concluded that while oral steroids are efficacious and are accepted as the standard of care, there is a need for steroid-sparing medication. Results of the SR did however not yield any clear recommendations on the relative safety or efficacy of the DMARDs considered, and little practical advice could be given to clinicians on a proposed treatment algorithm.

CONCLUSION

International guideline recommendations support the use of DMARDs for the management of non-infectious uveitis, informed primarily by observational data and/or expert opinion. Despite the well-documented limitations of the published literature (appendix 8) and low quality of evidence, the literature consistently supports a favourable risk:benefit recommendation for the use of DMARDs for the management of non-infectious uveitis where corticosteroids are ineffective or tolerance is a concern.

Although blindness remains a significant consequence of severe non-infectious uveitis if inflammation is not controlled, a review of the literature does not provide for preferential consideration of any of the non-biological DMARDs under consideration or clear guidance for an algorithmic approach to the use of these agents.

In the absence of any further evidence to recommend one non-biologic DMARD over another, we recommend:

- For patients with non-infectious posterior or panuveitis requiring corticosteroid-sparing control, methotrexate should be considered (moderate certainty evidence), with dose tapering of corticosteroids to the lowest possible dose to control inflammation or discontinuation of corticosteroids when possible.
- For patients with non-infectious posterior or panuveitis refractory to oral corticosteroid therapy, methotrexate may be considered as add on therapy, with consideration of a steroid tapering based on individual patient response.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
CERTAINTY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** **Methotrexate** High ☐ Moderate ☐ Low ☒ Very low ☐ **Azathioprine** High ☐ Moderate ☐ Low ☒ Very low ☐ **Cyclosporine** High ☐ Moderate ☐ Low ☐ Very low ☒ *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	**MTX** Retrospective case series and cohort studies demonstrating moderate efficacy with control of inflammation, steroid-sparing ability and maintenance and/or improvement in VA. Low or very low certainty of evidence as observational data. No critical appraisal from source document available **AZA** Retrospective and prospective observational studies demonstrating moderate efficacy with control of inflammation, steroid-sparing ability. Low or very low certainty of evidence as observational data. No critical appraisal from source document available **CYC** The effect of cyclosporine plus oral steroid versus placebo plus oral steroid on the control of inflammation (RR 0.93, where > 1 favors cyclosporine plus steroid, 95% CI 0.06 to 13.37;) is described by the Cochrane reviewers to be based on very low certainty evidence. Doses used in RCTs no longer used in clinical practice. Evidence level – all 2B by guideline reviewers in (Dick AD et al, 2018).

EVIDENCE OF BENEFIT

What is the size of the effect for beneficial outcomes?

Methotrexate, Azathioprine, Cyclosporine

Large	Moderate	Small	None
☐	☐	☐	☐

Size of effect cannot be quantified as the evidence is primarily informed by non-RCT and non-comparative studies.

Due to the heterogeneity of outcomes reported in the cohort studies and the lack of a comparative treatment arms, the size of the beneficial effect cannot be quantified. However in view of the risks with long term corticosteroid use and the risk of blindness from uncontrolled inflammation, we consider the balance of benefit and harm to be favourable with the use of DMARDs.

MTX

(Samson CM et al., 2001)

- Control of inflammation = 76.2%
- Steroid-sparing effect = 56%
- Visual acuity maintained or improved = 90%
- Discontinuation within 1 year due to ineffectiveness 13% (n= 50);

(Gangaputra S et al. , 2009)

- Complete suppression of inflammation sustained for ≥28 days achieved within 6 months: Response rate ranged from 39% to 77% depending on type of inflammation or anatomical location.
- Corticosteroid-sparing effects (sustained suppression of inflammation with prednisone ≤10 mg/d) within 6 months: Response rate ranged from 21%-51% depending on type of inflammation or anatomical location.
- Overall, success within 12 months: 66% for sustained control and 58.4% for corticosteroid sparing ≤10 mg).
- Overall rate of remission = 11% (n=43)

AZA

(Pacheco PA et al. , 2008)

- Complete response =92%
- Remission at 12 months =85% (n=23)
- Relapse = 12% (n=3)

(Pasadhika, S et al, 2009)

- Sustained control of inflammation (for at least 28 days) by 12 months: 62% (95% CI, 50-74%)
- Complete inactivity of inflammation (for at least 28days) within 6 months ranged from 20% (95% CI, 3-80%) to = 69% (95% CI, 41-93%) depending on type of inflammation or anatomical location.
- Corticosteroid-sparing (patients on prednisolone >10mg reduced at 12 months to </=10mg per day: 46.9% (95% CI, 36.9 - 58.0)

CYC

(Kacmaz et al, 2010)

- Control of inflammation for at least 28 days at 1 year = 51.9% (45.5–58.5)
- Controlled inflammation (no activity at 12 months) ranged from 20.0% (3.1–79.6) to 62.3% (29.6–93.3) depending on type of inflammation or anatomical location.
- Corticosteroid-sparing at 1 year = 36.1% (95% CI, 30.5–42.2).

CERTAINTY OF EVIDENCE OF HARM

What is the certainty/quality of evidence?

Methotrexate

High	Moderate	Low	Very low
☐	☐	X	☐

Azathioprine

High	Moderate	Low	Very low
☐	☐	X	☐

Cyclosporine

High	Moderate	Low	Very low
☐	☐	X	☐

High quality: confident in the evidence

MTX

Retrospective case series and cohort studies demonstrating low or very low certainty of evidence as observational data. No critical appraisal from source document available.

AZA

Retrospective and prospective cohort studies demonstrating low or very low certainty of evidence as observational data. No critical appraisal from source document available.

CYC

RCTs data based on doses no longer used in clinical practice. Retrospective cohort study demonstrating low or very low certainty of evidence as observational data.

	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	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **Methotrexate, Azathioprine, Cyclosporine** Large ☐ Moderate ☐ Small ☐ None ☐ Size of effect cannot be quantified as the evidence is primarily informed by non-RCT and non-comparative studies.	**MTX** **(Samson CM et al., 2001)** • Discontinuation due to side effects = 18% • Potentially serious adverse reactions = 8.1% • n=8 with persistent elevated liver enzymes and n=3 with leukopenia **(Gangaputra S et al. , 2009)** • Discontinuation within 1 year due to side effects 16% (n=60), generally reversible with dose reduction or discontinuation **AZA** **(Pacheco PA et al. , 2008)** • None of the patients (n=27) needed discontinuation of AZA **(Pasadhika, S et al, 2009)** • Estimated discontinuation in first year due to adverse effects =24% (Gi upset, bone marrow suppression, elevated LFTs, infection, allergic reaction) and a further 15% were discontinued with reasons not specified **CYC** **(De Vries J et al, 1990)** • As no events were reported for cyclosporine A (0 of 14 participants) or placebo (0 of 13 participants) a risk ratio was not estimatable. **(Kacmaz et al, 2010)** • Discontinuation at 1 year due to toxicity=10.7% (95% CI, 7.6–15.1) with renal toxicity and hypertension most common. A further 12.4% of participants discontinued treatment with reasons unknown.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** **Methotrexate** Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐ **Azathioprine** Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐ **Cyclosporine** Favours intervention ☐ Favours control ☒ Intervention = Control *or* Uncertain ☐	Based on the evidence included in this review, we are uncertain if the desirable effects outweigh the undesirable harms. Based on expert opinion and what we know generally with the use of corticosteroids and DMARDs from other inflammatory conditions, the desirable effects of inflammation control and steroid sparing effects do outweigh the undesirable harms of continuing with long term oral corticosteroids or the risks of blindness from uncontrolled inflammation.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒	While oral corticosteroids may be used for the control of inflammation, DMARDs are intended when there is concern with the long term use of corticosteroids, where corticosteroids are contraindicated or ineffective.

FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Methotrexate and azathioprine are currently listed on the EML albeit for different indications.
RESOURCE USE	**How large are the resource requirements?** Based on drug acquisition costs only **Methotrexate** More intensive [ ] Less intensive [X] Uncertain [ ] **Azathioprine (dose dependent)** More intensive [ ] Less intensive [ ] Uncertain [X] **Cyclosporine** More intensive [X] Less intensive [ ] Uncertain [ ]	**COSTS:** Min-max doses as stated in (Jabs D et al, 2000) Based on 70kg patient – dose rounded to nearest whole tablet/capsule MHP List 1 Jul 2023. Excludes monitoring costs and costs related to treatment of adverse effects. **Prednisone oral** **Dose:** 1mg/kg/day to max 80mg/day **Cost per patient per annum: R932-R1 065** **Methotrexate oral** **Dose:** 7.5 mg to 25 mg per week + folic acid 5mg daily **Cost per patient per annum: R303-832** **Azathioprine oral** **Dose:** 1mg – 4mg/kg/day **Cost per patient per annum: R737-R2 211** **Cyclosporine oral** **Dose:** 2.5 mg to 10 mg/kg/ day **Cost per patient per annum: R11 502-R40 258**
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	Methotrexate, azathioprine and cyclosporine are already used in clinical practice for the management of panuveitis and posterior uveitis but this condition has been omitted from the AH EML. Patients with concomitant systemic disease are also treated with these medicines.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	Methotrexate, azathioprine and cyclosporine are already used in clinical practice for the management of uveitis. Inclusion on the EML will improve equity of access, allow for standardisation of care and avoid potential delays with initiating treatment.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	July 2023	ZA	Methotrexate supported for the management of non-infectious posterior uveitis or panuveitis in patients who are refractory to corticosteroids or who require ongoing corticosteroids to maintain inflammation control.

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Appendix 1: Pre-specified PICO that was subsequently amended.

Population	Adult patients with non-infectious posterior uveitis or panuveitis Inclusion criteria: *Adult patients with severe posterior uveitis and panuveitis treated with the following non-biological DMARDs (methotrexate, azathioprine, cyclosporine).* *Note: The pre-specified PICO was limited to posterior and panuveitis (based on anatomical classification). Intermediate uveitis which affects the vitreous forms part of the back two thirds of the eye and is defined as part of the posterior segment. Although the condition may be classified by anatomic location, it is not clear if they are truly separate conditions and treatment recommendations across these anatomic locations generally overlap. A number of eligible studies in patients with posterior and panuveitis included patients with intermediate uveitis and have therefore been included in our review.* Exclusion criteria: • *Studies where the sole therapeutic focus for uveitis included: 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* • *Studies that focused on related immunological aetiologies where ocular manifestations were not specifically and independently analysed e.g. rheumatoid arthritis, multiple sclerosis* • *Studies related to the management of uveitis requiring surgical intervention or other therapeutic modalities: 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 uveitis, infection-related uveitis, HLAB27, Fuchs heterochromic uveitis, spondyloarthropathy uveitis* • *Studies in patient under 18 years of age*
Intervention	• Methotrexate (MTX), OR • Azathioprine (AZA), OR • Cyclosporine (CS) *The non-biologic, disease-modifying anti-rheumatic drugs (DMARDs) methotrexate and azathioprine were selected for review because they are the agents most utilized in clinical practice due to their cost and perceived efficacy i.e. they are already available on the EDL, albeit for non-ophthalmology indications. Cyclosporine was also selected as there have been anecdotal reports of the use of cyclosporine by specialists in tertiary state facilities for specific cases of severe uveitis due to the perceived efficacy of cyclosporine for select presentations of severe posterior uveitis and panuveitis e.g. Behçet's disease and Vogt-Koyanagi-Harada (VKH) disease.*
Comparator	• Oral corticosteroids
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.

Appendix 2: Database search

Pubmed Search strategy for SR and MA (conducted 9 November 2022)

Search	Query	Results
#9	Search: **#1 AND #4** Filters: **Meta-Analysis, Systematic Review**	11
#8	Search: **#1 AND #3** Filters: **Meta-Analysis, Systematic Review**	11
#7	Search: **#1 AND #2** Filters: **Meta-Analysis, Systematic Review**	14
#6	Search: **#1 AND #2** Filters: **Systematic Review**	14
#5	Search: **#1 AND #2**	798
#4	Search: **cyclosporine**	61,406
#3	Search: **azathioprine**	24,450
#2	Search: **methotrexate**	59,185
#1	Search: **uveitis**	41,709

Search terms for Cochrane Library and Epistemonikos: 'uveitiis' and 'panuveitis'

Pubmed search strategy for RCTs (conducted on 25 January 2023)

Search	Query	Results
#12	Search: **#7 AND #10** Filters: **Randomized Controlled Trial**	1
#11	Search: **#9 AND #10** Filters: **Randomized Controlled Trial**	3
#13	Search: **#5 AND #10** Filters: **Randomized Controlled Trial**	0
#10	Search: **uveitis** Filters: **Randomized Controlled Trial**	510
#9	Search: **methotrexate** Filters: **Randomized Controlled Trial, from 2021 - 2023**	165
#8	Search: **methotrexate** Filters: **from 2021 - 2023**	4,597
#2	Search: **methotrexate**	59,578
#7	Search: **cyclosporine** Filters: **Randomized Controlled Trial, from 2021 - 2023**	49
#6	Search: **cyclosporine** Filters: **from 2021 - 2023**	2,284
#3	Search: **cyclosporine**	61,606
#5	Search: **azathioprine** Filters: **Randomized Controlled Trial, from 2021 - 2023**	21
#4	Search: **azathioprine** Filters: **from 2021 - 2023**	1,225
#1	Search: **azathioprine**	24,542
#0	Search: **Clipboard**	4

Appendix 2: Excluded studies – Title and abstract screen

No	Author	Date	Reason for Exclusion
TITLE & ABSTRACT REVEIW			
1	Angeles-Han ST	2019	Wrong patient population
2	Welzel T,	2021	Wrong patient population
3	Jari M	2020	Wrong patient population
4	Simonini G	2013	Wrong patient population
5	Maese J	2018	Wrong patient population
6	Gómez-Gómez A (PMID: 29049193)	2017	Wrong patient population
7	Jachiet M	2016	Wrong patient population
8	Halyabar O,	2019	Wrong patient population
9	Tallouzi MO	2019	Wrong patient population
10	Urruticoechea-Arana A	2019	Wrong treatment
11	Leccese P	2019	Wrong patient population
12	Hatemi I	2015	Wrong patient population & treatment
13	Yilmaz U,	2022	Wrong patient population
14	Demir S,	2019	Wrong patient population
15	Taylor J,	2014	Wrong patient population
16	Gómez-Gómez A (PMID: 29049193)	2017	Wrong patient population
17	Hutchison DM	2022	Wrong patient population
18	Ozguler Y	2018	Wrong patient population
19	Yilmaz U	2020	Wrong patient population
20	Christopher J B	2016	Wrong intervention
21	Brady CJ	2021	Wrong intervention
22	Barry RJ	2018	Wrong intervention
23	Rebton WD	2022	Wrong patient population
24	Leung TG	2014	Wrong patient population
25	Davies GR	2007	Wrong patient population
26	Horn J	2020	Wrong patient population
27	Shuster AK	2016	Wrong patient population
28	Hu K	2021	Wrong patient population
29	Lim BX	2016	Wrong patient population
30	Juthani VV	2017	Wrong patient population
31	Kroom F	2015	Wrong patient population
32	Denniston AK,	2015	Not treatment related
FULL TEXT REVIEW			
33	Rossi DC	2019	Not a systematic review
34	Espinosa G	2020	Consensus Statement
35	Saenz A	2000	Disease focused (Behcet's)
36	Hatemi G	2008	Disease focused (Behcet's)
37	Dammacco R	2022	Disease focused (RA)

Appendix 3: Types of outcomes measures considered in the 2022 Cochrane review and how they were defined or measured. (Key time points for these outcomes include follow-up at 6 and 12 months.)

CRITICAL OUTCOMES	Reported in SoF tables (Appendix 8) (Y/N)
Proportion of participants achieving control of inflammation, defined as a two-step reduction in vitreous haze grade/score or decrease to grade 0 (Jabs 2005; Nussenblatt 1985); or clinically comparable study definition	Y
Change in best corrected visual acuity (BCVA), measured as a continuous outcome on a logMAR (logarithm of the minimum angle of resolution) chart (or equivalent)	Y
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart)	Y
Proportion of participants with macular edema, confirmed by optical coherence tomography (OCT) (macular thickness, at the center point ≥ 240 µm) or by fluorescein angiogram (macular leakage ≥ 0.44 disc areas) or by slit-lamp biomicroscopy through a dilated pupil	Y
IMPORTANT OUTCOMES	
Mean time to relapse	
Reduction in cumulative hazard of disease relapse	
Proportion of participants with change in anterior chamber flare and cells, as defined by the SUN Working Group	
Mean change in central macular thickness (CMT), measured in microns on OCT imaging	
Change (resolution, yes/no) in other activity domains, including vitreous cells; vitreous 'snow-balls'; chorioretinal inflammatory lesions; and retinovascular inflammation	
Proportion of participants to achieve steroid-sparing control	Y
Proportion of participants to achieve reduction in oral steroid dose (to < 10 mg/day)	
Cost-effectiveness, e.g. the incremental cost-effectiveness ratio (ICER)	
Mean change in vision-related quality of life, measured using the Visual Function Questionnaire 25 (VFQ-25), or other validated questionnaire (Mangione 2001)	
Mean change in general health-related quality of life (HRQoL), measured using the EuroQoL five dimensions questionnaire (EQ-5D), or other validated questionnaire	
Adverse events: ◦ Proportion of participants experiencing any adverse effects, including ocular and systemic complications ◦ Proportion of participants experiencing complications or requiring cessation of medication, such as bone marrow suppression (absolute neutrophil count [ANC] < 1500 cells/ µL), hepatotoxicity (elevation in liver enzyme alanine transaminase [ALT] > 45 IU/L in men and ALT > 35 IU/L in women), as well as severe allergic reaction ◦ Proportion of participants experiencing ocular complications, including elevated eye pressure (≥ 21 mmHg), lens opacity, hypotony, choroidal neovascular membrane	Y (requiring cessation of medication)

Appendix 4: Characteristics of RCTs included in the Cochrane review (E Mayhew RG, 2022)

CITATION	STUDY DESIGN	POPULATION	INTERVENTION	COMPARISON	OUTCOMES MEASURED	Y= RCT included in (Gomez-Gomez A , 2020) & QUALITY RATING
(Cuchacovich M et al, 2010)	RCT	Adults N=21 VKH=100%	AZA + prednisone (n = 12) • Azathioprine dosed 2 mg to 3 mg/kg body weight/day for at least 1 year • Prednisone maintenance dose of either 5 mg or 10 mg/day for 1 year	CsA + prednisone (n = 9) • CSsA 3 mg to 5 mg/kg body weight/day for at least 1 year • Prednisone maintenance dose of either 5 mg or 10 mg/day for 1 year	Change in logMAR BCVA at 54 weeks	
(Deuter C, et al, 2018)	RCT	Adults N=41 VKH=nil	mycophenolate mofetil in combination with topical or oral steroid therapy (n=22) Tapering of oral prednisolone continued over approximately 3 months to a maintenance dose of 5 mg/day, plus • EC-MPS (Myfortic;Novartis, Basel, Switzerland) at a dose of 720 mg/day during the first week and 1440 mg/day from week 2 onwards.	Standard of care (n=19) Started on oral prednisolone (at an initial dose of 1 mg/kg bodyweight at the screening visit, followed by slow tapering over 3 months to maintenance dose of 5 mg/day.	Median time from study entry to the first relapse. Definition of relapse (at least 1 of the following): deterioration of BCVA ≥ 3 lines compared to best BCVA from baseline; at least 2-step increase of vitreous haze compared to lowest grade of vitreous haze from baseline or increase from 3+ to 4+; at least 2-step increase of anterior chamber cells compared to lowest grade of anterior chamber cells from baseline or increase from 3+ to 4+; new onset or worsening of pre-existing cystoid macular edema, proven by Optical Coherence Tomography (OCT); new onset or worsening of retinal vasculitis (sheating and/or leakage of retinal vessels), proven by fluorescein angiography (FA)	
(De Vries J et al, 1990)	RCT	Adults N=27 VKH=nil	cyclosporine in combination with oral steroid therapy (n = 14) • cyclosporine in a single dose of 10 mg/kg/day with dose reduction of 25% of dose of cyclosporine allowed, combined with • low dose of prednisone (0.3-20 mg/kg/day)	Placebo in combination with oral steroid therapy: (n=13) • placebo, with dose reduction of placebo allowed, combined with • low dose of prednisone (0.3-20 mg/kg/day)	Best corrected visual acuity: "best corrected visual acuity was determined at 6 m with charts which contain Landolt C optotypes ranging in unequal steps from a visual angle of 10' (that is visual acuity 20/ 200) to one of 0 5' (visual acuity 20/10). When the visual acuity of a patient was below 20/200 a second ordinal scale was used, namely, finger counting (FC), hand movements (HM), light perception (LP), and no light perception (NLP). In order to make comparisons between the two measurement scales the visual acuity of each eye was given a rank number. For example, visual acuities of hand movements in one eye and 20/80 in the other	Y *(Ref 22)* Jadad (good quality)

					were given the rank numbers 2 and 8 respectively."	
(Lee R et al, 2012)	RCT (non-inferiority)	Median age 31.3 N=35 VKH=nil	tacrolimus monotherapy +/- in combination topical steroid therapy (n = 16) All trial recruits started tacrolimus either before, or at the time of, enrolment in conjunction with 10 mg or more prednisone daily. Participants whose disease was inactive for 4 weeks while taking 10 mg prednisone daily in the presence of target tacrolimus levels (trough serum level of 8 ng to 12 ng/mL) were allocated randomly to: Intervention: tacrolimus and prednisone tapered rapidly and discontinued over 2 weeks	tacrolimus dual therapy in combination with oral steroid therapy +/- topical steroid therapy (n = 19) Comparator: tacrolimus and oral prednisone (10 mg/day for 3 months then tapering to a minimum of 7.5 mg/day).	Change in logMAR VA between randomization and study completion/withdrawal	
(Murphy C et ak, 2009)	RCT	Adults N=37 VKH=nil	cyclosporine in combination with oral steroid therapy (n = 18) 2.5 to 5.0 mg/kg daily, adjust based on clinical response and blood level up to 100 to 225 ng/L or lower with remission • Oral prednisone dosage not specified	tacrolimus in combination with oral steroid therapy (n = 19) 0.03 to 0.08 mg/kg daily, adjust based on clinical response and blood level up to 8 to 12 ng/L or lower with remission • Oral prednisone dosage not specified	logMAR BCVA • Binocular indirect ophthalmoscopy (BIO) score • Treatment failures and relapses	Y *(Ref 24)* Jadad = good quality
(Nussenblatt RB, et al, 1991)	RCT	Adults and children (10-61 years) N=56 VKH=5.4%	cyclosporine A (n = 28) 10 mg/kg of body weight/day as a starting dosage. Dosage of each therapeutic alternative depended on the clinical status of the participant. The dosage of cyclosporine could be as high as 15 mg/kg of body weight/day, but only for a short interval.	prednisolone (n = 28) Participants were given a dose of prednisolone (64 mg) that was pharmacologically equivalent to 80 mg of prednisone if they weighed 70 kg or more, or the equivalent of 60 mg of prednisone (42 mg of prednisolone) if they weighed less than 70 kg. Maximal dose of prednisolone was the prednisone equivalent of 80 mg/day for all participants in that therapeutic alternative	Treatment success at three months: • improvementin visual acuity of 15 letters [three lines] or more in at least one eye or an improvement of at least two increments on the vitreal haze scoring scheme, no more than 20 mg/day of prednisone); or • lack of treatment failure (failure reached if after maximal therapy of one week, visual acuity in one eye decreased 10 letters from baseline value, or if disease appeared to be progressing into the macula, or if there was uncontrolled systemic hypertension, diabetes, ulcer, or impaired hepatic function	Y *(Ref 23)* Jadad = low quality
(Nussenblatt RB et al, 1993)	RCT Parallel group (4-arm)	Adults Mean age: 33.8 N=32 VKH=3.1%	Cyclosporine A in combination with oral steroid therapy •15 mg prednisone orally which could be increased to 30 mg/day plus • escalating doses of cyclosporine A (2.5, 5, 7.5, or 10 mg/kg body weight/day) in two divided doses 12 hours apart, diluted in juice		Therapeutic success: visual acuity improvement of 2 lines or more over baseline or a decrease of two increments to the vitreous inflammation in either eye) at 16 weeks	Y *(Ref25)* Jadad = low quality

			Intervention: cyclosporine G in combination with oral steroid therapy • 15 mg prednisone orally which could be increased to 30 mg/day plus • escalating doses of cyclosporine G (2.5, 5, 7.5, or 10 mg/kg body weight/day) in two divided doses 12 hours apart, diluted in juice			
(Ono T et al, 2021)	RCT (non-inferiority trial parallel group VKH=100%	Adults (N=70)	Cyclosporin A combination with prednisolone (n = 34) Cyclosporine (3 mg/kg/day) was administered daily with • Oral prednisolone at "a daily dose of 1 mg/kg or 60 mg (the smaller dose was adopted for each patient) for 1 week, followed by 50 mg for another week. The dose was then reduced every 2 weeks with the following dosages: 40, 35, 30, 25, 20, 17.5, 15, 12.5, 10, 7.5, 5, and 3 mg, after which oral prednisolone was completely discontinued." However, acute hyponatremia, nausea, and vomiting were observed in the first participant in the combination group. Then, for safety purposes, the combination therapy protocol was changed to cyclosporine initiation when oral prednisolone reached a daily dose of 35 mg (4 weeks after prednisolone initiation) until completion of the oral prednisolone administration.	corticosteroid pulse therapy (n = 36) V methylprednisolone 1000 mg (or 500 mg in certain cases, such as elderly cases) for the first 3 days, then • Switch to oral prednisolone in the same dosing schedule as the other arm above.	ncidence of a composite of recurrence (serous retinal detachment by OCT; recurrence of systemic VKH symptoms) or worsening (two-step increase in AC cells and vitreous haze, or an increase from grade 3+ to 4+ according to SUN criteria)	
(Rathinam SR et al, 2014)	RCT parallel grp VKH=53.8%	Adults N=80	methotrexate in combination with topical or oral steroid therapy (n = 41) • Maintenance dose: 25 mg a week oral methotrexate • Induction dose for the first two run-in weeks: 15 mg a week oral methotrexate	mycophenolate mofetil in combination with topical or oral steroid therapy (n = 39) • Maintenance dose: 1 g twice daily oral mycophenolate mofetil • Induction dose for the first two run-in weeks: 500 mg twice daily oral mycophenolate mofetil	• Ttreatment success as defined "achieving corticosteroid-sparing control of inflammation in both eyes at the 5- and 6-month visits. This was defined by the following: ◦ ≤ 0.5 + anterior chamber cells, ≤ 0.5 + vitreous cells, ≤ 0.5 + vitreous haze, and no active retinal or choroidal lesions; ◦ ≤ 10 mg of oral prednisolone daily and ≤ 2 drops of prednisolone acetate 1% (or equivalent) a day; ◦ ≤ no declaration of treatment failure because of intolerability or safety concerns."	Y *(Ref 26)* Jadad = good quality
(Rathinam SR et al, 2019)	RCT parallel grp VKH=43.1%	Adults N=216	methotrexate in combination with topical or oral steroid therapy (n = 107) • Initial dose 15 mg by mouth weekly for 2 weeks, then increased to maintenance dose of 25 mg by mouth	: mycophenolate mofetil in combination with topical or oral steroid therapy (n = 109) Initial dose 500 mg, twice a day, for 2 weeks, then increased to maintenance dose of 1.5 mg by mouth, twice a day; dose	Proportion with treatment success - defined by the following: less than or equal to 0.5 + anterior chamber cells by SUN criteria, less than or equal to 0.5 + vitreous haze clinical grading using the NEI	

			weekly; dose reductions allowed for intolerability	reductions allowed for intolerability	scale, and no active retinal or choroidal lesions; and • no more than 7.5 mg of oral prednisone daily and less than or equalto 2 drops of prednisolone acetate 1% (or equivalent) per day; and • no declaration of treatment failure due to intolerability or safety concerns.	
(Wiederholt M et al, 1986)	RCT parallel grp	Adults N=8 VKH= not reported	cyclosporine in combination with topical steroid therapy (n = 4 Cyclosporine A treatment was carried out with the drinking solution "Sandimmun" or cyclosporine in castor oil, diluted in milk and given in 2 doses, twice a day; ~8 mg/kg per day. After 1 week dose was changed so that concentration of cyclosporine A was ~400-800 ng/mL. Levels were determined 12 hours after the last intake.	standard of care (e.g. topical steroids, with or without systemic steroids) (n = 4) Prednisolone given in a tablet form of 80 mg to 100 mg per day for 2 weeks and then reduced in alternating therapy (every other day) within three months	Visual acuity	

Appendix 5: Summary of 3 small RCTs identified in (Gomez-Gomez A , 2020) and not included in the Cochrane review (E Mayhew RG, 2022)

Citation	Study and size	Comparison & intervention	Description	Reason for exclusion
(de Smet MD, 1992)	RCT (n=10)	Cyclosporine +/- ketoconazole	Patient with endogenous uveitis in clinical remission attributable to treatment with cyclosporine and prednisone. were randomly assigned to ketoconazole or placebo to assess relapse of disease over a 3 month follow up	Wrong comparator
(Ozyazgan Y, 1992)	RCT (n=23)	cyclosporin A versus pulsed cyclophosphamide	Cyclosporin A 5 mg/kg/day versus monthly 1 g intravenous boluses of cyclophosphamide was conducted among 23 patients with Behçet's syndrome and active, potentially reversible uveitis. The trial was unmasked after a mean of 12 (SD 2) months for the cyclosporin A group (n = 12) and a mean of 10 (SD 3) months for the cyclophosphamide group (n = 11). During the initial 6 months the visual acuity significantly improved ($p < 0.001$) in the cyclosporin A group whereas this was not observed in the cyclophosphamide group. The subsequent follow-up of patients up to 24 months suggested that the initial improvement in visual acuity with cyclosporin A was not sustained.	Wrong comparator
(Shen E, 2016)	Sub-analysis of RCT (n=27)	25 mg oral methotrexate weekly or 1 g mycophenolate mofetil twice daily, with a corticosteroid taper.	Twenty-seven patients were randomized to methotrexate and 16 to mycophenolate mofetil; 30 had acute VKH. The odds of achieving corticosteroid-sparing control of inflammation with methotrexate were 2.5 times (95% CI: 0.6, 9.8; P = .20) the odds with mycophenolate mofetil, a difference that was not statistically significant. The average improvement in visual acuity was 12.5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. On average, visual acuity for patients with acute VKH improved by 14 more ETDRS letters than those with chronic VKH (P < .001), but there was no difference in corticosteroid-sparing control of inflammation (P = .99). All 26 eyes with a serous retinal detachment at baseline resolved, and 88% achieved corticosteroid-sparing control of inflammation. The majority of patients treated with antimetabolites and corticosteroids were able to achieve corticosteroid-sparing control of inflammation by 6 months. Although patients with acute VKH gained more visual improvement than those with chronic VKH, this did not correspond with a higher rate of controlled inflammation.	VKH = 100% *Sub-analysis of the* (Rathinam SR et al, 2014) study

Appendix 6: Summary of studies included in the AAO guideline for methotrexate, azathioprine and cyclosporine.

	Study description	Efficacy outcomes	Adverse effects	Comments
METHOTREXATE				
(Samson CM et al., 2001) Methotrexate therapy for chronic non-infectious uveitis	Retrospective non-comparative interventional case series at 1 institution in US (1985-1999). n=160 Panuveitis = 15%, Intermediate and posterior uveitis = 20% Anterior disease = 65%	Control of inflammation = 76.2% Steroid-sparing effect = 56% Visual acuity maintained or improved = 90%	Discontinuation due to side effects = 18% Potentially serious adverse reactions = 8.1% (n=8 with persistent elevated liver enzymes and n=3 with leukopenia)	Patients were typically started on MTX 7.5mg orally, once a week with 1 mg/day folic acid. MTX was increased at dose increments of 2.5 to 5mg every six weeks as needed until a therapeutic response was achieved. Average maintenance dose of 12.3mg per week (range, 7.5-40mg weekly). Concomitant cyclosporine therapy n=14. Other immunosuppressant n=2.
(Gangaputra S et al. , 2009) Methotrexate for non-infectious ocular inflammation *Sub-study of SITE study*	Retrospective cohort study across 4 clinics in US (1979-2007). n=384 (639 eyes) Anterior uveitis = 32.8% Intermediate uveitis 9.9% Posterior or panuveitis= 21.4% Scleritis =14.6% Ocular mucous membrane pemphigoid = 15.1% Other forms of ocular inflammation = 6.3%	Complete suppression of inflammation sustained for ≥28 days achieved within 6 months: Anterior uveitis =55.6% Intermediate uveitis = 47.4% Posterior or panuveitis =38.6% Scleritis =56.4% Ocular mucous membrane pemphigoid =39.5% Other forms of ocular inflammation=76.7% Corticosteroid-sparing effects (sustained suppression of inflammation with prednisone ≤10 mg/d) within 6 months: Anterior uveitis=46.1% Intermediate uveitis -41.3% Posterior or panuveitis =20.7% Scleritis =37.3% Ocular mucous membrane pemphigoid =36.5% Other forms of ocular inflammation =50.9% Overall, success within 12 months: 66% for sustained control 58.4% for corticosteroid sparing ≤10 mg) Remission 11% (n=43)	Discontinuation within 1 year due to : Ineffectiveness 13% (n= 50); Side effects 16% (n=60), generally reversible with dose reduction or discontinuation	Duration of therapy: methotrexate monotherapy for a median of 0.73 years (interquartile range, 0.31–1.59)
AZATHIOPRINE				
(Pacheco PA et al. , 2008) Azathioprine in the management of autoimmune uveitis	Prospective, open-label observational study (1998-2004) n=27	Complete response =92% Remission at 12 months =85% (n=23) Relapse = 12% (n=3) **Secondary outcomes:**	*Predetermined indications for withdrawal of AZA were leukocyte count <3500/mm3, platelet count <105/mm3, Hb <7g/dL or LFT*	Patients were judged to require a second-line agent on the basis of either the diagnosis of active disease resistant to a dose of 30 mg/day of prednisolone, or

	Anterior uveitis (n=3) Pars planitis (n=1) Idiopatic panuveitis (n=4) VKH (n=8) Behcet disease (n=3), Choroidoretinopathies (n=8) Pred + AZA Prednisolone was started at a dose of 0.5 mg/kg/day for 4 weeks and tapered to a maintenance dose of 5–10 mg/day during the next 3 months, titrated against disease activity; if the inflammatory activity continued beyond 4 weeks then the dose was tapered more gradually. Prednisolone was then continued for 1 year at a maintenance dose of 5–10 mg/day. AZA was given in a dose of 2–3 mg/kg body weight/day for 1 year	Improved BVCA = 59% (n=16) Maintained BVCA = 22% (n=6) BVCA worse =19% (n=5) *Statistically significant improvement in BVCA* Corticosteroid –sparing: Median daily dose reported as: Baseline: 45 mg/day (range, 25–60). At 1 month: 35 mg/day (20–40); At 3 months: 15 mg/day (10–30); At 6 months, 5 mg/day (5–10).	*increase to more than double baseline.* Ineffective: n=1 Adverse effects: None of the patients needed discontinuation of AZA	disease in remission, but requiring a maintenance dose > 20 mg/day prednisolone to remain in remission. All study participants were caucasian patients. 2 patients with Behcets received additional immunosuppressive treatment
(Pasadhika, S et al, 2009) Azathioprine for Ocular Inflammatory Diseases *Sub-study of SITE study*	n=145 Uveitis =63% of which *Anterior dx =23%* *Intermediate =20%* *Posterior/panuveitis=57%* Scleritis = 11% MMP = 23% Other =3% (three with peripheral ulcerative keratitis and two with orbital inflammation).	*Success in achieving complete inactivity of inflammation sustained for at least 28 days varied by the site of ocular inflammation.* Sustained control of inflammation (for at least 28 days) by 6 months: 41% (95% confidence interval (CI), 31-52% Sustained control of inflammation (for at least 28 days) by 12 months: 62% (95% CI, 50-74%) Complete inactivity of inflammation (for at least 28days) within 6 months: Anterior uveitis=24% (95% CI, 10-52%) Intermediate uveitis = 69% (95% CI, 41-93%) Posterior or panuveitis patients = 44% (95% CI, 28-64%) MMP =43% (95% CI, 26-66%) Scleritis =20% (95% CI, 3-80%) Corticosteroid-sparing (patients on prednisolone >10mg reduced at 12 months to </=10mg per day: 46.9% (95% CI, 36.9 - 58.0) </=5mg per day: 40.6% (95% CI, 30.8 - 52.2) 0mg per day =9.5% (95% CI, 5.2 - 17.1) *Posterior or panuveitis : 7% (95% CI, 2-21%) of participants completely discontinued prednisone while maintaining sustained control of inflammation for at least 28 days.*	Discontinuation (median follow up of 230 days)=68% Estimated discontinuation in first year: Ineffectiveness =17% (further 9% has add on therapy) Adverse effects =24% (Gi upset, bone marrow suppression, elevated LFTs, infection, allergic reaction) Not specified=15% Remission (at end of study period) =14%	Patients with HIV infection and those with infectious ocular inflammation were excluded At the inception of azathioprine therapy, 48% of patients were receiving systemic prednisone > 10 mg daily. Patients with intermediate uveitis and mucous membrane pemphigoid generally were more likely to achieve both control of inflammation and corticosteroid-tapering success than the other groups. Prior use of antimetabolites other than azathioprine was associated with an approximate 60% lower likelihood of control of inflammation. Intermediate uveitis responded significantly better to azathioprine than anterior uveitis, with 89.8% achieving complete control of inflammation sustained for at least 28 days and 68.2% meeting corticosteroid-sparing objectives before 12 months of therapy. *This pattern of*

				response was not observed in our study of patients treated with methotrexate, (Gangaputra study) suggesting that azathioprine might be especially effective for intermediate uveitis.
(Saadoun et al, 2010) Azathioprine in Severe Uveitis of Behcet's Disease	Retrospective cohort study at one site in France (1970-2006) in patients with Behcet's Disease n=157 Active posterior uveitis or panuveitis, had to receive corticosteroids and azathioprine Oral AZA 2.5 mg/kg/day initiated in association with oral prednisone (0.5–1 mg/kg/day)	Partial or complete response) of ocular lesions =92.9% After a mean +/-SD followup of 71.5 +/- 68.6 months: Complete responders = 51.6% Partial responders =41.4% Non-responders =7% Visual acuity : In better eye progressed from 4.49 to 6.8/10 (P< 0.0001) Worse eye progressed from 4.18 to 6.45/10 (P<0.0001) Loss of useful vision (baseline) =37.6% Loss of vision (end of followup) =19.6% (P< 0.01) Steroid-sparing: The mean +/- SD oral prednisone threshold decreased significantly from 55.3+/- 13.8 mg/day (range 25– 80) to 10.5 +/- 6.5 mg/day (range 5–25; P< 0.001). Non-responders (n=14) Relapse rates: Cumulative relapse rate at 1yr=11% Cumulative relapse rate at 5yrs=32.6%	Side effects of azathioprine were noted in 67 patients (42.6%) and mainly included gastrointestinal events (19.1%), cytopenia (18.4%), and infections (17.8%). There were 3 withdrawals due to toxicity during azathioprine therapy, 2 for hepatotoxicity and 1 for septicemia.	Thirty-one patients (19.6%) had been previously treated by another regimen (i.e., cyclophosphamide, cyclosporin, chlorambucil, and interferon [IFN] alfa-2a) The median duration of azathioprine therapy was 3.4 years (range 1–5 years)
(Kim et al, 2007) Use of low dose azathioprine in VKH	Retrospective case series at a single centre in Seoul (1999-2005) N=34 (VKH) All patients were treated with high-dose systemic corticosteroid therapy with either oral prednisone (1.0 mg/kg/day) or intravenous methylprednisolone (1000 mg/day) followed by oral corticosteroids over 6 months. Topical corticosteroids and cycloplegics were also used for the control of anterior segment inflammation.	*Acute uveitic* Corticosteroid sparing=86.5% Median time to corticosteroid sparing = 4 months (range, 1–8) *Chronic recurrent group* Corticosteroid sparing=90% Median time to corticosteroid sparing =2.5 months (range 1–9) *There were no significant differences in recurrence rate, cumulative corticosteroid dose, and ocular complication rates*	Adverse effects of AZA GI discomfort n=3 Mildly elevated LFTs n=2 All patients showed improvement after the dose was decreased or azathioprine therapy was discontinued	In 2 patients, cyclosporine (2.5–5.0 mg/kg/day) was added due to insufficient control of inflammation.

	Azathioprine at 1.0– 2.5 mg/kg/day was added in the following cases: (1) If serous retinal detachment associated with acute visual disturbance was persistent or recurred despite high-dose systemic corticosteroid therapy with slow tapering (2) Chronic recurrent uveitis with posterior involvement nonresponsive to corticosteroid therapy 3) Intolerable side effects of systemic corticosteroid therapy. According to the time phase when azathioprine was given, patients with azathioprine therapy were divided into 2 groups: *Acute uveitic phase (evidence of bilateral diffuse choroiditis such as serous retinal detachment).* *Chronic recurrent phase (phase when there was recurrent or chronic uveitis in patients with a history of early manifestations of VKH disease and ocular depigmentation).* Patients receiving AZA=47.1% Corticosteroid only =52.9%	*between the azathioprine therapy group and corticosteroid group.*		
CYCLOSPORINE				
(Kacmaz et al, 2010) Ciclosporin for ocular inflammatory diseases *Sub-study of SITE study*	Retrospective cohort study across 4 clinics in the US (1979-2007) N=373 (681 eyes) Anterior uveitis = 20.1% Intermediate uveitis=26.5% Posterior or panuveitis =45.8% Scleritis = 4.0% Ocular mucous membrane pemphigoid=1.6% Other forms of ocular inflammation =1.9% including lichen planus of conjunctiva, peripheral ulcerative keratitis, and idiopathic orbital pseudotumor	Control of inflammation for at least 28 days at 1 year = 51.9% (45.5–58.5) Controlled inflammation (no activity at 12 months) Anterior uveitis = 54.3% (40.0–69.9) Intermediate uveitis= 51.8% (40.4–64.2) Posterior or panuveitis = 51.7% (42.6–61.6) Scleritis = 62.3% (29.6–93.3) Ocular mucous membrane pemphigoid= 20.0% (3.1–79.6) Other forms of ocular inflammation = 33.3% (5.5–94.6) Corticosteroid-sparing at (spanning at least 28 days with corticosteroid tapered to </=10mg) at 6 months Anterior uveitis=28.5% Intermediate uveitis = 24.1% Posterior or panuveitis patients = 16.2% Scleritis =52.8% Ocular mucous membrane pemphigoid= 20%	Discontinuation at 1 year Toxicity=10.7% (95% CI, 7.6–15.1) Renal toxicity and hypertension most common Unknown=12.4%	Compared with patients aged 18 to 39 years, discontinuation for toxicity was progressively more frequent with increasing age, particularly among patients aged between 55 and 64 years (adjusted RR = 3.25; CI, 1.54–6.88) and patients aged more than 65 years (adjusted RR = 5.66; CI, 2.14–14.98, P =0.0005). Cyclosporine doses of 151 to 250 mg/day (approximately 2–3.5 mg/kg/day assuming an average body weight) were associated with an increased likelihood of control of inflammation (adjusted relative risk [RR]= 1.89; CI, 1.15–3.09) with respect to 150 mg/day or less, but the likelihood of corticosteroid-sparing success was similar across all dosage groups. Doses more than 250

		Corticosteroid-sparing at 1 year = 36.1% (95% CI, 30.5–42.2). Only 8.2% of the total population were able to discontinue corticosteroids completely at 12 months		mg/day were not associated with further therapeutic advantage. Approximately half of patients continued taking cyclosporine throughout the available follow-up, with 65 patients (17%) subsequently starting another immunosuppressive drug along with cyclosporine and 126 patients (34%) continuing cyclosporine as the only noncorticosteroid immunosuppressive drug for the remainder of (variable) follow-up

Appendix 7: Summary of findings table from the Cochrane review (E Mayhew RG, 2022)

SUMMARY OF FINDINGS

Summary of findings 1. Non-biologic disease-modifying antirheumatic drugs (DMARDs) versus steroid for NIIPPU

Non-biologic disease-modifying antirheumatic drugs (DMARDs) versus steroid for NIIPPU

Patient or population: NIIPPU

Setting: ophthalmology clinics (Netherlands, Germany)

Intervention: DMARDs (CsA, EC-MPS plus steroid)

Comparison: control (placebo plus steroid or steroid alone)

Outcomes	Anticipated absolute effect (95% CI)*		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with control	Assumed risk with DMARDs				
Proportion of participants achieving control of inflammation (higher number of events is better) Follow-up: 0 to 12 months	21 events per 100 participants	**59 events per 100 participants** (2 to 100)	**RR 2.81** (95% CI 1.10 to 7.17)	41 (1 RCT)	⊕### **Very low**[a,b]	One study comparing CsA plus steroid with placebo plus steroid also reported this outcome but used CsA doses no longer in practice (De Vries 1990); thus, we did not include it in meta-analysis.
Change in BCVA (lower logMAR indicate better vision) Follow-up: 0 to 6 months	Right eyes MD -0.03 logMAR (95% CI -0.96 logMAR to 0.90 logMAR); Left eyes MD -0.10 logMAR (95% CI -0.27 logMAR to 0.07 logMAR)		-	82 eyes (1 RCT)	⊕### **Very low**[a,b]	
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart) (higher scores indicate better vision)	No data were reported for this outcome		-	-	-	-
Proportion of participants with confirmed macular edema	No data were reported for this outcome		-	-	-	-

(lower number of events is better) Follow-up: 0 to 6 months					
Proportion of participants achieving steroid-sparing control (higher number of events is better) Follow-up: 0 to 12 months	No data were reported for this outcome	-	-	-	-
Proportion of participants experiencing complications or requiring cessation of medication (lower number of events is better) Follow-up: 0 to 12 months	See comment	-	41 (1 RCT)	⊕### **Very low**[b,c]	One event reported in DMARDs group (RR 2.61, 95% CI 0.11 to 60.51). Another study reported this outcome but used CsA doses no longer in practice (De Vries 1990).

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

BCVA: best-corrected visual acuity; **CI:** confidence interval; **CsA:** cyclosporin A; **DMARD**: disease-modifying antirheumatic drug;**EC-MPS:** enteric-coated mycophenolate sodium; **logMAR:** logarithm of the minimum angle of resolution;**MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence:
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[a]Downgraded (-2) for risk of bias (unclear risk of bias for the randomization process, deviations from intended interventions, and high risk of bias overall)
[b]Downgraded (-1) for imprecision (small sample size)
[c]Downgraded (-2) for risk of bias (unclear risk of bias for the randomization process and missing outcome data, and high risk of bias for measurement of outcome, selection of the reported result, and high risk of bias overall)

Summary of findings 2. Methotrexate versus mycophenolate for NIIPPU

Mycophenolate versus methotrexate for NIIPPU
Patient or population: NIIPPU
Setting: ophthalmology clinics (India, United States, Australia, India, Mexico, Saudi Arabia)
Intervention: methotrexate

Comparison: mycophenolate

Outcomes	Anticipated absolute effect (95% CI)*		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with mycophenolate	Assumed risk with methotrexate				
Proportion of participants achieving control of inflammation§ (higher number of events is better) Follow-up: 0 to 6 months	55 events per 100 participants	**67 events per 100 participants** (55 to 88)	**RR 1.23** (1.01 to 1.50)	261 (2 RCTs)	⊕⊕⊕⊝ **Moderate**[a]	
Change in BCVA (lower logMAR indicate better vision) Follow-up: 0 to 6 months	The mean BCVA score across the control group ranged from -0.12 to -0.19 logMAR	**The mean logMAR was 0.01 higher (worse) on average** (0.04 lower to 0.05 higher logMAR)		490 eyes (2 RCTs)Φ	⊕⊕⊕⊝ **Moderate**[a]	
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart) (higher scores indicate better vision) Follow-up: 0 to 6 months	No data were reported for this outcome		-	-	-	-
Proportion of participants with confirmed macular edema (lower number of events is better) Follow-up: 0 to 6 months	46 events per 100 participant eyes	**23 events per 100 participant eyes** (9 to 60)	**RR** 0.49 (0.19 to 1.30)	35 eyes (1 RCT)†	⊕⊝⊝⊝ **Very low**[b,c]	
Proportion of participants achieving steroid-sparing control§ (higher number of events is better) Follow-up: 0 to 6 months	55 events per 100 participants	**67 events per 100 participants** (55 to 88)	**RR 1.23** (1.01 to 1.50)	261 (2 RCTs)	⊕⊕⊕⊝ **Moderate**[a]	
Proportion of participants experiencing complications or requiring cessation of medication (lower number of events is better)	7 events per 100 participants	**7 events per 100 participants** (3 to 17)	**RR 0.99** (0.43 to 2.27)	296 (2 RCTs)	⊕⊕⊝⊝ **Low**[a,d]	

Follow-up: 0 to 6 months

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

BCVA: best-corrected visual acuity; **CI:** confidence interval; **logMAR:** logarithm of the minimum angle of resolution;**MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VKH:** Vogt-Koyanagi-Harada

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence:
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[3]Study primary outcome of steroid sparing control of inflammation defined as ≤ 0.5 + anterior chamber cells, ≤ 0.5 + vitreous cells, ≤ 0.5 + vitreous haze, and no active retinal or choroidal lesions; ≤ 2 drops of prednisolone acetate 1% a day in both studies and daily prednisolone ≤ 10 mg in one study and ≤ 7.5 mg/day in the other study
[b]Visual acuity of uveitic eyes only
[f]Subgroup of VKH participants' eyes with macular edema at baseline

[a]Downgraded (-1) for imprecision (small sample size)
[b]Downgraded (-1) for indirectness (single study subgroup of VKH in India)
[c]Downgraded (-2) for serious imprecision (small sample size)
[d]Downgraded (-1) for risk of bias (both studies have some concern for risk of bias in outcome measurement)

Summary of findings 3. Steroids with or without azathioprine versus cyclosporine A for NIIPPU

Steroids with or without azathioprine versus cyclosporine A for NIIPPU						
Patient or population: NIIPPU **Setting:** ophthalmology clinics (Germany, Japan, Chile, USA) **Intervention:** Steroids with or without azathioprine (oral steroids, IV steroids, or azathioprine) **Comparison:** cyclosporine A (CsA)						
Outcomes	**Anticipated absolute effect (95% CI)***		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk with cyclosporine A	**Assumed risk with steroids ± azathioprine**				

Proportion of participants achieving control of inflammation (higher number of events is better) Follow-up: 0 to 12 months	87 events per 100 participants	**73 events per 100 participants** (61 to 88)	**RR 0.84** (0.70 to 1.02)	112 (2 RCTs)[a]	⊕⊝⊝⊝ **Very low**[a,b,c]	Two other studies reported this outcome but used CsA doses no longer in practice (Nussenblatt 1991; Wiederholt 1986).
Change in BCVA (lower logMAR indicate better vision) Follow-up: 0 to 12 months	The mean BCVA score across the CsA group ranged from -0.32 to -0.21 logMAR	**The mean logMAR was 0.04 lower (better) on average** (-0.14 to 0.07 logMAR)	-	91 eyes (2 RCTs)[a]	⊕⊝⊝⊝ **Very low**[a,b,c]	
Proportion of participants achieving a 2-line improvement in visual acuity (Snellen chart) (higher scores indicate better vision) Follow-up: 0 to 6 months	See comment	-	-	-	-	One study reported this outcome but used CsA doses no longer in practice (Wiederholt 1986).
Proportion of participants with confirmed macular edema (lower number of events is better) Follow-up: 0 to 6 months	See comment	-	-	-	-	One study reported this outcome but used CsA doses no longer in practice (Nussenblatt 1991).
Proportion of participants achieving steroid-sparing control (higher number of events is better) Follow-up: 0 to 12 months	78 events per 100 participants	**50 events per 100 participants** (26 to 97)	**RR 0.64** (0.33 to 1.25)	21 (1 RCT)[a]	⊕⊝⊝⊝ **Very low**[a,b,c]	
Proportion of participants experiencing complications or requiring cessation of medication (lower number of events is better) Follow-up: 0 to 12 months	7 events per 100 participants	**6 events per 100 participants** (1 to 24)	**RR 0.85** (0.21 to 3.45)	91 participants (2 RCTs)[§]	⊕⊝⊝⊝ **Very low**[a,b,c]	One other study reported this outcome but used CsA doses no longer in practice (Nussenblatt 1991).

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

BCVA: best-corrected visual acuity; **CI:** confidence interval; **CsA**: cyclosporin A; **IV:** intravenous**logMAR:** logarithm of the minimum angle of resolution;**MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VKH:** Vogt-Koyanagi-Harada

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence:
High certainty: further research is very unlikely to change our confidence in the estimate of effect
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low certainty: we are very uncertain about the estimate

[a]Downgraded (-2) for risk of bias (one or more studies with unclear or high risk of bias overall, randomization process, deviations from intended interventions)
[b]Downgraded (-1) for imprecision (small sample size)
[c]Downgraded (-1) for indirectness (VKH not representative of all NIIPPU)
[§]Only VKH participants

Appendix 8: Key Limitations of the published literature

1. Lack of standardisation - disease and outcomes

While the SUN working group (The Standardization of Uveitis Nomenclature (SUN) Working Group , 2005) has made progress with standardizing the approach to reporting clinical data in uveitis research, studies conducted prior to this publication, lacked standardization with the anatomic classification of uveitis. This does present limitations with undertaking the determination of effect sizes, particularly given the small sizes of most studies. Lack of standardised nomenclature also impedes the extrapolation of results to any select population cohorts.

A SR by (Denniston et al, 2015) investigated the heterogeneity of outcome measures used in recent clinical trials (n=104 clinical trials) for intermediate, posterior, and panuveitis. According to this review, current study designs prioritize clinician-observed measures of disease activity and measurement of visual function as outcome measures which prevents comparison of studies and meta-analyses, and weakens the evidence available to stakeholders. Furthermore, even when the same outcome was used, there was often variation in the way it was measured, analysed, and reported, with many of the tools used to monitor outcomes were reliant on subjective scoring either by patients or healthcare providers. In assessing the degree of consensus or otherwise in the choice of primary outcome measures related to uveitis, 74% included one or more variables related to disease activity as primary outcome measures; 52% included visual acuity as a primary outcome measure and 4% included one or more variables of disease-associated tissue damage or complications as primary outcome measures. None of the studies identified by (Denniston et al, 2015), included a measure of patient reported visual function as a primary outcome measure. A subsequent publication by (Kelly NK et al., 2021) assessing VR-QoL and HR-QOL measures has been identified, and included in this review.

Following a five year consensus process which included patient, caregiver, and healthcare professional representatives, a list of 16 outcomes of sufficient importance to be included in a 'core outcome set' (COS), for non-infectious uveitis of the posterior segment (NIU-PS) in clinical trials was published by (Tallouzi MO et al, 2021). It remains to be seen whether these outcomes will be adopted for use in clinical trials going forward, however any benefits from adoption will likely only be realised in decades to come. The authors note that further work is required to determine and validate the optimal measurement tool for each of the recommended outcome measures.

2. Lack of standardisation – drug doses

As most DMARDs are used off-label for the management of uveitis, there is a of lack standardisation with recommended doses of DMARDs. The reported doses of methotrexate range from 7.5 mg to 25 mg per week, and cyclosporine doses ranged from 2.5 mg to 15 mg/kg/ day (higher doses reported in the older cyclosporine studies that have now fallen out of clinical practice). Head to head studies have also been incongruent where high doses of one DMARD e.g. methotrexate 25mg was compared to standard dose mycophenolate mofetil 2grams.

The dosing regimens of corticosteroid comparators also varied considerably with doses ranging from 10-100mg daily with variable dose tapering regimens, although steroid tapers were generally aimed to achieve a dose of 5 to 10mg daily.

3. Heterogeneity of studies

Most studies on uveitis involve different anatomic locations and usually included patients with variable underlying systemic disease.

4. Age cohorts

Similar to our review, the Cochrane SR (E Mayhew RG, 2022) intended to include only adults in their population cohort. The Cochrane methodology was subsequently revised to include trials with a mix of adults, adolescents, and children but excluded trials where all participants were under 18 years old. Most RCTs in the Cochrane review included only adult participants, except for (Cuchacovich M et al, 2010), which included one child aged five years, and the two FAST trials, (Rathinam SR et al, 2014) and (Rathinam SR et al, 2019) w which included participants 16 years of age and older.

5. Combination therapy

There is a lack of good quality studies with head to head comparisons of DMARDs. In the small number of head to head studies many included combination therapy with corticosteroids or other immunomodulatory therapies limiting the ability to assess the efficacy of any single DMARD.

6. Therapeutic management – uveitis vs underlying disease

Our review as well as that of the two SRs included above, focussed on the management of the anatomical classification of ocular manifestations of uveitis which is associated with of a wide range of underlying immune-mediated aetiologies. The indication of the DMARD, the course of the disease and the response to treatment could be different regarding the ocular and the systemic manifestations of the underlying conditions. According to (Denniston et al, 2015), the option of syndrome-specific clinical trials has not been possible, despite making "biological sense", because of logistic challenges, particularly around recruitment. This does then follow that the authors of both SRs included in this review [(E Mayhew RG, 2022) and (Gomez-Gomez A , 2020)], acknowledge the limitations with being able to develop a treatment algorithm for the management of uveitis. Instead, it is recommended that treatment strategies be informed on a case by case basis tailored to individual patient's needs.

Furthermore, many of the underlying systemic conditions associated with uveitis follow a relapsing and remitting course. One such example is Behcet's disease with eye involvement, where visual acuity regresses during an acute attack but often improves with time even if untreated. Reliance on small RCTs or case series with a measure of visual acuity over time for such conditions may inaccurately imply efficacy of drug treatment (Hatemi G et al, 2009).

7. Comprehensiveness of included studies

Given that patients with bilateral posterior and panuveitis are a subgroup of patients included in most studies, there is a risk of relevant articles being missed with any given search strategy, due to indexing, particularly if the study population has not been included in the title or abstract of the publication.

8. Generalisability to the local population

While the Cochrane review (E Mayhew RG, 2022) included studies spanning a wide geographic region [USA, Western Europe, Mexico, Chile, Australia, Japan, Saudi Arabia, and India], no studies from the African subcontinent were included. The prevalence of certain aetiological conditions such as VKH disease is reportedly higher in population cohorts with pigmented skin, such as Asians, Middle Easterners, Hispanics and Native Americans. VKH is very infrequent among persons of African descent (Rao NA et al, 2010), who were most likely under-represented in the Cochrane review (E Mayhew RG, 2022) given the sizeable populations of VKH in a number of the RCTs cited. The high proportion of VKH in some of the included RCTs may make the results of this SR less generalizable to our local population. The SITE cohort study (Kempen JH et al, 2008) excluded people living with HIV.

South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: Eye conditions

MEDICINE REVIEW

1. Executive Summary

Date: 9 February 2023
Medicine (INN): Hyaluronidase
Medicine (ATC): B06AA03
Indication (ICD10 code): Cataract surgery H26.0-4/H26.8-9/H59.0
Patient population: Adult patients
Prevalence of condition: The prevalence of cataract surgery in South African is not known. However, an estimated 60 000 cataract surgeries were reportedly performed in the public sector for the period April 2019 to March 2020 *(Source: NDoH, DHIS data on file).*
Level of Care: Adult Hospital Level (regional and district level of care)
Prescriber Level: Specialist consultation
Motivator/reviewer name(s): G Thom, T Kredo, T Leong, N Gloeck, M Mthethwa
PTC affiliation: GT - KZN Provincial PTC

Key findings

- We conducted a review of clinical practice guidelines (CPGs), systematic reviews of randomised controlled trials (RCTs) and RCTs.
- One systematic review, two RCTs and one CPG were identified that included comparisons of interest
- NICE CPG (2017) was assessed as high quality using AGREE II tool. Recommendations include consideration of hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly if trying to stop the eye moving during surgery (akinesia); low certainty evidence, conditional recommendation.
- The systematic review reported on intraoperative pain, surgical (surgeon) satisfaction and patient satisfaction.
- The effect of hyaluronidase on intraoperative pain during eye surgery is uncertain.
- Moderate quality evidence showed improved patient satisfaction scores (2 RCTs; n=122, p<0.05) with the use of hyaluronidase. Each study had assessed satisfaction using a different method, and therefore no meta-analysis was conducted.
- Studies assessing surgical satisfaction could not be meta-analysed as outcome measures were heterogeneous. Moderate quality evidence shows improved surgical satisfaction scores in 2 RCTs (n=144, p=0.02 and p<0.001) with the use of hyaluronidase, but no difference in another study (1 RCT; n= 20, p=0.96).
- No harms were reported in the studies associated with anaesthesia solution with or without hyaluronidase.
- The use of hyaluronidase to improve akinesia during surgery is supported by the NICE CPG (2017) and Rowley 2000, but available evidence is conflicting, and use may be determined by surgeon preference.

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: The Committee suggests a conditional recommendation for the use of hyaluronidase as an adjunct to anaesthesia for peri-orbital block. Its potential for improved akinesia may be beneficial in certain clinical settings, (extracapsular cataract surgery or manual small incision cataract surgery is still the predominant method used at many

sites locally). As the technique uses larger incisions and it is difficult to stabilize the eye with one instrument, movement of the eye increases the risk of posterior capsule rupture with vitreous loss resulting in poor visual outcomes. **Rationale:** Operating with good akinesia is of utmost importance for trainee and inexperienced surgeons performing extracapsular surgery which is of lesser importance when phacoemulsification is used with smaller incisions and two hands available to stabilize the eye. Hyaluronidase also assists with spreading fluid in the tissues, which reduces the risk of elevated intraocular pressure. A high coincidence rate exists between sharp rise of IOP and undesirable intraoperative complications such as: shallowing of anterior chamber, herniation of iris through incision site and stromal corneal oedema. Javrishvili (2021)). **Level of Evidence: Low quality evidence** **Review indicator:**
NEMLC RECOMMENDATION (MEETING OF 23 FEBRUARY 2023): NEMLC supports the recommendation of the Expert Review Committee as detailed above.
Monitoring and evaluation considerations
Research priorities

2. **Name of author(s)/motivator(s):** G Thom, T Leong, N Gloeck, T Kredo, M Mthethwa

3. **Author affiliation and conflict of interest details**

   GT (KwaZulu-Natal Department of Health), TK (Cochrane South Africa, South African Medical Research Council (SAMRC), Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, co-director of the South African GRADE Network), TL, NG and MM (Cochrane South Africa, South African Medical Research Council (SAMRC) have no interests related to hyaluronidase.

   TK, TL, NG and MM are partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies).

4. **Introduction/ Background**

   Hyaluronidase is an endoglycosidase enzyme that breaks down hyaluronic acid in the extracellular matrix (Jung 2020). In clinical practice, this agent has routinely been administered with local anaesthetic injection to improve the rate of onset of analgesia and akinesia (Rüschen 2018, Atkinson, 1949). Optimal anaesthetic blocks in ophthalmologic surgery require adequate spread of local anaesthetic through the orbital cavity. However, connective tissue membranes impede distribution of local anaesthetic which may be addressed with the adjunctive administration of hyaluronidase (Rüschen 2018, Koornneef 1988, Buhren 2016). Hyaluronidase in local anaesthetic fluid also appears to prevent increases in intraocular pressure during surgery (Rüschen 2018, Dempsey 1997). Furthermore, expert opinion is that hyaluronidase allows smaller volumes of local anaesthesia to be used. In South Africa, a large proportion of eye surgery is performed by medical officers and non-specialist cataract surgeons often in district hospitals with the background of pressure on surgical outputs due to a large unmet burden of preventable blindness due to cataracts. For these clinicians optimal blocks are essential for good surgical outcomes. Akinesia associated with hyaluronidase, is thus considered an important outcome by most of the local ophthalmologists. However, the available evidence is uncertain with conflicting results.

   An evidence review is being undertaken which will inform the decision of whether to include or exclude hyaluronidase on the Adult Hospital Level Essential Medicine List. Hyaluronidase is being considered as an adjunct to local anaesthesia to improve the quality of anaesthesia and analgesia in cataract surgery.

5. Purpose/Objective i.e., PICO

Population	Adult patients (≥18) undergoing peri-ocular blocks for eye surgery
Intervention	Hyaluronidase co-administered with local anaesthetic agent(s)
Control	Placebo or local anaesthesia only (lidocaine, bupivacaine)
Outcomes	Akinesia during surgery Intraoperative pain Adverse outcomes (surgical complications) Patient satisfaction Surgeon satisfaction
Study designs	Systematic reviews of RCTs or RCTs. Observational studies will only be sourced if the latter are unavailable.

6. Methods:

a. Data sources:
Clinical Practice Guidelines sources searched were the Guidelines International Network (GIN) Library and the National Institute for Health and Care Excellence (NICE). Systematic reviews and randomised controlled trials were sought in PubMed and Epistemonikos. To identify planned and ongoing studies, WHO's International Clinicals Trials Registry Platform (ICTRP) as well as ClinicalTrials.gov were searched.

b. Search strategy – A search strategy was developed for PubMed and Epistemonikos (Appendix 1).

c. **Screening, data extraction and analysis, evidence synthesis:** Records were retrieved (MM and TL) and screened independently and in duplicate (GT and TL). Thereafter, full text screening was done by two reviewers (GT and TL). Any discrepancies were discussed with TK. We screened for systematic reviews, followed by screening for any additional RCTs that were not included in the eligible systematic review(s). Data extraction for systematic reviews and RCTs was done by one reviewer and checked by a second reviewer. Eligible clinical guidelines were appraised by two reviewers (GT and NG) using the AGREE II tool; systematic reviews with the AMSTAR II Checklist (GT and NG), and RCTs assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool. Data were extracted into Characteristics of Included studies tables (tables 2 and 3). For dichotomous outcomes, we reported risk ratios (RR) with 95% confidence intervals (CI) and results from the review or trial where possible. Where available, we reported on the GRADE (level of certainty) of the evidence, considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness.

Excluded studies: Reasons for excluding full-texts were agreed in duplicate (GT and TL) with a third reviewer (TK) resolving any disputes, as required.

7. Results

We searched PUBMED and Epistemonikos on 12 August 2022 and retrieved 20 records for screening. One duplicate record was excluded and another that was not available in English. Sixteen records were excluded for having the incorrect population, comparator and/or intervention and study design, after full-text assessment. One systematic review and one RCT were considered for evidence synthesis. There were no ongoing trials identified. See appendix 2 for the PRISMA flow diagram, appendix 3 for characteristics of included studies and appendix 4 for list of excluded studies and the rationale for exclusion.

a. Guidelines

We identified one guideline, a NICE Guideline: Cataracts in adults: management, 2017 (NICE, 2017). This guideline was assessed using the AGREE II tool as good quality and suggests hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly for akinesia (see table below and appendix 5).

Guideline citation and website	Recommendation	Appraisal AGREE II
NICE 2017 Cataracts in Adults: management: https://www.nice.org.uk/guidance/ng77	Consider hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly if trying to stop the eye moving during surgery (akinesia); *low certainty evidence, conditional recommendation* Trade off between benefits and harms: "…evidence showed lower levels of anaesthetic were necessary to achieve a sub-Tenon's block when hyaluronidase was added, but noted this did not represent the volume of anaesthetic necessary for adequate pain control, but rather the volume necessary to achieve eye akinesia (an outcome which some surgeons may consider highly desirable, but one which others may not be particularly concerned with)." Secondary Comment: Low-quality evidence from 1 RCT of 62 participants showed that those who received anaesthesia with hyaluronidase had a 2.4-fold reduction in median effective local anaesthetic volume needed to achieve a sub-Tenon's block. 1 study showed that a high average volume (6.4mL) of anaesthetic was needed in people randomised not to receive hyaluronidase. The injection of this volume into the sub-Tenon's space could elevate the risk of vitreal compression.	Overall assessment 92% See appendix 5.

Table 1: AGREE 2 assessment of the 2017 NICE Clinical Guideline on cataract management in adults

b. **Systematic review and randomised controlled trials**

Description of included studies:
One systematic review (Rüschen 2018) and one RCT (Swathi 2020) was eligible for review. In addition, a RCT (Rowley 2000) included in the systematic review but that was not reviewed for akinesia (as authors considered this not to be relevant for most cataract surgeries) has been reviewed.

- ***Systematic review:***
  Rüschen 2018: One systematic review of seven RCTs (of 500 study participants, 18 years or older presenting for ophthalmic surgery) was identified (Rüschen 2018) to determine if hyaluronidase as an adjuvant to local anaesthetic solutions reduced intraoperative pain. The primary outcome was intraoperative pain as measured by analogue rating scales. Secondary outcome measures included incidence of harm (reported as a narrative); participant and surgical satisfaction, as documented by scoring systems, and economic outcomes or cost calculations (reported as a narrative). See the characteristics of included studies table in appendix 3 for details.

  Akinesia was not reported as the authors stated that, due to most modern surgical techniques, the majority of surgeons could carry out most operations without depending on fully established akinesia (except in difficult operations or training situations where profound akinesia is necessary). However, as the NICE guideline (2017) recommends hyaluronidase as an adjunct to sub-Tenon's anaesthesia, particularly for akinesia, the RCT by Rowley et al (2000) that reports on akinesia and was included in the systematic review will be reviewed (see appendix 4).

The systematic review was assessed as high quality using the AMSTAR 2 tool (see table 2 and appendix 6). However, according to GRADE, the quality of the reviewed RCTs for intraoperative pain was assessed as low quality (due to imprecision and inconsistency, lack of data and small sample size); and for patient and surgical satisfaction as moderate quality (downgraded due to imprecision secondary to small sample size).

Systematic review	Recommendation	Appraisal AMSTAR 2
Rüschen H, et al. Use of hyaluronidase as an adjunct to local anaesthetic eye blocks to reduce intraoperative pain in adults. Cochrane Database Syst Rev. 2018 Mar 2;3(3):CD010368.	The effects of adding hyaluronidase to local anaesthetic fluid on pain outcomes in people undergoing eye surgery are uncertain due to the low quality of evidence available. A well designed RCT is required to address inconsistency and imprecision among the studies and to determine the benefit of hyaluronidase to improve analgesia during eye surgery. Participant and surgical satisfaction is higher with hyaluronidase compared to the control groups, as demonstrated in moderate quality studies.	High Quality Review. See appendix 6

Table 2: AMSTAR 2 assessment of the systematic review by Rüschen et al (2018)

- ***Randomised controlled trials:***

  Swathi et al (2020): This single eligible RCT selected for review, was conducted in a single hospital in India, where adult patients (n=202) presented with uncomplicated cataracts, over a period of 15-months. Patients were scheduled for Manual Small Incision Cataract, and randomly assigned to either a control group (n=100), administered local anaesthesia without hyaluronidase, or a treatment group (n=102), administered adjuvant hyaluronidase, dosed at 50IU/ml. The aim of this study was to determine whether hyaluronidase was necessary as an anaesthetic adjuvant for peribulbar anaesthesia during cataract surgery and to assess differences in anaesthetic outcomes (extra ocular movements, ease of procedures and orbicularis oculi action) utilising a surgeon score card. Post operatively, the patient was given a visual analogue scale (0–10) to grade the perceived pain at the beginning and end of surgery.

  Rowley et al (2000):
  This RCT was summarised as it was included in both the systematic review by Rüschen et al (2018) and the NICE CPG (2017) and reported specifically on akinesia which was not reported in the systematic review. The study was conducted in a single hospital in the United Kingdom on 150 patients scheduled for elective cataract surgery. Patients were randomly assigned to a control group (n=74) who had routine local anaesthesia administration and a treatment group (n=76) who had 30IU/ml hyaluronidase added to the anaesthetic solution. The aim of this study was to determine the effect of hyaluronidase on the quality of the local anaesthesia blocks, assessing akinesia and eyelid movements. The degree of akinesia was measured using a four-point scale: 0 = complete movement remaining, 1 = moderate movement, 2 = slight movement (<3 mm in any direction), 3 = no movement). Eyelid movement was assessed using a three-point scale: (0 = normal movement, 1 = reduced movement, 2 = absent movement).
  Pain was assessed intraoperatively, immediately after injection and perioperatively, immediately after surgery, using a 10-point visual analogue scale (0 being no pain, 10 excruciating pain).

Effectiveness of hyaluronidase *vs*. no hyaluronidase

- **Pain**

  - **Intraoperative pain** (Rüschen 2018)
    The effect of hyaluronidase on intraoperative pain is uncertain.

    Dichotomous data: (4 RCTs, n=289)
    - 0.25% (25/1000) vs 0.30% (301/1000); RR 0.83 (95% CI 0.48 to 1.42); I^2=41, low certainty evidence due to imprecision and inconsistency.

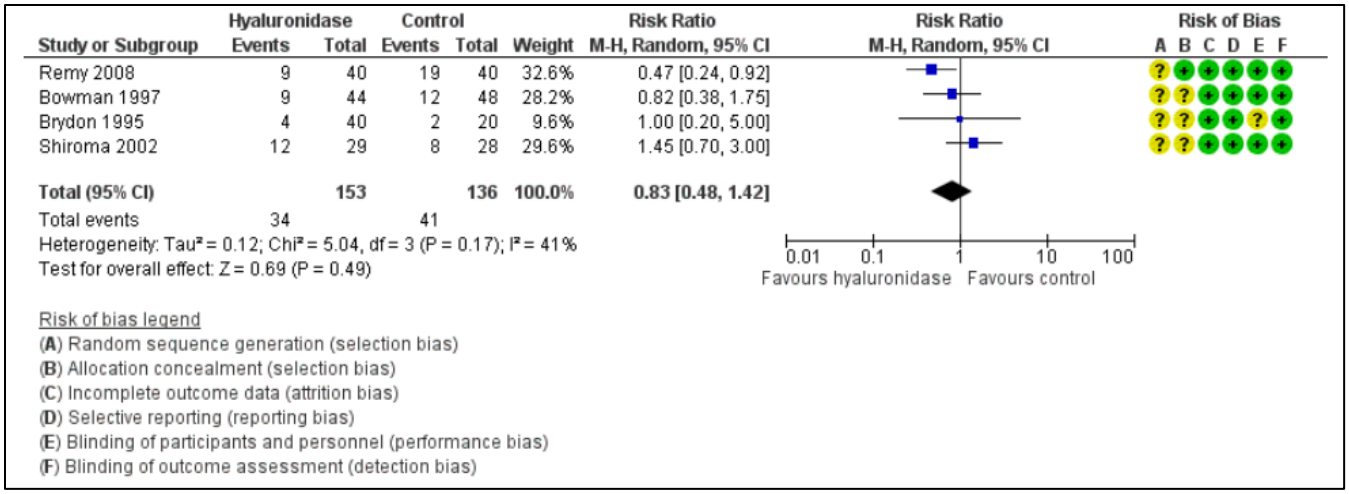

Figure 2: Forest plot of hyaluronidase versus control for intraoperative pain (dichotomous data as measured by analogue rating scales)

Continuous data: (3 RCTs, n=211)

- Study data could not be meta-analysed as outcome measures were not consistent. Khandwala et al (2008) and Rowley et al (2000) did not report standard deviations (SDs). We are uncertain of the effect of hyaluronidase on intraoperative pain in these groups. Sedghipour et al (n=42) suggested there may be a reduction in intraoperative pain. Quality of evidence was low due to imprecision and inconsistency in measurement, lack of data and small sample size.

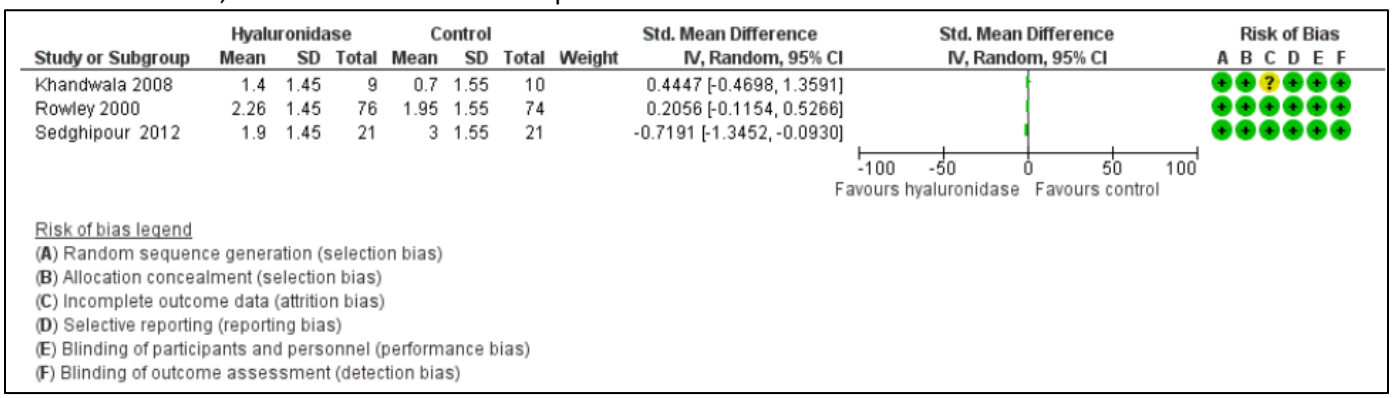

Figure 3: Forest plot of hyaluronidase versus control for intraoperative pain (continuous data as measured by analogue rating scales)

- **Patient pain score** (Swathi 2020): Prior to surgery, eight patients in the treatment group vs seven in the control group reported a pain score of 6 or more (p=0.44). After surgery, no patients in the treatment group vs one in the control group scored 6 or more (p=0.093).

- **Post injection pain score** (Rowley 2000): Treatment group 2.26 versus control group 1.95, p value reported as not significant.

- **Post operative pain score** (Rowley 2000): Treatment group 1.04 versus control group 1.03, p value reported as not significant.

- **Participant satisfaction** (Rüschen 2018)
  - Hyaluronidase treatment group had significantly higher participant satisfaction scores (Two RCTs; n=122, p<0.05; moderate certainty evidence due to imprecision secondary to small sample size).

Hyaluronidase increased participant satisfaction scores.

- **Surgical satisfaction** (Rüschen 2018)
  - Hyaluronidase showed superior surgical satisfaction compared to control in two RCTs; n=121 (Remy 2008, p<0.001; Sedghipour 2012, p=0.02), but no difference in one small RCT of 20 participants, p=0.96 (Khandwala 2008); moderate certainty evidence due to imprecision secondary to small sample size.

  Hyaluronidase increased surgical satisfaction scores.

- **Incidence of harm**
  - *Rüschen 2018:* No reported harm due to the addition of hyaluronidase in any of the studies.
  - *Swathi 2020:* Intraoperative complications were not attributed to the anaesthetic solution (with or without hyaluronidase).
  - *Rowley 2000:* Surgical complications were not associated with anaesthetic block (with or without hyaluronidase).

- **Akinesia and analgesia**

  Swathi 2020:
  - **Time for onset to akinesia:** Treatment group: 1.5–5 min (mean 2.3±SD 0.6; 95% CI 2.2–2.4 min) *vs*. Control: 1.5–5.5 min (mean 2.5±SD 0.7; 95% CI: 2.4–2.6 min); p=0.004.
  - **Time for onset to analgesia:** Treatment group: 1.4–3.5 min (mean 2.2±SD 0.4; 95% CI: 2.1–2.2 min) vs. Control: 1.5–4.25 min (mean 2.3±SD 0.5; 95% CI: 2.2–2.4 min); p=0.005.
  - ~~o~~ **Anaesthetic augmentation:** Five patients in the treatment group compared to nine patients in the control group required augmentation of the anaesthetic block (p=0.3).
  - **Extra ocular movements:** Nine patients in the treatment group vs 11 patients in the control group had unsatisfactory akinesia, graded as moderate movements or more by the operating surgeon (one patient in the control group had no restriction of movements despite repeat peribulbar anaesthesia, but due to adequate analgesia and patient co-operation, the surgery was completed). There was no difference in surgeon scoring of akinesia, comfort/ease during surgery and orbicularis oculi action.

  A faster onset of akinesia and analgesia was observed with the use of hyaluronidase (as an adjuvant), but the difference is clinically negligible, as the mean difference between the two groups was less than 30 seconds.

  Rowley 2000:
  - **Akinesia score (10 minutes after performance of block):** Treatment group 2.32 vs control group 1.43. (p<0.01)
  - **Akinesia:** Complete akinesia was achieved in 40 cases in the treatment group compared to 10 cases in the control group (p value not provided).

  Adjunctive hyaluronidase resulted in quicker onset of akinesia and greater rate of akinesia, but the absolute effect may not be clinically significant.

8. **Alternative agents:** Not applicable

9. **Conclusion:** There is uncertainty regarding the use of adjuvant hyaluronidase to local anaesthetic solution to reduce pain during eye surgery due to the low quality of the available evidence. Moderate quality evidence shows improved patient and surgical satisfaction scores with the use of hyaluronidase. Use of hyaluronidase to improve akinesia during surgery is supported by the NICE guideline and Rowley 2000, but available evidence is conflicting and use may be determined by surgeon preference.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** • **Analgesia** High: ☐ Moderate: ☐ Low: ☒ Very low: ☐ • **Surgical satisfaction** High: ☐ Moderate: ☒ Low: ☐ Very low: ☐ • **Patient satisfaction** High: ☐ Moderate: ☒ Low: ☐ Very low: ☐ • **Akinesia** High: ☐ Moderate: ☒ Low: ☐ Very low: ☐ *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	• **Analgesia** Low quality evidence due to marked heterogeneity, imprecision and inconsistency, lack of data and small sample size. • **Surgical satisfaction** Moderate quality evidence due to imprecision secondary to small sample size. • **Patient satisfaction** Moderate quality evidence due to imprecision secondary to small sample size. • **Akinesia** Moderate quality evidence due to imprecision secondary to small sample size.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** • **Analgesia** Large: ☐ Moderate: ☐ Small: ☐ None: ☒ • **Patient satisfaction** Large: ☐ Moderate: ☒ Small: ☐ None: ☐ • **Surgical satisfaction** Large: ☐ Moderate: ☒ Small: ☐ None: ☐ • **Akinesia** Large: ☐ Moderate: ☒ Small: ☐ None: ☐	• **Analgesia** *Dichotomous scores:* RR 0.83 (0.48 to 1.42) *Continuous scores:* Uncertain • **Patient satisfaction** Improved patient satisfaction scores with the use of hyaluronidase (2 RCTs; n=122, p<0.05) • **Surgical satisfaction** Improved satisfaction overall: Improved satisfaction in 2 RCTs (n=144, p=0.02 and p<0.001) with the use of hyaluronidase, but no difference in another study (1 RCT; n= 20, p=0.96). • **Akinesia** Quicker onset and rate of akinesia with hyaluronidase vs control, but difference may be clinically negligible. Rowley (2000) reported that the degree of akinesia and reduction of eyelid movement, measured 10 minutes after administration of the anaesthetic, was significantly better (p<0.01) in the hyaluronidase group with higher rates of complete akinesia in the treatment group (40) versus the control group (10) out of 150 study participants. Swathi (2018) reported no statistically significant difference between the groups (p = 0.22, 0.68 and 0.98). This difference can be explained by surgery in Swathi being performed by experienced consultants and using a subjective score of akinesia depending on the surgeon's assessment while Rowley had surgeons of varying experience and used an objective scoring system. Swathi also excluded all patients at risk of complications.

QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [X] Low [ ] Very low [ ] *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	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] None [X]	Surgical complications were similar in both groups and not felt to be related to the agent used. The systematic review found no evidence of harm attributed to the use of hyaluronidase. Rüschen(2018)
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	For extracapsular surgery, which, is done predominantly at District care level by less experienced doctors, a single instrument is used and surgeons do not have both hands available to keep the eye stable. When non-specialists and trainees do surgery, akinesia is of utmost importance to prevent complications. In the case of phaco surgery, two instruments are used and surgeons have both hands available to keep the eye still. In the studies reviewed phacoemulsification was the method of surgery used in the vast majority of cases. Intra-orbital eye pressure: the use of hyaluronidase facilitates improved tissue penetration into the orbit which results in less pressure and exudate which facilitates improved surgical management. A high coincidence rate exists between sharp rise of IOP and undesirable intraoperative complications such as: shallowing of anterior chamber, herniation of iris through incision site and stromal corneal oedema. Javrishvili (2021))
THERAPEUTIC INTERCHANGE	**Therapeutic alternatives available:** n/a	n/a
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Hyaluronidase is SAHPRA-registered and available on the market.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [X] Uncertain [ ]	**Price of medicines/ treatment course –** **Medicine** | **Tender price *** | **SEP**100%** | **SEP ** 60%** Hyaluronidase (1500IU) | R391.18 | R480.25 | R288.15 *Contract circular HP07-2020DAI, August 2022: Hyaluronidase 1500 IU = R391.18 and 150 IU = R39.18. ** SEP database, 31 August 2022: Hyaluronidase 1500 IU = R4802.52 and 150IU = R480.25 **Actual Current Usage** July 2020-October 2022 (28 months): 2012 vials at a cost of R848739.58 (Average spend = R30 312 per month and R363 745 per annum) **Cost per patient:**

		Depends on the operating list as 1 vial can be used for 10 patients: If used for 1 patient cost is: R391.18 and for 10 patients R39.12 per patient. **Other resources:** n/a
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	See above.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

Version	Date	Reviewer(s)	Recommendation and Rationale

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- Sedghipour M, Mahdawifard A, Fouladi RF, Gharabaghi D, Rahbani M, Amiraslanzadeh G, et al. Hyaluronidase in sub-Tenon's anesthesia for phacoemulsification, a double-blind randomized clinical trial. Int J Ophthalmol. 2012;5(3):389-92. https://pubmed.ncbi.nlm.nih.gov/22773994/
- Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. https://pubmed.ncbi.nlm.nih.gov/28935701/

Appendix 1: Search Strategy

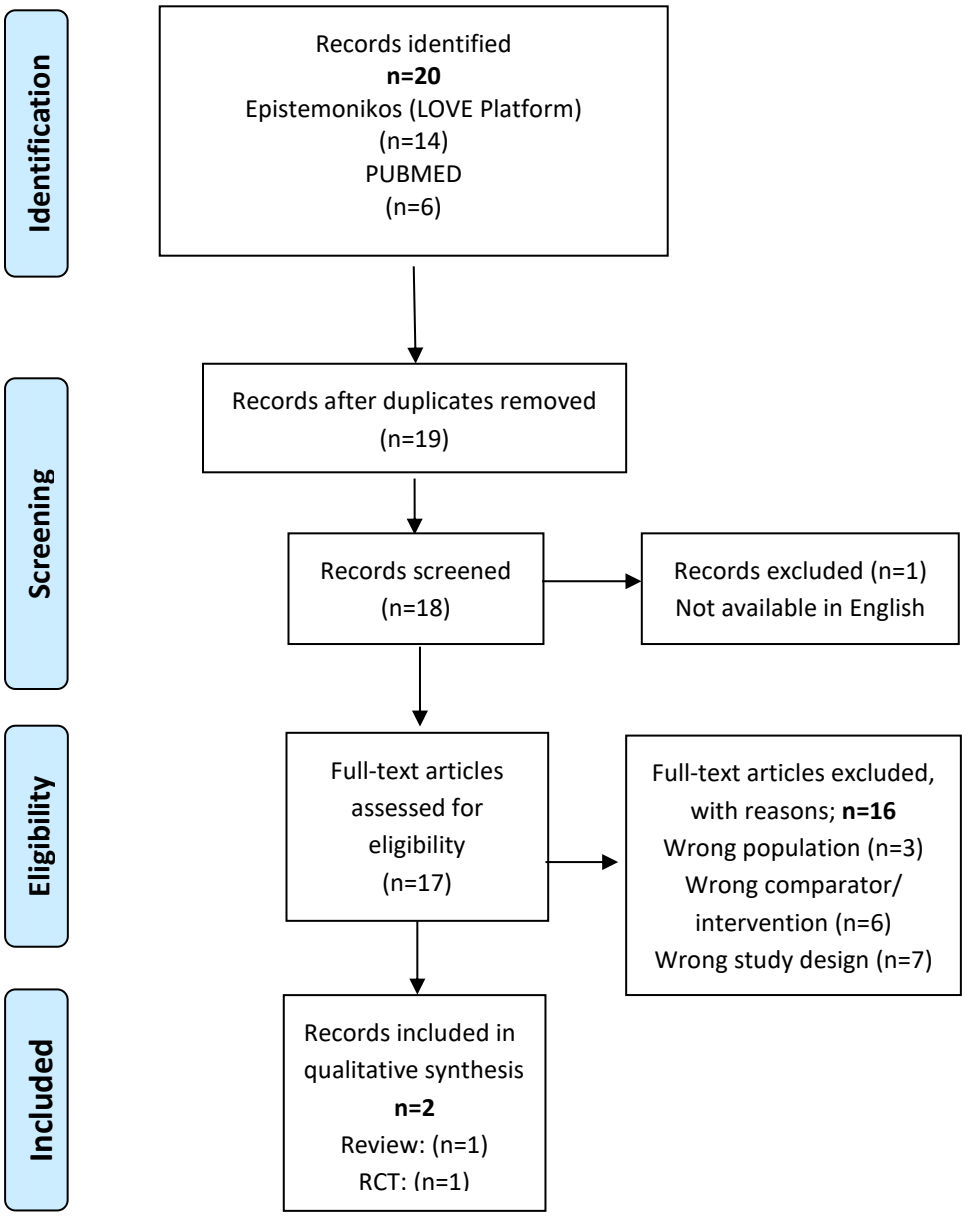
A: PUBMED

SEARCH	QUERY	RESULTS
#16	Filters: from 2017/5/1 - 2022/8/3	14
#15	#13 AND #14	154
#14	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	4,792,867
#13	#4 AND #7 AND #11 AND # 12	250
#12	Search: Hyaluronoglucosaminidase [Mesh] OR hyaluronidase [tiab] OR vitrase [tiab] OR wydase [tiab] or hyalase [tiab] or hylenex [tiab]	12,267
#11	#8 OR #9 0R #10	58,927
#10	Search: Anesthesia, Local [Mesh] OR local anaesthe* [tiab] OR local anesthe*[tiab]	55,168
#9	Search: Nerve Block [Mesh] OR Lidocaine [Mesh] OR Lidocaine [tiab] OR Lignocaine [tiab] OR Mepivacaine [Mesh] OR Isocaine [tiab] Bupivacaine [Mesh] OR Marcain* [tiab]	4,902
#8	Search: peribulbar block [tiab] OR retrobulbar block [tiab] OR sub-tenon block [tiab] or subtenon* [tiab]	1,594
#7	#5 OR #7	4,581,315
#6	transplant* [Mesh] OR graft* [tiab] or extract* [tiab] OR cataract [tiab] OR refractive [tiab] OR oculoplast* [tiab] OR ophthalmosurg*[tiab]	1,819,502
#5	surg*[tiab] OR operat*[tiab]	3,074,295
#4	#1 OR #2 OR #3	2,620,067
#3	Search: glaucoma [Mesh] OR glaucomas [tiab] OR conjuncti*[tiab] OR uveitis [Mesh] OR uveitides [tiab] OR macula* oedema [tiab] OR macular edema [Mesh] OR strabismus [Mesh] or squint [tiab] OR astigmati* [tiab] OR myopia [Mesh] OR myopi* [tiab] OR Hyperopia [Mesh] OR hypermetropia [tiab] OR trachoma [Mesh]	297,541
#2	Search: **visual [tiab] OR vision [tiab] OR sight [tiab] or see* [tiab] or view* [tiab] or blind*[tiab]**	1,493,276
#1	Search: Eye [Mesh] OR Ophthalm* [tiab] OR Vision, ocular [Mesh] OR ocular [tiab] OR Cornea* [Mesh] OR retin* [Mesh] OR Ora serrata [tiab] OR sclera* [Mesh] OR vitreous body [Mesh] OR vitre*[tiab] OR iris [Mesh] OR pupil [tiab] OR orbit*[Mesh] OR eye socket [tiab] OR choroid* [Mesh] OR intraocular [tiab] OR intra-ocular [tiab] OR extraocular [tiab] OR extra-ocular [tiab] OR monocular [tiab] OR oculo* [tiab] OR oculi* [tiab] OR optic* [tiab]	1,215,341
Output: 14 records retrieved, 12 excluded as PICO criteria not met, 2 records selected for inclusion (1 systematic review and 1 RCT)		

B: Epistemonikos

Search strategy: (title:((title:(hyaluronidase) OR abstract:(hyaluronidase)) AND (title:(ophthalmic surgery) OR abstract:(ophthalmic surgery))) OR abstract:((title:(hyaluronidase) OR abstract:(hyaluronidase)) AND (title:(ophthalmic surgery) OR abstract:(ophthalmic surgery)))) Search restricted to systematic reviews
Output: 6 records and all excluded - 1 record retrieved from the PUBMED search (duplicate), 1 record (1999 RCT) only available in Italian and 4 records did not meet the PICO criteria

Appendix 2: PRISMA flowchart



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 3: Characteristics of included studies

Author, date	Type of study	Population (n)	Comparators	Primary outcome	Effect sizes	Comments

Rüschen H *et al.* Use of hyaluronidase as an adjunct to local anaesthetic eye blocks to reduce intraoperative pain in adults (Review). Cochrane Database Syst Rev. 2018 Mar 2;3(3):CD010368.	Systematic review of 7 RCTs (n=500)
	
	Studies conducted in UK (4 RCTs), Germany (1 RCT), Brazil (1 RCT) and Iran (1 RCT)
		n=500
		
		Study participants:
		Adults, ≥ 18 years, presenting for ophthalmic surgery undergoing a retrobulbar, peribulbar or sub-Tenon block.
		
		Age range: 66 to 77 years.
		
		Gender: Studies were balanced with regards to gender.
			Local anaesthetic eye blocks containing hyaluronidase
			
			vs.
			
			Local anaesthetic eye blocks containing no hyaluronidase
			
			Dose: 15 to 150 IU/mL.
				Primary outcome:
				Intraoperative pain, as measured by analogue rating scales (measured on day of surgery).
				
				Secondary outcomes:
				• Incidence of harm (narrative).
				• Participant satisfaction
				• Surgical satisfaction
				• Economic outcomes or cost calculations (narrative)
					Hyaluronidase *vs* no hyaluronidase:
					
					• **Intraoperative pain** (reported dichotomous): 0.25% vs 0.31% (RR 0.83; 95% 0.48, 1.42), 4 RCTs (n=289), *low certainty evidence*
					
					• **Incidence of harm:** NR
					
					• **Participant satisfaction:** Increased satisfaction in treatment group; 2 RCTs (n=122), p<0.05; *moderate certainty evidence*
					
					• **Surgical satisfaction:** Increased satisfaction in treatment group in two RCTs, but no difference between groups in one RCT; n=141, *moderate certainty evidence*
					
					• **Economic outcomes or cost calculations:** NR
						• AMSTAR 2 assessed as high-quality SR
						• *Overall risk of bias:* **Low** to **moderate risk**
						  ○ *Randomisation (and allocation concealment)*: **Low** to **moderate risk**
						  ○ *Missing outcome data*: **Low** to **moderate risk**
						  ○ *Performance bias (blindingof the (patients/personnel):* **Low** to **moderate risk**
						  ○ *Measurement of the outcome (blinding of the assessors):* **Low risk**
						  ○ *Selection of the reported results:* **Low risk**
						• High heterogeneity of data for patient and surgical satisfaction prevented metanalysis of data.
						• Akinesia was not reported on, as the authors of the review initially considered akinesia as an important outcome measure (prioritized over analgesia). Authors reasoned that the majority of surgeons can carry out most operations without depending on fully established akinesia. It was, however, acknowledged that hyaluronidase may be needed where profound akinesia is required for more difficult operations or for training purposed.

Swathi N *et al*. Does the addition of hyaluronidase improve the quality of peribulbar anesthesia in cataract surgery? A randomized double blinded study. Saudi J Ophthalmol. 2018 Jul-Sep;32(3):204-210.	Randomised Double Blinded Study. Single-centre, cataract surgery performed over 15-month period (February 2015–May 2016) by the author, SN, a qualified specialist/ consultant ophthalmologist.	n=202 n1 =100 (no HYA) n2=102 (HYA) *Inclusion criteria:* Adult patients reporting for senile cataracts (first eye only). *<u>Exclusion criteria:</u>* *-First eye only:* Patients with pre-existing pathology where complicated surgery was expected; Pre-existing extra ocular movement restriction and requiring sedation/ general anaesthesia or with systemic contraindication to the use of adrenaline in 1:200000 concentration as noted by the physician during pre-operative work up; *-One-eyed patients:* inflamed eye like phacolytic, phacomorphic glaucomas; pupillary dilatation of <6 mm requiring iris manipulation to	3 ml of 2% lignocaine and adrenaline (1:200000) and 2ml of 0.5% bupivacaine with or without hyaluronidase Group 1 without and Group 2 with hyaluronidase (50IU/ml)	• Surgeons' score for akinesia • Patients' score for analgesia • Augmentation of block • Extra ocular movements on first post-operative day.	*<u>Control: No Hyaluronidase vs Treatment hyaluronidase:</u>* **Unsatisfactory akinesia graded as moderate movements or more by the operating surgeon**: Control: :11/100 (11%) vs Treatment :9/102 (8,8%) , difference of 2.2% **Requirement of additional anaesthesia (as ocular movement):** *Peribulbar and adjunctive subconjunctival (if needed)* Control: 9/100 (9%) Treatment: 5/102 (4,9%) Difference: 4,1% more in Control. (p=0.3) *Peribulbar injection:* Control: 7/100(7%) Treatment : 1/102 (2%) Difference: 5% more in Control. *Subconjunctival injection:*Control : 2/100(2%) Treatment : 3/102 (2,9%)	• *Overall risk of bias:* **Low risk** ○ *Randomisation*: **Low risk** ○ *Deviations from intervention:* **Low risk** ○ *Missing outcome data:* **Low risk** ○ *Measurement of the outcome:* **Low risk** ○ *Selection of the reported result(s):* **Low risk** • Blocks and surgery performed by experienced specialist surgeons on low risk patients in whom no complications were anticipated. • No objective measurement of akinesia done. • Surgical Complications: Posterior capsule rupture: Treatment group: 4, Control Group: 2. p=0,8. Iridodialysis: treatment Group:1. Control group :2. Intraoperative complications not attributed to the anaesthetic solution.

		deliver the nucleus.			Difference: 0,9% more in Treatment. **Pain Score more than 6 at the beginning of surgery:** Control :7/100 (7%) Treatment: 8/102 (7,8%) Difference: 0,8% more in Treatment Akinesia: 0.68 vs 0.98, p=0.22 Analgesia/ anesthetic augmentation: 0.44 vs 0.09, p=0.3 Onset of akinesia and analgesia: Earlier in Group 2 (p = 0.004 and p = 0.005 respectively)	

Abbreviations: HYA = hyaluronidase;

Appendix 4: Characteristics of study (Rowley et al, 2000) not reviewed by Ruschen et al (2018)

Author, date	Type of study	Population (n)	Comparators	Primary outcome	Effect sizes	Comments
Rowley et al. Sub-Tenon's local anaesthesia: the effect of hyaluronidase. British Journal of Ophthalmology 2000;84(4):435-6	Prospective, randomized double blind study performed in a single hospital.	n=150 n1=76 with HYA n2=74 without HYA Inclusion criteria: Patients (age 37-93) scheduled for elective cataract surgery Exclusion: Patients who would not be able to cooperate or safely undergo local anaesthesia. No exclusions for expected complicated surgery.	Hyaluronidase compared to no hyaluronidase (placebo) Both groups received 3 ml lignocaine 2% and adrenaline 1:200 000 with the hyaluronidase group having (30IU/ml) hyaluronidase added	**Akinesia and eyelid movement** was assessed by the ophthalmologist administering the block 10 minutes after administration using a 4 point scale for akinesia and a 3 point score for eyelid movement. (Higher scores allocated to absent movement.)	Akinesia score:(p<0.01) Hyaluronidase:2.32 No Hyaluronidase:1.43 Post injection pain score: (p not provided) Hyaluronidase:2.26 No Hyaluronidase:1.95 Post operative pain score: (p not provided) Hyaluronidase:1.04 No Hyaluronidase:1.03	• *Overall risk of bias:* **Low risk** ○ *Randomisation*: **Low risk** ○ *Deviations from intervention:* **Low risk** ○ *Missing outcome data:* **Low risk** ○ *Measurement of the outcome:* **Low risk** ○ *Selection of the reported result(s):* **Low risk** This study was part of the included studies for both the NICE Guideline review and the Cochrane systematic review. Both the reviews only

				Pain during administration of the block and perioperatively using a Visual Pain Analogue scale by a trained ophthalmic theatre nurse		considered the pain outcomes and not those related to akinesia. Provided objective assessment of akinesia 10 minutes after the block was performed. The incidence of surgical complications was the same in both groups with 1 case of posterior capsule rupture and 2 cases of incomplete capsulorhexis in each group. In none of these cases were the complications assessed as being due to the quality of the block.

Appendix 5: Excluded studies

	Author, date	Study type	Reason for exclusion
1	Khokhar S, et al. Intraoperative aberrometry in cataract surgery with topical versus peribulbar anesthesia. Indian J Ophthalmol. 2020 May;68(5):776-779.	NRSI	PICO criteria not met (wrong intervention)
2	Sharma DSC, et al. Use of hyaluronidase in plastic surgery: A review. J Plast Reconstr Aesthet Surg. 2021 Jul;74(7):1610-1614.	Review article	PICO criteria not met (wrong population)
3	Ibrahim M, et al. Efficacy of midazolam addition to local anesthetic in peribulbar block: Randomized controlled trial. Anaesthesist. 2019 Mar;68(3):143-151.	RCT	PICO criteria not met (wrong intervention)
4	El-Emam EM, et al. Efficacy of Ultrasound-Guided Caudal Epidural Calcitonin for Patients with Failed Back Surgery Syndrome. Anesth Essays Res. 2020 Jan-Mar;14(1):132-136. doi: 10.4103/aer.AER_98_19. Epub 2019 Aug 2.	RCT	PICO criteria not met (wrong population)
5	Pilger D, et al. Use of topical anaesthesia and peribulbar anaesthesia in Descemets membrane endothelial keratoplasty. Eur J Ophthalmol. 2021 May;31(3):1431-1436. doi: 10.1177/1120672120950935. Epub 2020 Aug 27. PMID: 32854539.	NRSI	PICO criteria not met (wrong comparator)
6	Patil V, et al. Effect of the addition of rocuronium to 2% lignocaine in peribulbar block for cataract surgery. J Anaesthesiol Clin Pharmacol. 2017 Oct-Dec;33(4):520-523.	RCT	PICO criteria not met (wrong intervention/ comparator)
7	El Fawal SM, et al. Minimum effective volume of local anesthetic in peribulbar block: does it differ with the eyeball axial length? Braz J Anesthesiol. 2021 Nov-Dec;71(6):635-641.	NRSI	PICO criteria not met (wrong intervention/ comparator)
8	Mohamed AA, et al. Safety and efficacy of addition of hyaluronidase to a mixture of lidocaine and bupivacaine in scalp nerves block in elective craniotomy operations; comparative study. BMC Anesthesiol. 2018 Sep 15;18(1):129.	RCT	PICO criteria not met (wrong population)
9	Malagola R, et al. Peribulbar anesthesia in sclero-retinal surgery: two quadrants vs single injection. G Chir.2018 Jul-Aug;39(4):227-231.	RCT	PICO criteria not met (wrong intervention/ comparator)
10	Moolagani VR, et al. Ropivacaine plus lidocaine versus bupivacaine plus lidocaine for peribulbar block in cataract surgery: A prospective, randomized, double-blind, single-center, comparative clinical study. J Anaesthesiol Clin Pharmacol. 2019 Oct-Dec;35(4):498-503.	RCT	PICO criteria not met (wrong intervention/ comparator)
11	Hakim KY, et al. Comparative Study between the Efficacy of Fentanyl, Antihistamines, and Dexmedetomidine in Suppressing Photic Sneeze Reflex during Peribulbar Block. Anesth Essays Res. 2019 Jan-Mar;13(1):40-43.	RCT	PICO criteria not met (wrong intervention/ comparator)
12	Alsaeid MA. Dexamethasone versus Hyaluronidase as an Adjuvant to Local Anesthetics in the Ultrasound-guided Hydrodissection of the Median Nerve for the Treatment of Carpal Tunnel Syndrome Patients. Anesth Essays Res. 2019 Jul-Sep;13(3):417-422.	RCT	PICO criteria not met (wrong population)
13	Costa P, et al. loco-regionali in oculistica: monofarmacologici o miscela con jaluronidasi? Studio prospettico randomizzato [Loco-regional block in ophthalmic surgery: single drug or drug combination with hyaluronidase? Randomized prospective study]. Minerva Anestesiol. 1999 Nov;65(11):775-83. Italian.	RCT	Not available in English
14	Rüschen H, et al. Use of hyaluronidase as an adjunct to local anaesthetic eye blocks to reduce intraoperative pain in adults. Cochrane Database Syst Rev. 2018 Mar 2;3(3):CD010368.	SR	Duplicate
15	Sarvela PJ. Comparison of regional ophthalmic anesthesia produced by pH-adjusted 0.75% and 0.5% bupivacaine and 1% and 1.5% etidocaine, all with hyaluronidase. Anesth Analg. 1993 Jul;77(1):131-4.	NRSI	PICO criteria not met (wrong intervention/ comparator)
16	Sarvela PJ, et al. Comparison of pH-adjusted bupivacaine 0.75% and a mixture of bupivacaine 0.75% and lidocaine 2%, both with hyaluronidase, in day-case cataract surgery under regional anesthesia. Anesth Analg. 1994 Jul;79(1):35-9.	NRSI	PICO criteria not met (wrong intervention/ comparator)
17	Johnson DA. Persistent vertical binocular diplopia after cataract surgery. Am J Ophthalmol. 2001 Dec;132(6):831-5.	NRSI	PICO criteria not met (prevalence study)
18	Pacella E, et al. Levobupivacaine vs. racemic bupivacaine in peribulbar anaesthesia: a randomized double blind study in ophthalmic surgery. Eur Rev Med Pharmacol Sci. 2010 Jun;14(6):539-44. PMID: 20712261.	RCT	PICO criteria not met (wrong intervention/ comparator)

NRSI=non-randomized study of interventions; RCT=randomized controlled study; SR=systematic review

Appendix 6: AGREE 2 appraisal summary - NICE Guideline, 2017

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall Assessment
NICE (2017) Clinical Guidelines for cataract surgery	94%	83%	79%	89%	77%	58%	92%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigour of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Appendix 7: AMSTAR 2 assessment of Rüschen et al, 2018 using the AMSTAR 2 tool (Shea 2017)[1]

No	Criteria	Yes/ Partial Yes/ No	Comment(s)
1	Research questions and inclusion criteria for the review included the components of PICO	Yes	-
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	Yes	https://doi.org/10.1002/14651858.CD010368
3	Review authors explained selection of the study designs for inclusion in the review	No	RCT only used without explicit motivation
4*	Review authors used a comprehensive literature search strategy	Yes	-
5	Review authors perform study selection in duplicate	Yes	-
6	Review authors perform data extraction in duplicate	Yes	-
7	Review authors provided a list of excluded studies and justify the exclusions	Yes	Discrepancies resolved by discussion
8*	Review authors described the included studies in adequate detail	Yes	-
9	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	Yes	-
10*	Review authors reported on the sources of funding for the studies included in the review?	Yes	-
11	For meta-analyses, review authors used appropriate methods for statistical combination of results	Yes	-
12*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	Yes	-
13	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes	-
14*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes	-
15	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	Yes	-
16*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	-

** Critical domains*

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Systematic review by Rüschen et al was assessed to be of high quality.
Rationale: There was only one non-critical weakness and thus the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

[1] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

South African National Essential Medicine List
Adult Hospital Medication Review Process
Component: AH Chp 18 - Eye

MEDICINE REVIEW

1. Executive Summary

Date: 31 August 2023
Medicine (INN): Mitomycin C and 5-fluorouracil (5-FU)
Medicine (ATC): L01DC03 and L01BC02
Indication (ICD10 code): H40
Patient population: Adjunctive therapy in adult patients requiring trabeculectomy surgery for glaucoma
Prevalence of condition: The overall prevalence of glaucoma in South Africa is stated at 4.5% (Baboolal SO et al, 2018), with estimates of 5 to 7% in the black population and 3 to 5% in the white population (Schellack N et al., 2017)
Level of Care: Adult Hospital Level (regional level of care)
Prescriber Level: Specialist
Motivator/reviewer name(s): G Thom , Z Adam, F Moti, L Visser, M McCaul
PTC affiliation:

Key findings

- In 2020, there were an estimated 76 million people with glaucoma worldwide. Africa has the highest incidence and prevalence of blindness compared to other regions, with glaucoma accounting for 15% of blindness.(Baboolal SO et al, 2018).
- Lowering intra-ocular pressure (IOP) is the only modifiable risk factor in the management of glaucoma. Treatment includes pharmacological management, laser therapy or surgery. Trabeculectomy is the most common type of surgery for glaucoma management for patients unresponsive to pharmacological management. Based on estimates by content expert reviewer (LV), less than 1000 trabeculectomies are conducted in the public sector locally. Adjunctive therapy with the antimetabolites mitomycin C (MMC) and 5 fluorouracil (5-FU) is reported to be effective in managing the risks of bleb failure (failure of the drainage flap created during trabeculectomy due to scarring) through a reduction in postoperative scarring.
- We conducted a review of efficacy and safety of intraoperative MMC or 5-FU for the management of adult glaucoma sufferers undergoing filtration surgery (trabeculectomy).
- We identified two systematic reviews (Wilkins M et al., 2005) (Green E et al., 2014) as relevant to our review question.

MMC:

- Patients at high risk of surgical failure who received intraoperative MMC were less likely to have failed surgery at 12 months) when compared to placebo/no intraoperative treatment, resulting in 35 fewer per 100 (from 22 to 46 fewer) surgical failures. Control 49/97 (50%) failed vs MMC 15/96 (15%) failed, ARR 35%, NNT 3 (95% CI 2 to 5) to prevent one failed surgery. (RR 0.32, 95% CI 0.20 to 0.53, 4 trials, n= 193 participants, moderate certainty of evidence).
- Patients undergoing surgery for the first time were less likely to have failed surgery at 12 months, relative to no antimetabolite or placebo, resulting in 20 fewer per 100 (from 12 to 30 fewer) with MMC. Control 30/107 (28%) vs intervention 18/231 (8%) ARR 20%, NNT 5 to prevent one failed surgery (95% CI 3 to 9), (RR 0.29, 95% CI: 0.16 to 0.53, 4 trials, n= 338 participants, moderate certainty of evidence).

- Intraoperative use of MMC reduced mean intraocular pressure (IOP). The mean pressure difference was -5.31 mmHg (95% CI: -3.85 to -6.76 mmHg) in high risk patients and -5.41 mmHg, 95% CI: -3.49 to -7.34 mmHg) in patients operated on for the first time, when compared to placebo or no antimetabolite. In clinical practice, a 1mmHg reduction in IOP can be regarded as significant.
- Overall, there was no increase in serious sight threatening side effects such as endophthalmitis with MMC. This analysis is limited by lack of power. Only one study reported on this outcome in patients receiving surgery for the first time: no cases of endophthalmitis occurred (0/229 in the MMC group compared to 0/71 in the control group.

5-FU

- Early trials with 5-FU were primarily focused on the postoperative injections which are now rarely used due to the more labour intensive follow up by clinicians and inconvenience for patients due to the series of postoperative injections. In more recent trials, 5-FU has been administered intraoperatively using sponges moistened with 25mg/mL or 50mg/mL 5-FU solution, applied to the sclera for 5 minutes.
- We did not find any RCTs of 5FU in patients at high risk of surgical failure. RCT evidence for the intraoperative use of 5-FU is limited to low risk patients undergoing primary trabeculectomy.
- Patients undergoing surgery for the first time treated with intraoperative 5-FU had a lower risk of failure at 12 months, than those treated with placebo/no intraoperative treatment. There were 9 fewer failures per 100 (from 3 to 15 fewer) with 5-FU compared to placebo/no intraoperative treatment. There were 96/359 failures (27%) with placebo/no treatment vs 63/352 failures (18%) with 5-FU. ARR 9% NNT 11 (95% CI 7 to 37), to prevent one surgical failure. RR 0.67 (95% CI 0.51 to 0.88, 4 trials, n= 711 participants, high certainty of evidence)
- Intraoperative use of 5-FU in patients undergoing surgery for the first time, reduced mean intraocular pressure (IOP) compared to placebo/no intraoperative treatment. The mean difference in intraocular pressure was -1.04 mm Hg (95% CI -0.43 to -1.65) when comparing patients receiving 5-FU to those receiving placebo/ no intraoperative treatment. This small difference may not be clinically significant.
- The systematic review did not find an increased risk of sight-threatening complications with 5-FU, however other complications such as hypotonous maculopathy and epithelial toxicity were more common with 5-FU.

MMC versus 5 FU

- In patients at high risk of surgical failure (intraoperative and postoperative use, any application method), MMC resulted in fewer surgical failures at 12 months. There were 19/139 failures (14%) with MMC vs 34/125 failures (27%) with 5-FU. ARR 14% NNT 7 (95% CI 4 to 26 fewer with MMC). RR 0.49 (95% CI 0.22 to 1.08, 5 trials, n= 264 participants, low certainty of evidence)
- In patients at low risk of surgical failure (intraoperative and postoperative use, any application method), MMC resulted in fewer surgical failures at 12 months. There were 9/181 failures (5%) with MMC vs 14/189 failures (7%) with 5-FU. ARR 2% NNT 41 (95% CI 13 fewer to 37 more with MMC). RR 0.64 (95% CI 0.19 to 2.2, trials, n=370 participants, low certainty of evidence.
- In a subgroup analysis of patients who were treated with either MMC or 5-FU with an intraoperative sponge application, MMC resulted in fewer surgical failures at 12 months. There were 10/167 failures with MMC vs 17/154 failures with 5-FU. ARR 5% NNT 20 (95% CI 9 fewer to 89 more with MMC). RR 0.52 (95% CI 0.13 to 2.08, 4 trials, n= 321 participants, low certainty of evidence).
- Local management of patients with a failed trabeculectomy involves follow up surgery with the use of Ahmed valves (local cost R5500 – R7200 per valve). Utilizing a NNT of 20, the cost of treating 20 patients with intraoperative sponge application of MMC is R5000 to prevent 1 additional surgical failure which translates to a cost aversion of R5500-7200 for an Ahmed valve (excluding other related surgical costs).

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: The committee suggests that adult patients with glaucoma undergoing filtration surgery (trabeculectomy) should receive intraoperative mitomycin compared to No mitomycin-C, No 5-fluorouracil, placebo or sham *(conditional, low certainty of evidence).* *Rationale: Intraoperative sponge application of MMC results in fewer surgical failures at 12 months compared to No mitomycin-C, No 5-fluorouracil, placebo or sham. The benefits of 5-FU versus placebo or control is limited to low risk patients only. Furthermore, while the cost per unit of MMC is greater than 5-FU, utilizing an ARR 5%, (NNT 20) for MMC versus 5-FU, the cost of treating 20 patients with intraoperative sponge application of MMC is R5000 to prevent 1 additional surgical failure that would result in a cost of R5500-7200 being averted for an Ahmed valve which is used in follow up surgery, as the current standard of care for patients with failed trabeculectomies.* **Level of Evidence:** MMC vs placebo or no antimetabolite (moderate certainty evidence) and MMC v 5-FU (low certainty of evidence **Review indicator: New evidence on efficacy or safety of MMC**					
NEMLC RECOMMENDATION (MEETING OF 30 November 2023): NEMLC supports the ERC's recommendation as stated above.					
Monitoring and evaluation considerations					
Research priorities					

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INTRODUCTION/BACKGROUND

Glaucoma is a mixed group of eye disorders with related optic neuropathy (Marais A et al., 2017). While the pathophysiology of glaucoma is not well understood (Schellack N et al., 2017), glaucoma is reported to be responsible for 30% of blindness, the second leading cause of blindness worldwide after cataracts (Cook, 2009). In Africa, glaucoma is said to account for 15% of blindness with the highest incidence and prevalence of blindness relative to other regions worldwide (Baboolal SO et al, 2018).

Glaucoma can present as either a primary inherited disorder or as secondary disorder as a result of trauma, adverse effects to medicines, concomitant disease or congenital abnormalities. Patients may present with open angle glaucoma in which the trabecular meshwork remains open but undergoes morphological changes that results in impaired drainage of intraocular fluid, or closed angle glaucoma in which the pupil of the eye compresses the drainage canal between the iris and cornea, resulting in a raised intraocular pressure (Marais A et al., 2017). Primary open angle glaucoma is cited as being the most common presentation (Marais A et al., 2017) (European Glaucoma Society, 2021).

The number of people with glaucoma was estimated to be 76 million in 2020 worldwide (European Glaucoma Society, 2021), and based on global incidence reports, glaucoma has been suggested to have an ethno-genetic disease pattern (Kapetanakis VV et al, 2016). The overall prevalence of glaucoma in South Africa is stated at 4.5% (Baboolal SO et al, 2018), with estimates of 5 to 7% in the black population and 3 to 5% in the white population (Schellack N et al., 2017). Primary open angle glaucoma is most prevalent in black populations with Asian ethnicity being a risk factor for the less common angle closure glaucoma. A local study by (Salmon JF et al, 1993) conducted in Mamre, a village near Cape Town with strong ancestry links to Southeast Asians, identified primary angle closure glaucoma as a significant public health problem in the Western Cape Province.

The lowering of intra-ocular pressure (IOP) is the only modifiable risk factor in the management of glaucoma and has been considered to be part of established clinical practice over a century ago (Wilkins M et al., 2005), although good evidence in support of this intervention has only more recently been demonstrated (Kass MA et al, 2002) (Heijl a et al, 2002). A systematic review by (Maier PC et al, 2005) concluded that lowering IOP in patients with glaucoma significantly delays visual field deterioration (Hazard ratio =0.65, 95% CI (0.49 to 0.87), P = 0.003; NNT = 7). According to (Marais A et al., 2017), *"the goal of treatment in treating POAG (primary open angle glaucoma) is to establish and maintain the intraocular pressure at a range where visual field loss will have the least negative impact on the patient's perceived visual disability."* In view of the relatively poor sensitivity of measuring intraocular pressure, nearly half of patients with primary open angle glaucoma will present with an IOP below 22mmHg – IOP targets therefore require patient individualization.

Treatment of glaucoma includes pharmacological management, laser therapy or surgery. A Cochrane review by (Burr J et al, 2012) concluded that in severe open angle glaucoma, surgery lowered IOP significantly more than medications (pilocarpine, an older drug not currently widely used) and reduced the risk of progressive loss of visual field. Furthermore, a longitudinal follow up of a sub-group of patients enrolled in the Collaborative Initial Glaucoma Treatment Study (CIGTS) (Gillespie B et al, 2003), 9 years after treatment initiation concluded that initial surgery was beneficial for participants with more advanced visual field loss at presentation but detrimental for patients with diabetes (Musch DC et al, 2009).

Trabeculectomy is the most common type of surgery for glaucoma management and involves the drainage of fluid through surgical incision at the wall of the eye, creating a fistula that drains aqueous humour from the eye to the subconjunctival space thus creating a filtering bleb. Trabeculectomy is cited as the surgery of choice in African eyes even though the risks of failure of filtration blebs is well documented (Cook, 2009). Adjunctive therapy with antimetabolites (mitomycin C and 5 fluorouracil) is reported to be effective in managing the risks of bleb failure through a reduction in postoperative scarring. A negative consequence to inhibiting wound healing is that the conjunctiva overlying the sclerostomy may become very thin, and during the early postoperative period, greater flow of aqueous through the sclerostomy could lead to hypotony. Over time, holes can form in the conjunctiva with bacterial infection resulting in endophthalmitis (Wilkins M et al., 2005).

While mitomycin C is used routinely in clinical practice as an adjunct during trabeculectomy there is no Standard Treatment Guideline for trabeculectomy with no suitable alternative listed on the Essential Drug List. The aim of this review is to assess the efficacy and safety of the use of two commonly used antimetabolites (mitomycin C and 5 fluorouracil) used as adjunctive therapy during trabeculectomy to reduce bleb failure.

ELIBILITY CRITERIA FOR REVIEW

Research Question: Should intraoperative antimetabolites (either MMC or 5-FU) be used in adult patients undergoing trabeculectomy?

Table 1: Purpose/Objective i.e., PICO

Population	Adult patient ≥18 years with glaucoma undergoing filtration surgery (trabeculectomy)
Intervention	Intraoperative mitomycin-C (topical) or 5-fluorouracil (5-FU)
Control	No mitomycin-C, No 5-fluorouracil, placebo or sham
Outcomes	Trabeculectomy failure, change in intraocular pressure (pre- vs post-surgery), need for repeat surgery, adverse events and adverse reactions.
Study designs	Systematic reviews of RCTs or RCTs. Observational studies will only be sourced if the latter are unavailable.

METHODS:

a. Data sources:

The websites of organisations identified by local experts as credible authorities for guideline development (NICE, European Society of Ophthalmology, Royal College of Ophthalmologists, American Academy of Ophthalmology) were searched for relevant guidelines. Additionally, a free text google search was undertaken to identify clinical guidelines/reviews from recognized clinical bodies/authorities within the ophthalmology specialty. Systematic reviews (SRs) of randomised controlled trials (RCTs) were sought in PubMed, the Cochrane Library, and Epistemonikos.

b. Search strategy:

A search for systematic reviews and meta-analyses was conducted on the 2nd August 2023 from the following databases

COCHRANE: mitomycin AND glaucoma yielded 28 results and fluorouracil and glaucoma yielded 21 results

PUBMED: See Appendix 1 for the Pubmed search history which yielded 28 results

EPISTEMONIKOS: mitomycin AND glaucoma yielded 28 results and fluorouracil and glaucoma yielded zero results

c. Screening, data extraction and analysis, evidence synthesis:

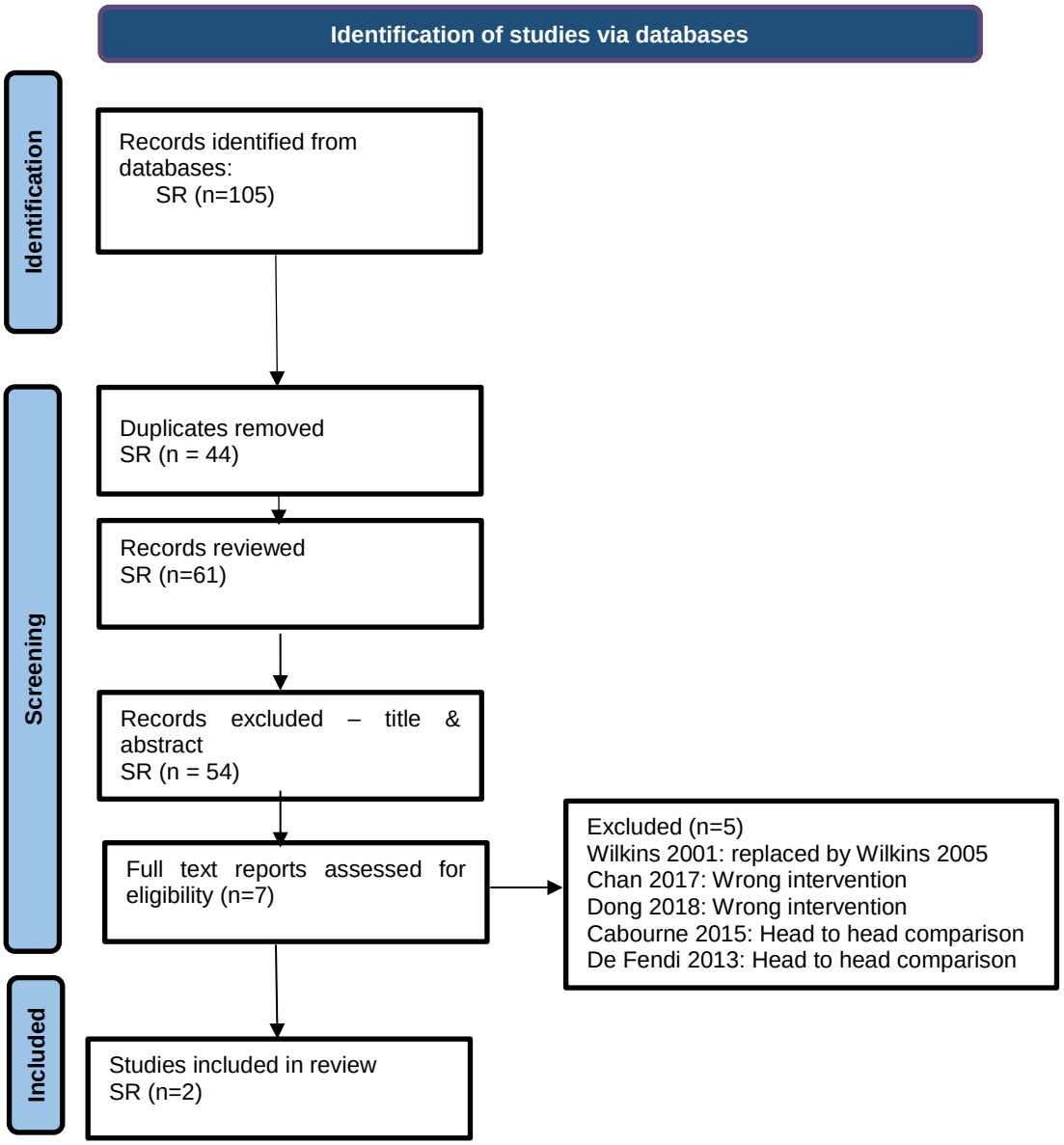
Titles and abstracts were screened independently (ZA) with a second check by (GT). Full text screening was by (ZA) with second checks by (GT). Eligible clinical guidelines were appraised with the AGREE II tool and eligible systematic reviews were appraised using the AMSTAR II Checklist independently by two reviewers (ZA and GT), with discrepancies resolved following discussion.

RESULTS

a. Search Results

Refer to Figure 1 below the Prisma flow diagram. Following removal of duplicates, 61 records were reviewed by title and abstract, with 54 being excluded as not aligned to the PICO. Studies involving congenital glaucoma, non-penetrative procedures (e.g. trabeculoplasty) or trabeculectomy involving cataract surgery or other procedures were excluded. The full text references of 7 studies were assessed for eligibility and a further 5 references were excluded as not specific to our PICO.

Figure 1: Prisma flow diagram



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

The following SRs were identified for inclusion in the review:

- (Wilkins M et al., 2005) Intraoperative Mitomycin C for glaucoma surgery.
- (Green E et al., 2014) 5-Fluorouracil for glaucoma surgery.

DESCRIPTION OF CLINICAL GUIDELINES, SYSTEMATIC REVIEWS AND RCTs IDENTIFIED

a. Guidelines

Six guidelines were assessed and the key recommendations as relevant to our PICO are summarised in Table 1 below, which includes the AGREE II scores for each.

Table 1. AGREE II assessments of guidelines

Guideline citation and website	Recommendations	AGREE II Appraisal
Glaucoma: diagnosis and management (Jan 2022) (National Institute for Health and Care Excellence (NICE), 2022)	Mitomycin-C is an antimetabolite used during the initial stages of trabeculectomy to prevent excessive postoperative scarring and therefore reduce the risk of failure. NICE recommendations: Treatment for people with advanced COAG • Offer people with advanced COAG, glaucoma surgery with pharmacological augmentation (MMC) as indicated. Give them information on the risks and benefits of surgery. Treatment for people with Chronic open angle glaucoma (COAG) (Use of mitomycin-C off label). Indicated for the following: • Treatment for people with advanced COAG: Offer people with advanced COAG, glaucoma surgery with pharmacological augmentation (MMC) as indicated. Give them information on the risks and benefits of surgery • An option for people with good medication adherence and instillation technique with eye drops where IOP not sufficiently reduced to prevent progression of sight loss • An option for people with COAG who are at risk of progressing to sight loss despite treatment with medicines from 2 therapeutic classes • An options for people with COAG who cannot tolerate a pharmacological treatment -after treatment with medicines from 2 therapeutic classes has been trialed	83
(American Academy of Ophthalmology: Preferred Practice Pattern Glaucoma Committee:, 2020)	A 2005 Cochrane Systematic Review concluded that antifibrotic agents may be used intraoperatively and postoperatively to reduce the subconjunctival scarring after trabeculectomy that can result in failure of the operation, and therefore intraoperative MMC should be used. (I+, Moderate Quality, Strong Recommendation) Studies confirm this outcome in eyes at high risk of surgical failure and eyes that have not undergone previous surgery. A 2015 Cochrane Systematic Review concluded that there is low quality evidence that MMC may be more effective than intraoperative 5-fluorouracil (5- FU) in achieving long-term lower IOP. A 2014 Cochrane Systematic Review reported evidence that intraoperative 5-FU may improve the success rate of lowering IOP compared with no antifibrotic agents but requires multiple injections. Also, 5-FU is increasingly being used on an ad-hoc basis, for which there is no evidence. Therefore, the selection of intraoperative MMC or 5-FU should be left to the discretion of the treating ophthalmologist, in consultation with the individual patient. Intraoperative 5-FU and MMC were found to be equally safe and effective adjuncts to primary trabeculectomy in a multicenter, randomized clinical trial. The use of postoperative injections of 5-FU also reduces the likelihood of surgical failure in both high-risk eyes and eyes that have not undergone previous surgery. A 2014 Cochrane Systematic Review reported that postoperative injections of 5-FU were rarely utilized in postoperative regimens, perhaps because of patient preference and an increased risk of complications. Thus, the routine administration of postoperative 5-FU is not recommended, but should be based on individualized considerations for the patient.457 (I++, Moderate Quality, Strong Recommendation) . The use of an antifibrotic agent carries with it an increased risk of complications such as hypotony, hypotony maculopathy, late-onset bleb leak, and late-onset infection that must be weighed against the benefits when deciding whether to use these agents. These complications may be even more common in primary filtering surgery of phakic patients. A trend toward a lower concentration and shorter exposure time of MMC has been observed over time, and use of a fornix-based conjunctival flap with broad application of MMC has been advocated to avoid bleb-related complications.	75
Management of angle closure glaucoma guidelines (The Royal College of Ophthalmologists, 2022)	In medically uncontrolled **primary angle-closure glaucoma (PACG)** eyes without cataract, trabeculectomy with mitomycin C may be indicated, particularly in younger patients with accommodative ability. In a small RCT comparing the efficacy of phacoemulsification versus trabeculectomy with mitomycin-C in medically uncontrolled PACG eyes with clear lens, trabeculectomy group was found to be more effective than phacoemulsification, requiring on average 1.1 fewer drugs after surgery. Surgical complications were substantially higher in the trabeculectomy group than among those undergoing phacoemulsification (44% vs. 4% respectively). There were no differences between the two treatment groups in number of additional surgical interventions at 2 years, although one third of patients undergoing trabeculectomy developed significant cataract within this timeframe. However, in cases of advanced PACG, uncontrolled IOP and concurrent cataract, primary trabeculectomy with mitomycin-C may be a viable option. The sequence of cataract and glaucoma	75

	surgery need to be considered carefully. The benefits of sequential surgery versus combined phaco-trabeculectomy in more severe or advanced disease remain unclear.	
Terminology and guidelines for glaucoma. (European Glaucoma Society, 2021)	Antifibrotics such as 5-fluorouracil (5-FU) and mitomycin-C (MMC) are routinely used in patients undergoing glaucoma filtration surgery in order to reduce postoperative conjunctival scarring and improve drainage. Although 5-FU and MMC are not officially approved for ocular surgery, their off-label use in filtration surgery has become standard clinical practice and there is evidence supporting their use. The use of antifibrotics is potentially hazardous, and requires careful surgical technique to prevent complications. Early and late over drainage and hypotony, or a thin focal drainage bleb that is associated with a higher risk of infection, are more common with antifibrotics. The use of larger antifibrotic treatment areas and a fonix-based conjunctival flap may minimize the occurrence of thin cystic blebs. It is important to assess each individual case for risk factors, and/or for the need of low target IOP and choose the substance, concentration, volume and duration of exposure used. The use of antifibrotics will enhance the unfavourable effect of any imprecision during surgery. Administration 5-Fluorouracil: – Intraoperative use – Concentration: 25 or 50 mg/ml undiluted solution. Administration: on a filter paper or a sponge or by subconjunctival injection. – Time of exposure: usually 5 minutes. Rinse: with at least 20 ml of balanced salt solution. Mitomycin C: – Intraoperative use – Concentration: 0.1-0.5 mg/ml – Administration: intraoperatively on a filter paper or a sponge or by subconjunctival injection. – Time of exposure: 1-5 minutes if on a filter paper or sponge. – Rinse: with at least 10-20 ml of balanced salt solution.	58
(**Canadian Ophthalmological Society Glaucoma Clinical Practice Guideline** Expert Committee; Canadian Ophthalmological Society., 2009)	The use of perioperative locally applied antimetabolites has improved success rates, particularly in eyes at risk for failure. Postoperative 5-fluorouracil injected subconjunctivally was initially studied in a randomized prospective fashion with improved success in the group receiving the 5-fluorouracil and subsequently found to improve surgical success rates in several studies. 5-fluorouracil has largely been replaced by mitomycin C, which is a more potent antiscarring agent that can be applied in a more convenient fashion intraoperatively. Although antimetabolites do increase the success of trabeculectomy, they may also increase the risk of postoperative complications including wound leak, hypotony suprachoroidal hemorrhage, and bleb-related endophthalmitis.	42
The Japan Glaucoma Society guidelines for glaucoma 5th edition 2023 (Kiuchi Y et al, 2023)	Trabeculectomy This technique adjusts the filtration rate by fabricating a scleral flap, excising the limbus tissue below the scleral flap, and suturing the scleral flap. It is currently the most common glaucoma surgery for most types of glaucoma, including primary open-angle glaucoma (broad). The antimetabolic agents, mitomycin C or 5-fluorouracil are used intraoperatively and postoperatively to inhibit scarring at the filtration site.	42

b. Systematic reviews and randomised controlled trials

- ***Systematic review:***

Table 2. AMSTAR 2 assessment of the SRs

Systematic review	Conclusions	AMSTAR 2 appraisal
(Wilkins M et al., 2005) Intraoperative Mitomycin C for glaucoma surgery.	Intraoperative MMC reduces the risk of surgical failure in eyes that have undergone no previous surgery and in eyes at high risk of failure. Compared to placebo it reduces mean IOP at 12 months in all groups of participants in this review. Apart from an increase in cataract formation following MMC, there was insufficient power to detect any increase in other serious side effects such as endophthalmitis. It is possible that low event rates and varying definitions would prevent the detection of a true increase in complications such as infection and hypotony. The quality of evidence supporting these conclusions is at best moderate and often low.	Low quality review
(Green E et al., 2014) 5-Fluorouracil for glaucoma surgery.	This SR assessed the effects of both intraoperative application **and postoperative injections** of 5-FU in eyes of people undergoing trabeculectomy. (note that postoperative application of antimetabolites is outside the scope of our PICO).	Low quality review

	Postoperative injections of 5-FU are now rarely used as part of routine packages of postoperative care but are increasingly used on an ad hoc basis. This presumably reflects an aspect of the treatment that is unacceptable to both patients and doctors. None of the trials reported on the participants' perspective of care, which constitutes a serious omission for an invasive treatment such as this. The small but statistically significant reduction in surgical failures and intraocular pressure at one year in the primary trabeculectomy group and high-risk group must be weighed against the increased risk of complications and patient preference.	

MMC (Wilkins M et al., 2005)

The Cochrane review by (Wilkins M et al., 2005), considered the use of intraoperative mitomycin C compared to placebo as an adjunct in trabeculectomy surgery as a treatment for glaucoma. The SR included 11 RCTS with a total of 698 participants. The trials enrolled three types of participants (see Appendix 5). RCTs that were included in the review involved the use of intraoperative MMC at any concentration and dose (studies included doses that ranged from 0.1 to 0.5 mg/mL saline over 1 to 5 minutes) compared to placebo or control. The primary outcomes focused on the efficacy of MMC and was assessed as the proportion of failed trabeculectomies at 12 months after surgery and the mean IOP at 12 months after surgery. Failure was defined as repeat surgery or uncontrolled IOP (usually more than 22 mmHg) despite additional topical or systemic medications. Secondary outcomes focused on adverse effects which included wound leaks, hypotony, late endophthalmitis, expulsive haemorrhage, shallow anterior chamber and cataracts.

5-FU (Green E et al., 2014)

The Cochrane review by (Green E et al., 2014) was an update of a previous Cochrane review first published in 2000 with an update in 2009, that assessed the *postoperative* use of 5FU (not covered by our PICO) compared with control following trabeculectomy. Since the 2000 publication, new evidence on the use of intraoperative 5FU was published and the review authors took the decision to expand the scope of the original review to include intraoperative use of 5FU. For the purposes of the review, the interventions were divided into three subgroups of 5FU injections (intraoperative, regular dose postoperative and low dose postoperative) and participants were categorized into 3 subgroups (see Appendix 5). The review includes 12 RCTS encompassing 1319 participants, of which 5 trials that included a total of 770 participants involved the **intraoperative use of 5FU in patients undergoing primary trabeculectomy** - we have limited our reporting to the use of intraoperative 5FU only, in accordance with our pre-specified PICO. Intraoperative use of 5-FU included administration of moistened sponges with either 25mg/mL or 50mg/mL to the sclera for 5 minutes. The primary outcomes were the proportion of failed trabeculectomies at 12 months after surgery, and the mean IOP at 12 months. Secondary outcomes were reported as adverse event rates and included wound leaks, hypotony, late endophthalmitis, expulsive haemorrhage, shallow anterior chamber, corneal and conjunctival epithelial erosions and other complications.

- ***Randomised controlled trials:***

The Medline search for RCTs by (Wilkins M et al., 2005) was done until January 2010 and for (Green E et al., 2014) until July 2013. We conducted a further Pubmed search for relevant RCTs involving MTC and 5-FU since the literature search by (Wilkins M et al., 2005) and (Green E et al., 2014) respectively, to identify any updates since.

The following RCT was identified as relevant to our PICO:

MMC

(Shaheer M et al, 2018): **Comparison of mean corneal cell loss after trabeculectomy with and without mitomycin C**

Sixty patients with primary open angle glaucoma uncontrolled with medication were identified from an outpatient ophthalmology department in Pakistan to undergo trabeculectomy with (Group A) or without MMC (Group B). The objective of the study was to assess mean endothelial cell loss with or without MMC. Endothelial cell loss is a concern because the corneal endothelium is a monolayer of cells which play an important role in corneal hydration and transparency. Disruption to this layer of cells has a critical impact on physiological function, negatively impacting the drainage of intraocular fluid and corneal transparency which could lead to irreversible corneal oedema and blindness. These cells have limited replicative ability in vivo.

Additional RCTS that compared different doses of MMC and different surgical techniques using MMC were also identified. These were not deemed directly relevant to our PICO so have not been summarised in our results, however, relevant mention of these studies is included as part of our conclusion.

OUTCOMES

EFFECTIVENESS:

MMC (Wilkins M et al., 2005)

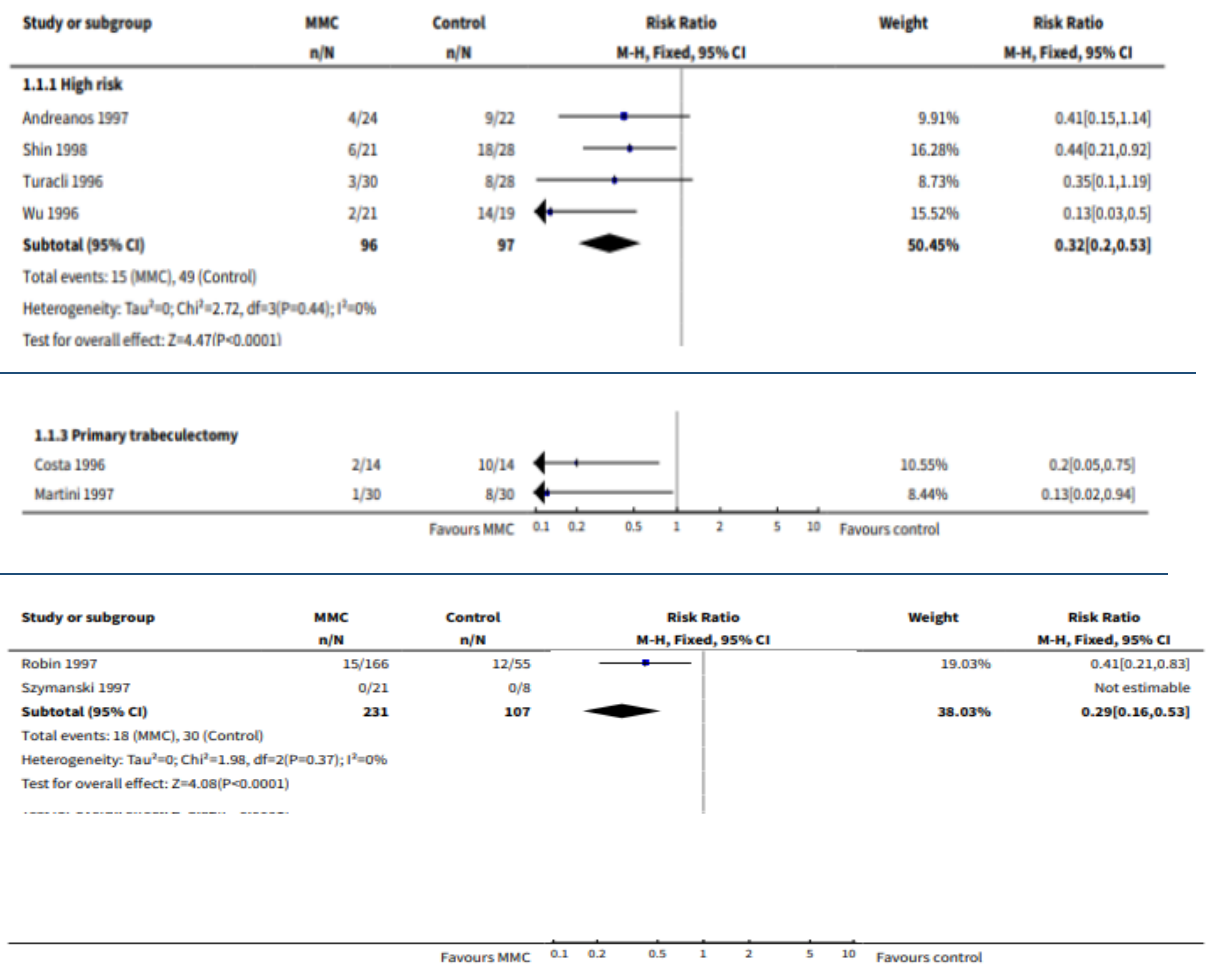
Refer to Appendix 2 for the summary of findings table for **Intraoperative Mitomycin C compared with no antimetabolite or placebo** for trabeculectomy surgery for glaucoma

Failure at 12 months:

High risk of failure group, Intraoperative MMC demonstrated a protective benefit against failure of surgery at 12 months (RR 0.32, 95% CI 0.20 to 0.53, 4 trials, n= 193 participants, moderate certainty of evidence) when compared to placebo/no intraoperative treatment, resulting in 35 fewer per 100 (from 22 to 46 fewer) surgical failures.

Primary trabeculectomy group: MMC demonstrated a 71% reduction in risk of surgical failure (RR 0.29, 95% CI: 0.16 to 0.53, 4 trials, n= 338 participants, moderate certainty of evidence) relative to no antimetabolite or placebo, resulting in 20 fewer per 100 (from 12 to 30 fewer) with MMC relative to no antimetabolite or placebo.

Figure 2 : Intraoperative MMC versus control, High risk and primary trabeculectomy – failure at 12 months

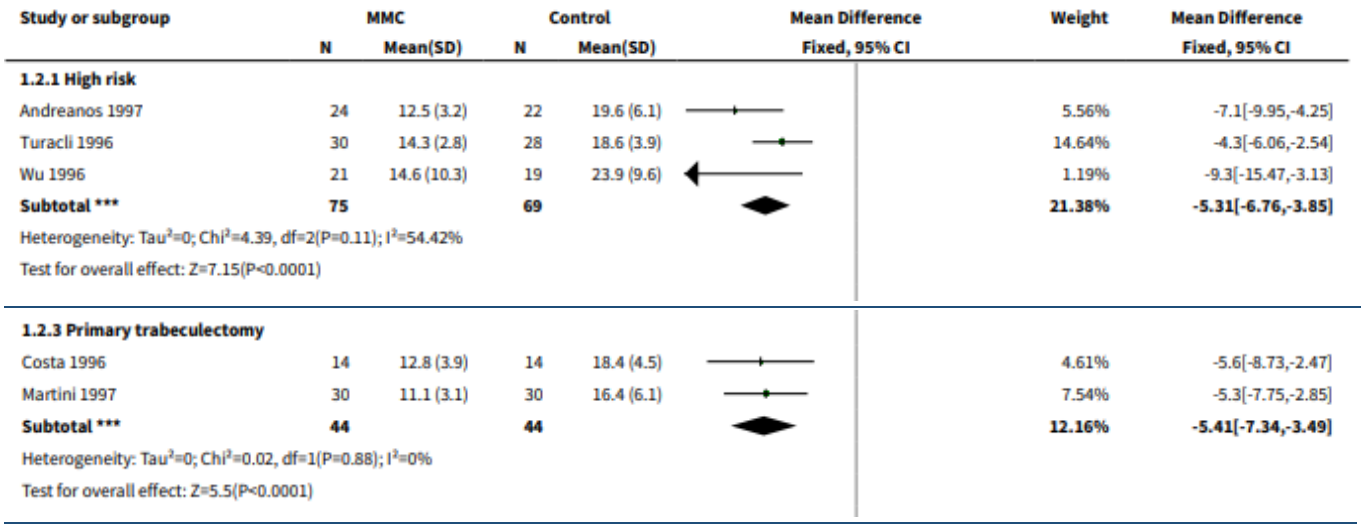


Mean intraocular pressure (IOP) at 12 months

High risk of failure group: Three trials reported that MMC produced a statistically significant reduction in IOP from baseline to 12 months with the weighted mean difference across the 3 trials combined, demonstrating that MMC lowers IOP by 5.31 mmHg more than placebo (95% CI: 3.85 to 6.76 mmHg).

Primary trabeculectomy group: The mean reduction in IOP at 12 months was similar across the 2 trials that reported this outcome, with a pooled estimate of effect favouring MMC over placebo (mean difference in decrease from baseline 5.41 mmHg, 95% CI: 3.48 to 7.34 mmHg).

Figure 3 : Intraoperative MMC versus control, High risk and primary trabeculectomy – mean IOP at 12 months



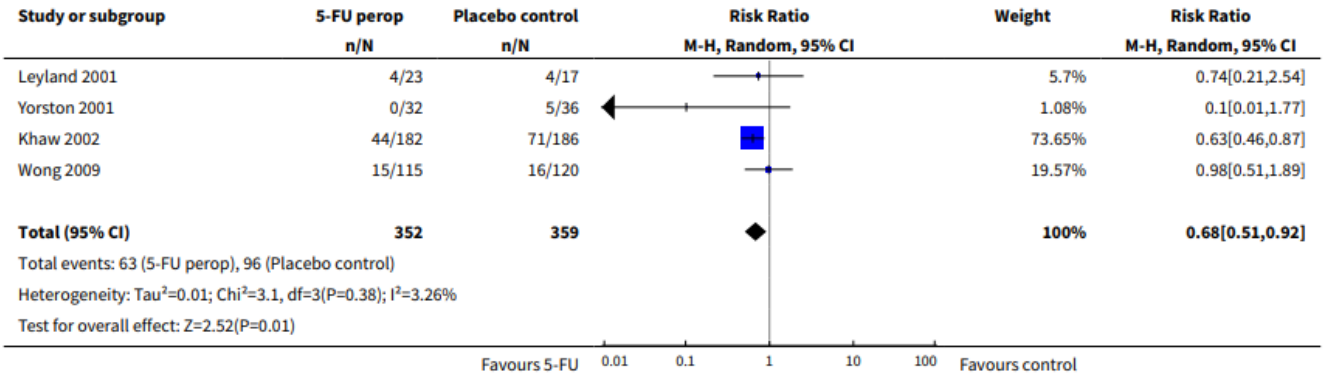
5-FU (Green E et al., 2014)

Refer to Appendix 3 for the summary of findings table for **Intraoperative 5-Fluorouracil versus placebo or control** for glaucoma surgery.

Failure at 12 months:

Primary trabeculectomy group: The reviewers report a substantial point estimate risk reduction of failure at one year of 0.68 (95% CI 0.51 to 0.92, 4 trials, n= 711 participants, high certainty of evidence) with 5-FU than those treated with placebo/no intraoperative treatment, resulting in 9 fewer per 100 (from 3 to 15 fewer) with 5-FU), Results were based primarily on outcomes from the to the Khaw (2002) study. According to the reviewers, the difference in effect estimates of the different trials did not reflect the lower dose of 5- FU used in Leyland 2001 and Yorston 2001.

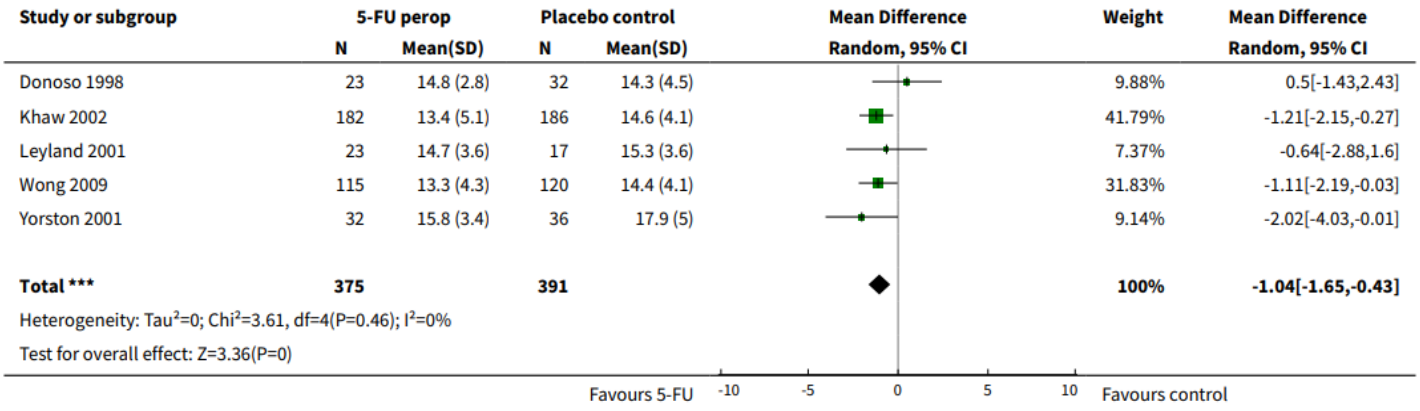
Figure 4 : Regular dose intraoperative 5-FU versus placebo or control, primary trabeculectomy – failure at 12 months



Mean intraocular pressure (IOP) at 12 months

Primary trabeculectomy group: A small overall reduction in IOP of 1.04 mm Hg (95% CI 0.43 to 1.65) was demonstrated which is statistically significantly but may not be clinically significant according to the review authors.

Figure 5 : Regular dose intraoperative 5-FU versus placebo or control, primary trabeculectomy –Mean IOP at 12 months



SAFETY

MMC

MMC (Wilkins M et al., 2005)

Wound leak:

High risk of failure group: No reported events in MMC or placebo groups.

Primary trabeculectomy group: While there were more events in the MMC group compared to placebo in the two studies that reported on this outcome, the difference was not statistically significant.

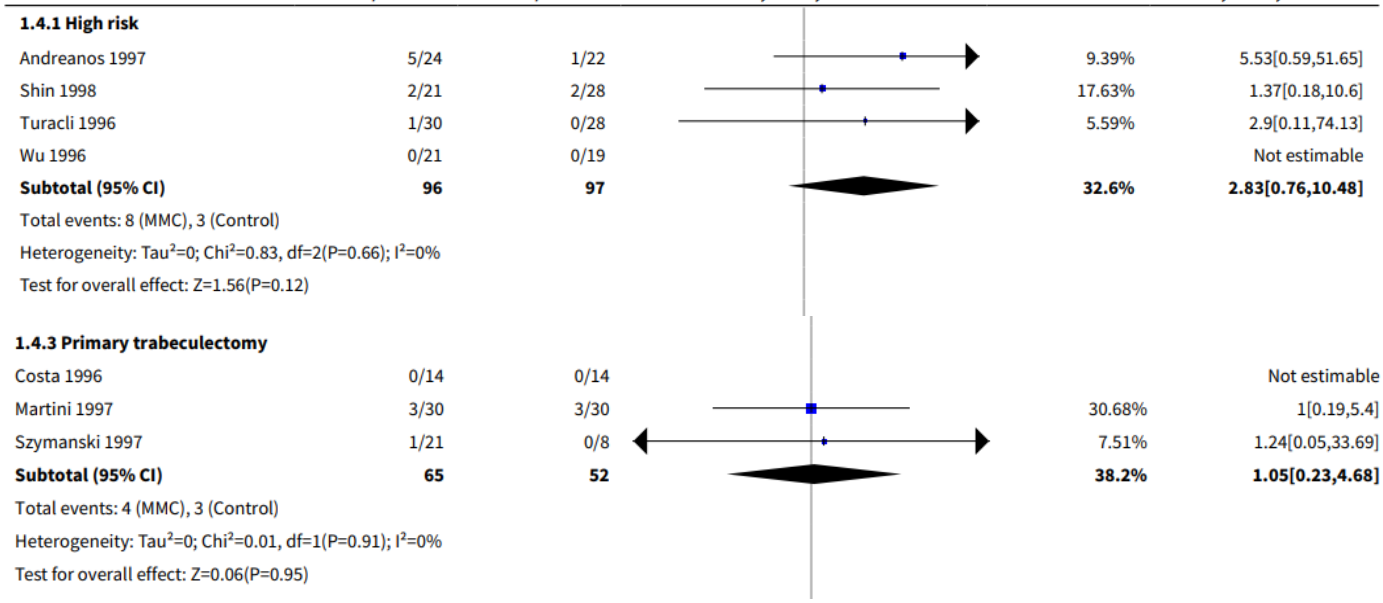
Hypotony:

High risk of failure group: Increased risk of hypotony reported with MMC OR 2.83, 95% confidence interval (CI): 0.76-10.48, 3 RCTs, 193 participants

Primary trabeculectomy group: Increased risk of hypotony reported as OR 1.05 95% confidence interval (CI): 0.23-4.68 RCTs, 117 participants

While the point estimate in all three risk groups show an increase in the risk of hypotony with MMC, the wide confidence intervals for the reported odds ratios in each group all cross 1, hence the results are not statistically significant.

Figure 6 : Intraoperative MMC versus control, Complications - hypotony



Endophthalmitis:

Primary trabeculectomy group: One study reported on this outcome in which no cases of endophthalmitis occurred (0/229 in the MMC group compared to 0/71 in the control group).

Shallow anterior chamber:

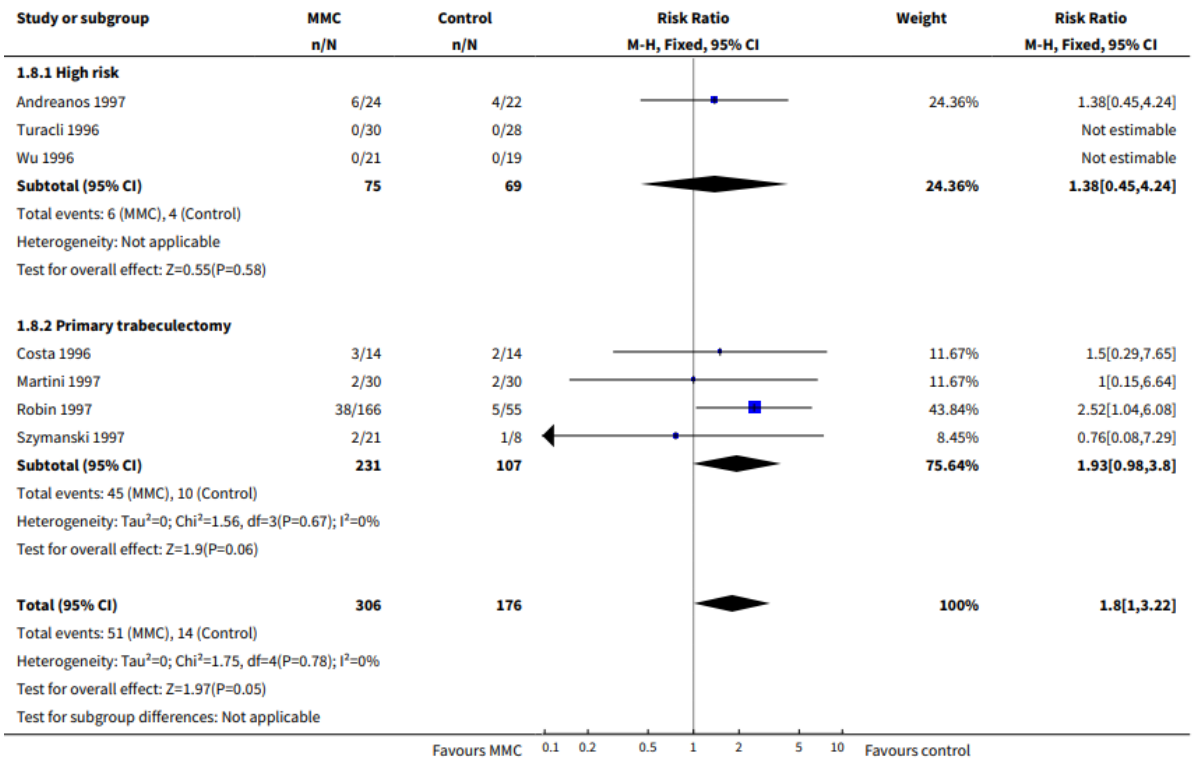
There was no reported difference between MMC and placebo across each of the risk groups and overall. However the rates of occurrence varied markedly from 0/57 to 8/30 across MMC and control groups which the review authors attribute most likely to variation in the definitions used as well as surgical technique.

Cataract:

Primary trabeculectomy group: one study (Robin 1997) reported a statistically significant increase in the risk of cataract associated with the use of MMC. Using a fixed-effect model, the pooled estimates of effect showed that the risk of cataract was possibly increased with MMC use in trials of participants in the primary trabeculectomy group (RR 1.93, 95% CI: 0.98 to 3.80), as well as for all participant groups analysed together (RR 1.80, 95% CI: 1.00 to 3.22).

Cataract was the only side effect that was significantly increased with the use of MMC, with a NNH=15 for one additional cataract.

Figure 7: Intraoperative MMC versus control: Complications – cataract



Endothelial cell loss: (Shaheer M et al, 2018)

The results of this small study (n= 60) demonstrate that the mean endothelial cell loss was three times greater with adjunctive MMC compared to trabeculectomy with no MMC. The median endothelial cell loss in group A was 283.00 (66.50), and in group B the median endothelial cell loss was 72.50 (19.25), which was statistically significant (p<0.001). No cases of corneal decompensation or other complication were noted despite the higher rate of endothelial cell loss.

Figure 8: Endothelial cell loss with and without MMC

Endothelial cell loss	Median	IQR	Minimum	Maximum
With MMC	283.00	66.50	179	356
Without MMC	72.50	19.25	44	105

P-value <0.001 (Mann-Whitney test was used as the data was not normal).

5-FU (Green E et al., 2014)

Figure 9: Risk of complications

Intervention	Complication (risk ratio (95% confidence interval))			
	Wound leak	Hypotonous maculopathy	Shallow anterior chamber	Epithelial toxicity
Primary trabeculectomy	1.36 (1.00, 184)	1.47 (0.42, 5.12)	1.99 (1.22, 3.22)	1.23 (0.85, 1.77)

Wound leak:
5-FU caused a 50% increase in the RR of wound leak, which is just significant with the summary estimate with no statistical heterogeneity or apparent dose-related response.

Hypotonous maculopathy:
Only one study (Khaw 2002) reported on this outcome which was slightly more common with 5-FU.

Late endophthalmitis and expulsive haemorrhage:
These outcomes were not reported in studies using intraoperative 5-FU.

Shallow anterior chamber:
The risk of this side effect was significantly increased with the use of intraoperative 5-FU, however one study (Wong 2002) did demonstrate an opposite risk.

Epithelial toxicity:
Reported as slightly more common with 5-FU in one (Wong 2009) of the two trials that reported on this outcome.

CONCLUSION

- While the use of MMC and 5-FU remain off-label during trabeculectomy, these agents are used routinely during glaucoma filtration surgery to reduce post-operative scarring and improve filtration. The use of antimetabolite agents (MMC and/or 5-FU) is recommended in a number of international clinical guidelines (as detailed above).
- Based on the results of our review, MMC results in a reduction in in surgical failure at 12 months in both low and high risk groups when compared to placebo or no antimetabolite. The absolute risk reduction is greater in patients at high risk of surgical failure compared to patients undergoing surgery for the first time.
- There were no RCTS of 5-FU in high risk patients
- Intraoperative 5-FU results in a small reduction in surgical failure at 12 months when compared to placebo/control in low risk patients undergoing trabeculectomy. The absolute risk reduction was smaller than that achieved with MMC. The magnitude of this benefit must be weighed against the potential risk of complications such as wound leak - RR 1.36 CI 1 to 1.84 (high certainty evidence) and shallow anterior chamber RR 1.99 CI 1.22 to 3.22 (high certainty evidence).
- Neither MMC nor 5-FU increased the risk of significant adverse effects. However studies were small, definitions of adverse effects were heterogeneous and there were no studies reporting on long term adverse effects

MMC v 5-FU
- Our pre-specified PICO does not include a comparison between MMC and 5-FU, however, our original literature search did include 2 SRs of RCTs (Cabourne E, et al., 2015) (De Fendi LI et al., 2013) where head to head comparisons were undertaken. As 5-FU is sometimes used in local clinical practice when there are supply constraints with MMC, we thought it useful to include a brief summary of the outcomes of the head to head comparison. Furthermore, 5-FU injection is considerable cheaper than MMC injection. As the more recent Cochrane review by (Cabourne E, et al., 2015) included all 5 of the RCTS included in (De Fendi LI et al., 2013), we limited our reporting to outcomes from the more recent Cochrane SR by (Cabourne E, et al., 2015).
- The SR by (Cabourne E, et al., 2015), included 11 trials with a total of 679 participants. Like the SRs by (Wilkins M et al., 2005) and (Green E et al., 2014), participants at high and low risk of trabeculectomy failure were included. Differences however are that in the (Cabourne E, et al., 2015) review, the **definition of high risk patients included patients of African origin** (see Appendix 5) which is of relevance for the local context. Another less important

difference in the review by (Cabourne E, et al., 2015) is that none of the studies included patients at medium risk of failure (combined trabeculectomy and cataract surgery), a cohort that is outside the scope of our PICO.

- There was also a high degree of heterogeneity in the application methods of the different interventions i.e. while the majority of studies for MMC used an intraoperative sponge application, one study used intraoperative subconjunctival injection).The doses of MMC used also varied between studies (see Appendix 4). The reviewers conducted a dose–response analysis which demonstrated a trend that increasingly favoured the use of MMC versus 5-FU as the intraoperative exposure to MMC increased. For 5-FU, studies varied between intraoperative and postoperative use (doses for postoperative injection varied) as well as between intraoperative sponge technique and subconjunctival injection. An analysis on the method of 5FU administration revealed that there was no significant effects on the overall outcome whether 5-FU was administered by postoperative subconjunctival injections or by intraoperative sponge application (subgroup difference P=0.93).
- (Cabourne E, et al., 2015) concluded that risk of failure of trabeculectomy was lower with MMC compared to 5-FU (RR=0.54, 95% CI 0.30 to 1.00; studies = 11; I^2=40% for the overall cohort (***intraoperative and postoperative use of MMC and 5-FU*** *and any administration method*). This translates to an ARR of 7 fewer per 100 (from 2 to 13 fewer) with MMC, however the confidence interval is wide and crosses the line of no effect. Overall, there was no evidence for any difference between the high and low risk groups (test for subgroup differences P=0.69) but due to the small number of trials in each group, the analysis was insufficiently powered to detect any differences. Refer to Appendix 4 for a more detailed **sub-group analysis focussing on the intraoperative sponge application which would be in line with local practice..**
- In the overall cohort (*intraoperative and postoperative use of MMC and 5-FU and any administration method)*, people treated with MMC had a lower IOP at one year compared to 5-FU (mean difference -3.05mmg Hg, 95% CI-4.60 to -1.50; I^2=52% [*inconsistency between trials with large range in the mean difference between studies]).* As illustrated in table 3 below, the mean difference was greater in the high risk group compared to the low risk group but according to the review authors, the test for interaction was not statistically significant (P=0.11).
- The reviewers report that adverse events were relatively rare with imprecise estimates of effect. Refer to Appendix 6 for a detailed list of the estimates of effect for the reported adverse effects. There is some evidence of less epitheliopathy (RR 0.23, 95% CI 0.11 to 0.47) and less hyphaema (RR 0.62, 95% CI 0.42 to 0.91) in the MMC group.
- The reviewers graded the quality of the evidence as low due to the risk of bias in the included studies and imprecision in the estimate of effects. (See Appendix 7 for the SoF table).
- In their evaluation of post-op complications, (Cabourne E, et al., 2015) reported a higher incidence of epitheliopathy and hyphaema with 5-FU compared to MMC. However, MMC was reported to have been associated with more bleb leaks, wound leaks, late hypotony and cataract formation versus 5-FU. The authors of the SR reported the quality of evidence to be low and caution against drawing any definitive conclusions given that adverse outcomes were rare.
- (Cabourne E, et al., 2015) concluded that MMC may be a more effective antimetabolite compared to 5-FU in achieving a lower IOP following trabeculectomy for both high and low risk sub-groups based on low quality evidence.
- Local management of patients with a failed trabeculectomy involves follow up surgery with the use of Ahmed valves (local cost R5500 – R7200 per valve) – refer to Table 3 for further comment.

Table 3: Outcomes of meta-analysis completed by (Cabourne E, et al., 2015)

Description of Analysis MMC vs 5-FU	Risk Ratio M-H, Random 95% CI	ARR	Excluding trials at high risk of bias in 1 or more domains***	Comparative cost of Ahmed valve due to surgical failure
Outcome: Failure of functioning trabeculectomy at one year (INTRAOPERATIVE & POSTOPERATIVE USE, ANY APPLICATION METHOD)				
High risk of failure**	**0.49 (0.22-1.08)**	Total events MMC = 19/139 Total events 5-FU = 34/125 ARR = 14% NNT= 7 95% CI 4 to 26 **14 fewer per 100 (from 4 to 26 fewer) with MMC**		The cost of treating 7 high risk patients with MMC is R1750 to prevent 1 additional surgical failure which would cost R5500-R7200 for an Ahmed valve (excluding other surgical costs).
Low risk of failure	0.65 (0.19-2.2)	Total events MMC = 9/181 Total events 5-FU = 14/189 ARR = 2% NNT = 41 95% CI -37 to 13 **2 fewer per 100 (from 8 fewer to 3 more) with MMC**		The cost of treating 41 low risk patients with MMC is R10 250 to prevent 1 additional surgical failure which would cost R5500-7200 for an Ahmed valve (excluding other surgical costs)
Overall	0.54 (0.3-1)	Total events MMC = 28/302 Total events 5-FU = 48/292 ARR = 7% NNT = 14 95% CI 8 to 56 **7 fewer per 100 (from 2 to 13 fewer) with MMC**	RR 1.02, 95% CI 0.5 to 2.04	
Outcome: Failure of functioning trabeculectomy at one year (SUBGROUP: INTRAOPERATIVE SPONGE APPLICATION)				
Overall	0.52 (0.13-2.08)	Total events MMC = 10/167 Total events 5-FU = 17/154 ARR = 5% NNT = 20 95% CI -89 to 9 **5 fewer per 100 (from 12 fewer to 1 more) with MMC**		The cost of treating 20 patients with MMC is R5000 to prevent 1 additional surgical failure which would cost R5500-7200 for an Ahmed valve (excluding other surgical costs)
Outcome: Intraocular pressure at 1 year (INTRAOPERATIVE & POSTOPERATIVE USE, ANY APPLICATION METHOD)				
High risk of failure**	**-4.188 (-6.73, -1.64)**			
Low risk of failure	-1.72 (-3.28,-0.16)			
Overall	-3.05 (-4.6, -1.5)		MD -1.72 mmHg, 95% CI -3.28 to -0.16	
*Low risk of trabeculectomy failure: (primary trabeculectomy): people who have received no previous surgical eye intervention. People who underwent previous laser procedures may be included in this group ****High risk of trabeculectomy failure**: people with previous glaucoma or extracapsular cataract surgery, **people of African origin** and people with secondary glaucoma or congenital glaucoma *** Excluding studies at high risk of bias (trials were from the high risk of failure cohort), improved the consistency (reduced I^2), altered the estimate of effect but the generally uncertainty of the results did not change.				

Evidence to decision framework

Should intraoperative antimetabolites (either MMC or 5-FU) be used in adult patients undergoing trabeculectomy?

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** **MMC** High ☐ Moderate X Low ☐ Very low ☐ **5-FU** High X Moderate ☐ Low ☐ Very low ☐ **MMC v 5-FU** High ☐ Moderate ☐ Low X Very low ☐ *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*	**MMC vs placebo or no antimetabolite** *Surgical failure at 12 months* Moderate quality of evidence (SoF Appendix 2) *Mean IOP* Moderate quality of evidence (SoF Appendix 2) **5-FU vs placebo or control** *Surgical failure at 12 months* High quality of evidence (SoF Appendix 3) *Mean IOP* High quality of evidence (SoF Appendix 3) **MMC v 5-FU** *Surgical failure at 12 months* Low quality of evidence (SoF Appendix 7) *Mean IOP* Low quality of evidence (SoF Appendix7)
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** **MMC** Large ☐ Moderate X Small ☐ None ☐ **5-FU** Large ☐ Moderate ☐ Small X None ☐ **MMC vs 5-FU** Large ☐ Moderate ☐ Small X None ☐ **Overall size of benefit is moderate**	**Intraoperative MMC vs placebo or no antimetabolite** *Surgical failure at 12 months* MMC resulted in a reduction of surgical failure *High risk:* 35 fewer per 100 (from 22 to 46 fewer) with MMC Control 49/97 (50%) failed vs MMC 15/96 (15%) failed, ARR 35%, NNT 3 CI 2 to 5 fewer with MMC to prevent one failed surgery. *Low risk:* 20 fewer per 100 (from 12 to 30 fewer) with MMC Control 30/107 (28%) vs intervention 18/231 (8%) ARR 20%, NNT 5 CI 3 to 9 fewer with MMC to prevent one failed surgery. *Mean IOP at 12 months* MMC reduced mean IOP *High risk:* mean difference of -5.31 mmHg (95% CI: -3.85 to -6.76 mmHg) with MMC *Low risk*: mean difference of -5.41 mmHg, 95% CI: -3.49 to -7.34 mmHg) with MMC. **5-FU vs placebo or control** *Surgical failure at 12 months* *High risk:* No data available *Low risk:* 9 fewer per 100 (from 3 to 15 fewer with 5-FU. There were 96/359 failures (27%) with placebo/no treatment vs 63/352 failures (18%) with 5-FU. ARR 9%. NNT 11 CI 7 to 37 fewer with 5-FU to prevent one surgical failure. *Mean IOP* *High risk:* No data available *Low risk:* mean difference of -1.04 mm Hg (95% CI -0.43 to -1.65) which is statistically significantly but may not be clinically significant. **MMC vs 5-FU**

		Surgical failure at 12 months (Subgroup – intraoperative sponge application only) 5 fewer per 100 (from 12 fewer to 1 more) with MMC, ARR 5% NNT 20 95% CI 9 fewer to 89 more failures. The estimate of NNT is imprecise with wide confidence intervals that cross zero, and therefore include increased harm with MMC *Note that in the Cabourne review, patients from African origin were identified as a high risk cohort which has relevance for our local context, although a sub-group analysis for high risk patients with intraoperative sponge application was not conducted)*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** **MMC** High [ ] Moderate [ ] Low [X] Very low [ ] **5-FU** High [ ] Moderate [X] Low [ ] Very low [ ] **MMC versus 5-FU** High [ ] Moderate [ ] Low [X] Very low [ ] *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	**MMC vs placebo or no antimetabolite** *Increased risk of wound leak, hypotony and shallow anterior chamber* Low quality of evidence (SoF Appendix 2) *Cataract formation* Moderate quality of evidence (SoF Appendix 2) **5-FU vs placebo or control** *Increased risk of wound leak and shallow anterior chamber* High quality of evidence (SoF Appendix 3) *Epithelial toxicity & hypotonous maculopathy* Moderate quality of evidence (SoF Appendix 3) **MMC versus 5-FU** *Hypotony* Low quality of evidence (SoF Appendix 7)
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **MMC** Large [ ] Moderate [ ] Small [X] None [ ] **5-FU** Large Moderate Small None	**MMC vs placebo or no antimetabolite** *Increased risk of hypotony* *High risk:* RR 2.69 95% (CI) 0.74 to 9.85, 5 more per 100 (from 2 fewer to 13 more), ARI 5%, NNH 19 95% CI 60 fewer to 8 more. *Low risk:* RR 1.07, 95% (CI) 0.25 to 4.56, ARI 0% NNH 260 95% CI 10 fewer to 10 more. *Wound leak and shallow anterior chamber* No significant differences noted in these effects between groups using MMC and those using placebo. Variation in the rates of shallow anterior chamber may be influenced by heterogeneity in definitions as well as surgical technique. *Cataract formation* *High risk:* RR 1.38 95% (CI) 0.45 to 4.24, 2 more per 100 (from 7 fewer to 11 more, ARI 2%, NNH 45 95% CI 9 fewer to 14 more with MMC. *Low risk:* RR 1.93, 95% (CI) 0.98 to 3.8, 10 more per 100 (from 2 to 17 more), ARI 10%, NNH 10 95% CI 6 fewer to 57 more with MMC. *Overall:* RR 1.80, 95% CI: 1.00 to 3.22). 9 more per 100 (from 0 to 14 more), ARI 9%, NNH 11 with MMC **5-FU vs placebo or control** *Wound leak and shallow anterior chamber* *High risk:* No data available

	[ ] [ ] [X] [ ] **MMC vs 5-FU** Large [ ] Moderate [ ] Small [X] None [ ]	*Low risk* A 50% increase in wound leak (RR= 1.36, CI (1.00,1.84) and increased risk of anterior chamber shallowing (RR=1.99 CI(1.22,3.22)) heterogeneity reported) with the use of 5-FU. *These are temporary effects that are not very common in clinical practice.* *Epithelial toxicity & hypotonous maculopathy* Epithelial toxicity reported as slightly more common with 5-FU RR=1.23 CI (0.85,1.77) **MMC versus 5-FU** There is some evidence of less epitheliopathy (RR 0.23, 95% CI 0.11 to 0.47) and less hyphaema (RR 0.62, 95% CI 0.42 to 0.91) in the MMC group. Patients who received MMC reported more bleb leaks, wound leaks, late hypotony and cataracts compared to 5-FU (appendix 7). Quality of evidence was low as adverse outcomes were rare leading to imprecise estimates of effect.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** **MMC** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ] **5-FU** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ] ***Applicable to patients at low risk of surgical failure only as no data for patients at high risk of surgical failure.*** **MMC vs 5-FU** Favours intervention [ ] Favours control [ ] Uncertain [X]	**MMC vs placebo or no-antimetabolite** MMC results in fewer surgical failures and a reduction in IOP at 12 months compared to placebo or no–antimetabolite (moderate certainty evidence), with a small increase in the risk of hypotony. **(moderate magnitude of benefit)** **5-FU versus placebo or control** There is no data available for patients at high risk of surgical failure. For patients at low risk of surgical failure, 5-FU results in fewer surgical failures at 12 months compared to placebo or control (high certainty evidence) with a small increase in wound leak and anterior chamber shallowing. **(small magnitude of benefit)** **MMC versus 5-FU** In the subgroup of patients with intraoperative sponge application, MMC resulted in fewer surgical failures at 12 months compared to 5-FU (low certainty evidence). In the Cabourne SR, the side effect profile is reported for the overall patient cohort (intraoperative and postoperative use by any application method) with no subgroup analysis in patients treated with intraoperative sponge application. **(small magnitude of benefit)** **(small magnitude of harm)**
THERAPEUTIC INTERCHANGE	**Therapeutic alternatives available:**	No therapeutic alternatives available on the EML

FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Both options are readily available in South Africa for other indications. MMC is already routinely used in clinical practice during trabeculectomy even though it is not listed on the EML. 5-FU has been used as an alternative to MMC during reported stock outs.
RESOURCE USE	**How large are the resource requirements?** **MMC** More intensive [X] Less intensive [ ] Uncertain [ ] **5-FU** More intensive [X] Less intensive [ ] Uncertain [ ] **MMC vs 5-FU** More intensive [ ] Less intensive [ ] Uncertain [ ]	**MMC** **Mitomycin 2mg** R249.75 per injection* **Mitomycin 10mg** R1092.73 per injection* Doses of mitomycin ranged from 0.1 to 0.5 mg/mL. Cost per application: R250 (assumes only 1 application obtained per 2mg vial). **5-FU** **Fluorouracil 50mg/mL injection (Floracor®):** R17.70 for a 5mL injection* R37.00 for a 10mL injection* Doses used: 25mg/mL or 50mg/mL Cost per application: R17.70 (assumes only 1 application obtained per vial) *Prices as per SEP database 20 July 2023 The resource requirements for trabeculectomy with adjunctive MMC or 5-FU will be greater compared to trabeculectomy without adjunctive therapy. While MMC and 5-FU are not listed on the EML for glaucoma management, anecdotal feedback suggests that it is already part of routine clinical practice. Inclusion on the EML is therefore unlikely to result in an incremental budget impact. Based on the current SEP, the cost per application with MMC is significantly more expensive compared to 5-FU. Utilizing an ARR 5%, (NNT 20 95% CI -89 to 9), the cost of treating 20 patients with intraoperative sponge application of MMC is R5000 to prevent 1 additional surgical failure that would result in a cost of R5500-7200 being averted for an Ahmed valve which is used in follow up surgery, as the current standard of care for patients with failed trabeculectomies. This excludes other surgical costs relating to re-operation.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	No reports of the participants' perception of their treatment for MMC (Wilkins M et al., 2005) or 5-FU (Green E et al., 2014). Both MMC and 5-FU are established in clinical practice and recognised as an option to reduce bleb failure in multiple international guidelines.
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	MMC is already routinely used during trabeculectomy even though it is not currently listed on the EML. Adding MMC to the EML will ensure access and reduce inequity.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	31 Aug 2023	GT, ZA, MM	

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Appendix 1: Pubmed Search History for SRs

Search	Query	Results
#8	Search: **#5 OR #7** Filters: **Systematic Review**	28
#5	Search: **#1 AND #2** Filters: **Systematic Review**	11
#7	Search: **#1 AND #3** Filters: **Systematic Review**	26
#6	Search: **#1 AND #3**	1,894
#4	Search: **#1 AND #2**	718
#3	Search: **"mitomycin"[MeSH Terms] OR "mitomycin"[All Fields] OR "mitomycin c"[All Fields])**	21,539
#2	Search: **"fluorouracil"[All Fields] OR "fluorouracil"[MeSH Terms] OR fluorouracil[Text Word]**	65,323
#1	Search: **(("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields] OR "glaucomas"[All Fields]) AND ("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgerys"[All Fields] OR "surgeries"[All Fields]))**	29,133
#0	Search: **Clipboard**	28

Pubmed Search History for RCTs for Mitomycin C and 5-Fluorouracil

Search	Query	Results
#6	Search: **fluorouracil AND glaucoma** Filters: **Randomized Controlled Trial, from 2013/7/1 - 2023/8/8**	12
#5	Search: **fluorouracil AND glaucoma** Filters: **Randomized Controlled Trial**	83
#4	Search: **fluorouracil AND glaucoma**	772
#3	Search: **mitomycin AND glaucoma** Filters: **Randomized Controlled Trial, from 2010/1/1 - 2023/8/8**	97
#2	Search: **mitomycin AND glaucoma** Filters: **Randomized Controlled Trial**	200
#1	Search: **mitomycin AND glaucoma**	1,987
#0	Search: **Clipboard**	97

Appendix 2: Summary of Findings Table (Wilkins M et al., 2005)

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Intraoperative Mitomycin C compared with no antimetabolite or placebo for trabeculectomy surgery for glaucoma

Patient or population: People undergoing trabeculectomy surgery with glaucoma

Settings: Eye clinics and hospitals

Intervention: Intraoperative Mitomycin C applied in any dose for any duration

Comparison: Placebo application or nothing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	control	mitomycin C				
Trabeculectomy failure at 12 months	**Low risk population**		RR 0.37 (0.26 to 0.51)	698 (11)	+++O moderate	medium risk population poorly designed studies may underestimate effect
	280 per 1000	77 per 1000 ([value] to [value])				
	Medium risk population					
	127 per 1000	135 per 1000 ([value] to [value])				
	High risk population					
	505 per 1000	156 per 1000 ([value] to [value])				
mean intraocular pressure mmHg at 12 months	The mean IOP ranged across control groups from 15.9 to 23.9 mmHg	The mean IOP in the intervention groups was 11.1 to 14.6 mmHg	the WMD was -4.1 mmHg [-4.68 to -3.34] mmHg	380 [8]	+++O moderate	

complications wound leak by 12 months	**Low risk population**		RR 1.84 (0.72 to 4.66)	333 (7)	++OO low	no events reported in trials of high risk patients
	45 per 1000	114 per 1000 ([value] to [value])				
	Medium risk population					
	84 per 1000	112 per 1000 ([value] to [value])				
	High risk population					
	inestimable	inestimable				
complications hypotony occurring up to 12 months	**Low risk population**		RR 1.8 (0.79 to 4.12)	488 (10)	++OO low	inconsistently defined and reported
	58 per 1000	61 per 1000 ([value] to [value])				
	Medium risk population					
	14 per 1000	37 per 1000 ([value] to [value])				
	High risk population					
	31 per 1000	83 per 1000 ([value] to [value])				
complications shallow anterior chamber occurring within 12 months	**Low risk population**		RR 1.14 (0.42 to 3.07)	441 (10)	++OO low	inconsistently defined and reported
	169 per 1000	151 per 1000 ([value] to [value])				
	Medium risk population					
	0 per 1000	9 per 1000 ([value] to [value])				
	High risk population					
	145 per 1000	200 per 1000 ([value] to [value])				

cataract formation by 12 months	**Low risk population**		RR 1.8 (1.00 to 3.22)	482 (7)	+++O moderate	outcome not relevant to medium risk population because these are combined cataract extraction and glaucoma procedures
	93 per 1000	190 per 1000 ([value] to [value])				
	High risk population					
	57 per 1000	80 per 1000 ([value] to [value])				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk Ratio; [other abbreviations, e.g.. OR, etc]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Appendix 3: Summary of Findings Table (Green E et al., 2014)

Summary of findings 6. Intraoperative 5-Fluorouracil versus placebo or control for glaucoma surgery

Intraoperative 5-FU versus placebo or control for glaucoma surgery

Patient or population: participants with glaucoma surgery
Settings:
Intervention: intraoperative 5-FU versus placebo or control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Peroperative 5-FU versus placebo or control				
Failure at 12 months Need for repeat surgery or uncontrolled IOP (usually more than 22 mm Hg) despite additional topical or systemic medications	**267 per 1000**	**182 per 1000** (136 to 246)	**RR 0.68** (0.51 to 0.92)	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Mean intraocular pressure at 12 months	The mean intraocular pressure at 12 months in the control groups was **14.89 mm Hg**	The mean intraocular pressure at 12 months in the intervention groups was **1.04 lower** (1.65 to 0.43 lower)	-	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Complications - wound leak Follow-up: 12 months	**156 per 1000**	**212 per 1000** (156 to 287)	**RR 1.36** (1 to 1.84)	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Complications - hypotonous maculopathy Follow-up: 12 months	**11 per 1000**	**17 per 1000** (5 to 58)	**RR 1.47** (0.42 to 5.12)	711 (4 studies)	⊕⊕⊕⊖ **moderate**	-
Complications - shallow anterior chamber Follow-up: 12 months	**61 per 1000**	**122 per 1000** (75 to 197)	**RR 1.99** (1.22 to 3.22)	711 (4 studies)	⊕⊕⊕⊕ **high**	-
Complications - epithelial toxicity Follow-up: 12 months	**103 per 1000**	**127 per 1000** (88 to 182)	**RR 1.23** (0.85 to 1.77)	711 (4 studies)	⊕⊕⊕⊖ **moderate** [1]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
5-FU: 5-Fluorouracil; **CI:** confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The broad confidence interval spans both a clinically advantageous and disadvantageous outcome. Consequently, the quality of evidence is reduced.

Appendix 4: Summary of the SR by (Cabourne E, et al., 2015): Head to head comparison

(Cabourne E, et al., 2015) **Mitomycin C versus 5-Fluoruracil for wound healing in glaucoma surgery**.

This SR included 11 RCTS with a total of 679 participants that were were grouped into 3 categories as detailed below and slightly different to those reported in the reviews by (Wilkins M et al., 2005) and (Green E et al., 2014):

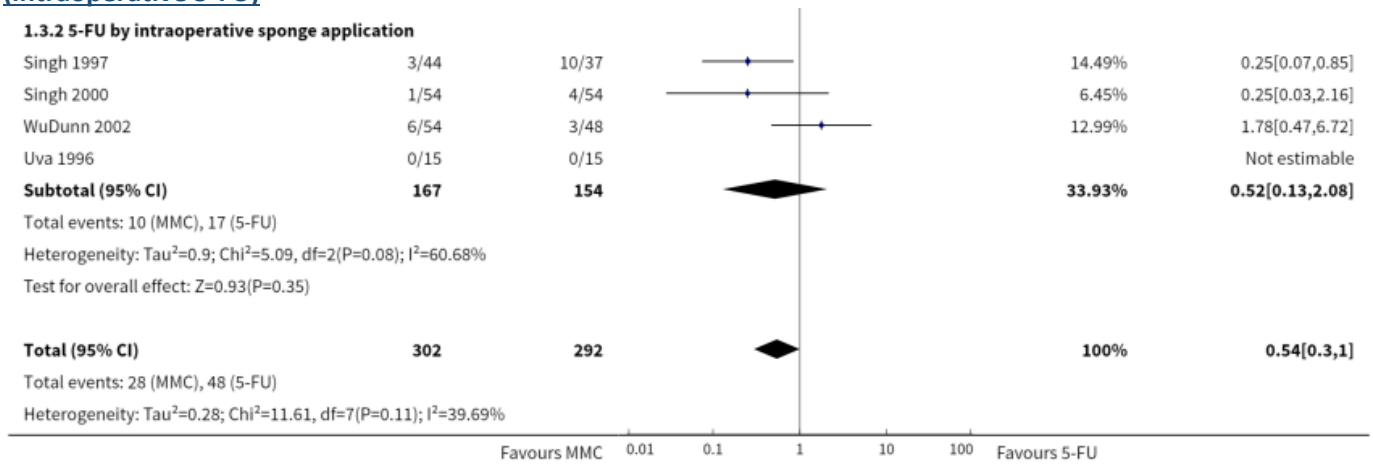
- High risk of trabeculectomy failure: people with previous glaucoma or extracapsular cataract surgery, people of African origin and people with secondary glaucoma or congenital glaucoma
- Medium risk of trabeculectomy failure: (combined surgery) people undergoing trabeculectomy with extracapsular cataract surgery
- Low risk of trabeculectomy failure: (primary trabeculectomy) people who have received no previous surgical eye intervention. People who underwent previous laser procedures could be included in this group.

Four interventions were considered:

- Use of intraoperative MMC versus intraoperative 5-FU,
- Use of intraoperative MMC versus post-operative 5-FU,
- Use of intraoperative MMC versus Intraoperative and postoperative 5-FU
- Use of intraoperative and postoperative MMC versus intraoperative 5-FU and post-operative 5-FU.

Results of the use of intraoperative MMC versus intraoperative 5-FU:

Figure 6: Outcome 3 – failure of functioning trabeculectomy at one year depending on 5-FU administration technique (intraoperative 5-FU)



Study	MMC	5-FU
Singh 1997 High risk of trabeculectomy failure	(44 eyes) Intraoperative sponge application Dose: 0.5mg/mL for 3.5 min Location: between scleral flap and conjunctiva	(37 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: between scleral flap and conjunctiva
Singh 2000 Low risk of trabeculectomy failure	(54 eyes) Intraoperative sponge application Dose: 0.4mg/mL for 2 min Location: not stated	(54 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: not stated
Wa Dunn 2002 Low risk of trabeculectomy failure	(58 eyes) Intraoperative sponge application Dose: 0.2mg/mL for 2 min Location: not stated	(57 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: not stated
Uva 1996 Low risk of trabeculectomy failure	(15 eyes) Intraoperative sponge application Dose: 0.2mg/mL for 2 min Location: between sclera and Tenon's capsule	(15 eyes) Intraoperative sponge application Dose: 50mg/mL for 5 min Location: between sclera and Tenon's capsule

Appendix 5: Comparison in the types of participants as defined in the 3 SRs included in this review

	MMC (Wilkins M et al., 2005)	5-FU (Green E et al., 2014)	MMC v 5-FU (Cabourne E, et al., 2015)
High risk of failure	People who have had previous glaucoma drainage surgery or previous surgery involving anything more than trivial conjunctival incision, including cataract surgery; people with one or more of the following forms of glaucoma: glaucoma secondary to intraocular inflammation, congenital glaucoma and neovascular glaucoma	People who have had previous glaucoma drainage surgery or surgery involving anything more than trivial conjunctival incision including cataract surgery, glaucoma secondary to intraocular inflammation, congenital glaucoma and neovascular glaucoma	People with previous glaucoma or extracapsular cataract surgery, **people of African origin** and people with secondary glaucoma or congenital glaucoma.
Trabeculectomy combined with cataract surgery *(outside of PICO)*	People undergoing trabeculectomy with extra-capsular cataract extraction and intraocular lens implant	People undergoing trabeculectomy with extracapsular cataract extraction and intraocular lens implant;	People undergoing trabeculectomy with extra-capsular cataract surgery
Primary trabeculectomy	People who have received no previous surgical intervention as defined above. This group may include people who have had previous medical therapy, laser procedures or both.	People who have received no previous surgical intervention as defined above. This group may include people who have had previous laser procedures.	People who have received no previous surgical intervention. People who have had previous laser procedures may be included in this goup.

Appendix 6: MMC versus 5-FU – Comparison of adverse effects

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 Postoperative Complications	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Bleb leak	2	154	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.32, 4.68]
8.2 Wound leak	6	391	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.51, 2.71]
8.3 Late hypotony	4	211	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.41, 4.63]
8.4 Maculopathy	4	342	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.35, 8.33]
8.5 Cataract	4	275	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.65, 4.61]
8.6 Shallow anterior chamber	5	311	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.67, 2.21]
8.7 Choroidal detachment	8	494	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.45, 1.63]
8.8 Epitheliopathy	8	419	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.11, 0.47]
8.9 Tenon cyst	3	177	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.20, 4.38]
8.10 Hyphaema	4	250	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.42, 0.91]
8.11 Suprachoroidal haemor-rhage	3	303	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.09, 5.66]
8.12 Endophthalmitis	4	315	Risk Ratio (M-H, Random, 95% CI)	3.89 [0.44, 34.57]

Appendix 7: SUMMARY OF FINDINGS – MMC versus 5-FU

Summary of findings for the main comparison. MMC compared to 5-FU for wound healing in glaucoma surgery

MMC compared to 5-FU for wound healing in glaucoma surgery

Patient or population: wound healing in glaucoma surgery
Settings:
Intervention: MMC
Comparison: 5-FU

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants/eyes (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	5-FU	MMC				
Failure of functioning trabeculectomy at 1 year	**Study population**		Low-risk population RR 0.65 (95% CI 0.19 to 2.20) High-risk population RR 0.49 (95% CI 0.22 to 1.08)	634 (11 RCTs: 6 including low-risk population and 5 including high-risk population)	⊕⊕⊙⊙ LOW [1,2]	
	Low-risk population: 74 per 1000 High-risk population: 272 per 1000	Low-risk population: 50 per 1000 High-risk population: 137 per 1000				
Intraocular pressure at 1 year	The mean intraocular pressure at 1 year ranged across 5-FU groups. Low-risk population: 10.9 to 14.3 mmHg High-risk population: 14.8 to 16.3 mmHg	The mean intraocular pressure at 1 year in the MMC groups had a range of values. Low-risk population: 9.9 to 11.6 mmHg High-risk population: 8.6 to 13.7 mmHg	-	386 (7 RCTs: 3 including low-risk population and 4 including high-risk population)	⊕⊕⊙⊙ LOW [1,3]	
Loss of 2 or more lines of Snellen visual acuity at 1 year	**Study population**		Low-risk population RR 2.00 (95% CI 0.53 to 7.59) High-risk population RR 0.81 (95% CI 0.36 to 1.80)	328 (5 RCTs: 2 including low-risk population and 3 including high-risk population)	⊕⊕⊙⊙ LOW [2,4]	
	Low-risk population: 47 per 1000 High-risk population: 115 per 1000	Low-risk population: 94 per 1000 High-risk population: 96 per 1000				
	Study population		RR 1.37 (95% CI 0.41 to 4.63)	211 (4 RCTs)	⊕⊕⊙⊙ LOW [2,4]	
Postoperative complications: late hypotony	37 per 1000	59 per 1000				
Postoperative complications: choroidal detachment	**Study population**		RR 0.86 (95% CI 0.45 to 1.63)	494 (8 RCTs)	⊕⊕⊙⊙ LOW [1,2]	
	68 per 1000	70 per 1000				
Postoperative complications: endophthalmitis	**Study population**		RR 3.89 (95% CI 0.44 to 34.57)	315 (4 RCTs)	⊕⊕⊙⊙ LOW [1,2]	
	0 per 1000	19 per 1000				
Quality of life at 1 year						Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
5-FU: 5-Fluorouracil; **CI:** confidence interval; **MMC:** mitomycin C; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for risk of bias: only one study at low risk of bias in all domains
[2]Downgraded for imprecision: wide confidence intervals
[3]Downgraded for inconsistency: $I^2 = 60\%$
[4]Downgraded for risk of bias: no study at low risk of bias in all domains