Forthcoming Events

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It gives me immense pleasure to act as an editor of Bengal Ophthalmic Journal (BOJ), the official publication of Ophthalmological Society of West Bengal. The feedback to the previous issue of BOJ (2017) has been indeed encouraging. We are happy that most readers have liked the format and contents of BOJ as well as OPTHABUZZ, the official news letter of OSWB.

This edition brings to you a review on Immunosuppressive agents in current treatment of uveitis. The discussion on Neurotrophic keratopathy will be helpful for the readers. The regular contents of original articles, short communications, case reports, journal scan are also present.

We have introduced the facility of the ‘online submission’ which will help the authors and reviewers to submit and track the manuscript. This present issue will be followed by another one in November 2018. Dear members, BOJ is your journal and we would welcome any critical comments. Our dream is to see BOJ to be an indexed journal and we are sure it is achievable in near future. But, indexing a journal requires maintaining its standards and regular publication. It is time to have a long term vision for BOJ which will help us all academically and also uplift the stature of OSWB.

Editorial board would like to thank all the reviewers for their outstanding support during the last year. We thank all the members of OSWB for their constant encouragement which has helped us to grow during last few years.

Editor-in-chief
Chandana Chakraborti, MD (AIIMS)
Bengal Ophthalmic Journal
Neurotrophic Keratopathy (NK) is a rare condition with reduced or absent corneal sensations where corneal epithelium breakdown leads to frank epithelial defect with or without stromal ulceration and melt. NK can be mild, moderate or severe. Moderate to severe NK can have profound effect on vision and quality of life of the affected. Current management aim is to treat etiopathogenesis and, at the same time to promote corneal healing. Medical management ranges from artificial tears to serum/plasma drops, anti-inflammatory agents, antibiotics and anti-proteases which provide non-specific relief that may be temporary. Contact lenses, punctal plugs, eye lid closure, conjunctival flaps and amniotic membrane also helps. Recently biologicals such as biopolymers like heparan sulfate; coenzyme Q10 and antisense oligonucleotide suppressing connexin 43 expression all showed promising results. Most recently approved recombinant nerve growth factor (cenergemin) targets the nerve pathology and is becoming a specific therapy for NK.

Key words: Neurotrophic keratopathy, recombinant nerve growth factors

The dynamic complex of ocular surface that includes the eye lids, tear film, conjunctiva and cornea functions as a single unit with mutual relationship between them\(^1\), and acts via cross-talk with the neural, endocrine, vascular, and immune regulatory systems.\(^2\) Nerve fibres protects cornea by modulating the blink response, stimulating the production of tears and trophic factors.\(^3\) When the epithelium is injured, the repair requires a controlled and collaborative system of communication between epithelial and neuronal cells to facilitate re-synthesis of the damaged matrix, cell migration and restoration of architecture.\(^4\) The purpose of this article is to describe aetiology, diagnosis, current and future treatment of NK based on the most recent studies.

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Definition
Magendie first described this condition as “neuroparalytic keratitis” in 1824. All previous definitions of NK describe it as a “degenerative disease”. For example, American Academy of Ophthalmology defined it as “Neurotrophic keratopathy (NK) is a degenerative disease of the corneal epithelium resulting from impaired corneal innervation. A reduction in corneal sensitivity or complete corneal anaesthesia is the hallmark of this disease and is responsible for producing epithelial keratopathy, ulceration and perforation”. But studies demonstrated the role of sympathetic innervation, and the occurrence of nerve hyper or aberrant regeneration in corneal pathology. So, use of term degenerative disease in the definition will be improper in evidence of regeneration. Very recently Dua et al proposed a new definition keeping all the above facts in mind as “Neurotrophic keratopathy is a disease related to alterations in corneal nerves leading to impairment in sensory and trophic function with consequent breakdown of the corneal epithelium, affecting health and integrity of the tear film, epithelium and stroma”.

Corneal Innervation - anatomy and physiology
Cornea is mainly supplied by sensory branch from the ophthalmic division of the Trigeminal (V cranial) nerve and autonomic innervation by sympathetic nerves from the superior cervical ganglion. A mixture of sensory and autonomic nerves pass through the limbus and lose their perineurium and myelin sheaths, and enter the corneal stroma, divide in branches to form the stromal plexus, and then to form the subepithelial plexus. Branches from the subepithelial plexus penetrate the Bowman’s layer to form the sub-basal nerve plexus, which supplies all layers of the corneal epithelium. Most of the corneal sensory nerves are polymodal. It contains nociceptors, cold thermoreceptors, and selective mechano-nociceptor neurons which are activated with near-noxious or noxious mechanical energy, heat, chemical irritants, endogenous chemical mediators from damaged corneal tissue and inflammatory cells. Inflammation sensitizes the receptors and causes hyperalgesia and allodynia and spontaneous pain.

Neuromediators expressed by corneal nerves like substance P(SP) and calcitonin gen-related peptide(CGRP) promote corneal epithelial cell proliferation, migration, adhesion and differentiation. Substance P and CGRP contribute to the inflammatory response following tissue injury (neurogenic inflammation). CGRP has immunosuppressive effects, while substance P acts as a potent pro-inflammatory neuropeptide. Nerve growth factor (NGF), epidermal growth factor (EGF), glial derived neurotrophic factor (GDNF) and brain derived neurotrophic factor (BDNF) plays a fundamental role in corneal wellbeing and healing. NGF modulate immune reactions of the cornea. Recent evidence indicates, that significant and complex interactions exist between the nervous and immune system. Primary sensory neurons seem to be involved in maintaining the cornea’s immune privilege.
Epidemiology of NK
Information regarding incidence and prevalence of NK is usually derived from associated conditions. NK (according to old definition) has been classified as a rare/orphan disease (ORPHA137596) affecting less than 5 individuals in 10,000. Most common associated conditions with NK are herpetic keratitis (incidence of 1.22/10,000) and post-surgical nerve damage (incidence of 0.02/10,000).²⁰

Causes of Neurotrophic Keratopathy
Common causes of severe NK are corneal herpes, ocular surface thermal and chemical burns, contact lens misuse, ablative procedures for trigeminal neuralgia, neurosurgery, head trauma or aneurysms.

Common causes of ocular surface nerve damage that may lead to neurotrophic keratopathy

Genetic
- Riley–Day syndrome (familial dysautonomia)
- Goldenhar–Gorlin syndrome
- Möbius syndrome
- Familial corneal hypoesthesia
- Congenital insensitivity to pain with anhidrosis

Systemic
- Diabetes mellitus
- Leprosy
- Vitamin A deficiency
- Amyloidosis
- Multiple sclerosis

Central nervous system
- Neoplasm
- Aneurysms
- Stroke
- Degenerative disorders (Alzheimer's, Parkinson's)
- Post neurosurgical procedures- acoustic neuroma, trigeminal neuralgia
- Ocular conditions
- Post-herpes simplex and herpes zoster
- Other infections e.g. acanthamoeba keratouveitis
- Chemical and physical burns
- Abuse of topical anaesthetics
- Drug toxicity (timolol, betaxolol, diclofenac sodium, sulphasalazine 30%)
- Chronic ocular surface injury or inflammation
- Orbital neoplasia
- Corneal dystrophies (lattice, granular)

Contact lens wear
Ocular surgery- Cataract surgery, Laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK), Penetrating keratoplasty (PK), deep anterior lamellar keratoplasty (DALK), Collagen crosslinking, Vitrectomy for retinal detachment and photocoagulation to treat diabetic retinopathy.

Adapted from author's own publication. (Bonini et al., 2003)²¹
Clinical presentation and classification

Symptoms
Early: Dry eyes, photophobia, impaired quality of vision and reduced blink, usually worse in the morning or in the presence of aggravating factors such as air conditioning, air travel, draught of hot air.

Late: Pain and discomfort may be less or absent paradoxically related to hypoesthesia or anaesthesia. Visual loss in central cornea involvement.

Signs
Early: Rapid tear-break up time (TBUT), narrow tear meniscus and inferior one third conjunctival and corneal punctate staining with fluorescein. Dull corneal reflex with epithelial irregularities, reduced blinking and signs related to underlying disease like lagophthalmos, previous herpetic scarring, iris atrophy lattice or granular dystrophy, limbal stem cell deficiency, advanced diabetic retinopathy or pan-retinal photocoagulation. Optic disc swelling, or atrophy.

Late: Frank epithelial defect (usually central), persistent epithelial defect (PED) with smooth or rolled and opaque edges. Stromal edema, striae and Descemet’s folds, melt and perforation, usually sterile, however may be secondarily infected. Anterior chamber reaction ranges from presence of cells to frank hypopyon (sterile or a sign of secondary infection). Variable corneal neovascularisation may be present.

Classification and staging
Traditional classification in 3 stages as described by Mackie\textsuperscript{22}:
Stage 1 of neurotrophic keratopathy demonstrates the following:
- Rose Bengal staining of the inferior palpebral conjunctiva
- Decreased TBUT
- More viscous mucous
- Punctate fluorescein staining of corneal epithelium

Stage 2 is characterised by:
- Epithelial defect - Usually oval and in the superior cornea and surrounded by a rim of loose epithelium with smooth and rolled edges.
- Stromal swelling with folds in the Descemet’s membrane
- Sometimes associated with anterior chamber inflammatory activity

Stage 3 is characterised by:
- Stromal lysis/melting
- May result in perforation
Recently Dua and associates proposed a new adapted grading which is more clinically relevant and indicate severity and prognosis.  

**Mild [Epithelial changes only without epithelial defect]:** Epithelial irregularity but no frank epithelial defect; tear film instability and symptoms (hyper-aesthesia) with reduced or absent sensations in one or more quadrants of the cornea.  

**Moderate [Epithelial defect without stromal defect]:** Frank persistent epithelial defect and corneal hypo-aesthesia/anaesthesia.  

**Severe [Stromal involvement]:** From corneal ulcer to lysis to perforation, with corneal hypo-aesthesia/anaesthesia.

![Grade 1 NK-persistent punctate erosion, decreased sensation with dry eyes](image1)

![Grade 2 NK- non resolving epithelial defect with surrounding rolled out borders](image2)

![Grade 3 NK- stromal melt started inferiorly](image3)

![Grade 3 NK- on slit image stromal thinning](image4)

**Diagnosis:** NK can be suspected in the presence of non-infectious epithelial lesions ranging from SPK to corneal ulcer, associated with /without ocular symptoms like dryness, photophobia, lacrimation and visual disturbance, absent or mild conjunctival hyperemia, and a decrease or absence of corneal sensitivity. Neuropathic corneal pain can be a presenting feature and severe corneal signs can be present with disproportional minimal pain.  

- **Clinical History:** History of previous ocular or brain surgery, systemic disease, trauma, use of topical and systemic medication  
- **Examination:**  
  1. **Neurologic examination - to localize trigeminal damage**  
     i. Association of the 3rd cranial nerve with 6th cranial nerve - cavernous sinus or intracranial aneurysm.  
     ii. Afferent pupillary defect with corneal hypoesthesia - intra-conal orbit  
     iii. Abnormalities of the 7th and 8th cranial nerve may indicate damage from acoustic neuroma or neuro-surgery
II. Ophthalmic Examination
   i. External exam (eyelids and conjunctiva): Any lagophthalmos (Bell's reflex), ectropion, entropion, trichiasis or ptosis, lid scarring, lack of conjunctival congestion or subconjunctival fibrosis
   ii. Slit lamp exam: previous corneal scar or recurrent ulcer, vascularization, punctate keratitis, epithelial defect with rolled border, anterior chamber flare, keratic precipitates, cells or frank hypopyon, iris atrophy

III. Vital Staining of ocular surface-Fluorescein and lissamine green dyes to assess surface damage, TBUT, Schirmer's test.

IV. Ocular fundus examination -diabetic retinopathy, optic nerve pallor (multiple sclerosis) or swelling from an intracranial mass.

c. Diagnostic tests:
   I. Corneal Sensation:
      i. Clinically, corneal sensation is assessed by using a ‘wisp’ of cotton applied to both corneas and compared between the eyes. NK patients typically show reduced blinking/sensation to the stimulus.
      ii. Semi quantitatively- measured by the Cochet-Bonnet aesthesiometer or the Belmonte non-contact gas aesthesiometer (BNGA)

II. Imaging Corneal Nerves:
   i. In vivo confocal microscopy (IVCM)- A normal sub-basal plexus presents in pre-ganglionic (trigeminal ganglion) and partial ganglion lesions, whereas in post-ganglionic or complete ganglionic lesions, the sub-basal plexus is attenuated or lost.

   ii. Anterior Segment Optical Coherence Tomography (ASOCT)- Current resolution is insufficient to resolve corneal nerve architecture changes in NK but useful to measure corneal thinning.

III. Additional exams for differential diagnosis:
   i. Microbiological exams
   ii. Cornea impression cytology: in presence of limbal stem cell deficiency(LSCD)
   iii. Conjunctival biopsy/ haematological examination: Altered in presence of corneal immune diseases

Differential diagnosis: following conditions may have overlapping features with NK

Dry eye, contact lens related disorders, blepharo-keratoconjunctivitis, limbal stem cell deficiency, exposure keratopathy, radiation keratopathy, topical drug and preservative toxicity and chronic eye rubbing.

Management
The objective is to halt progression and reverse any NK changes that have occurred. Treatment options include medical management, non-surgical and surgical management.

Options in Medical Management of NK
Treatment of concurrent inflammation and any associated infection makes no sense, Secondary infection should be treated with broad spectrum topical antibiotics (toxic aminoglycosides should be avoided unless sensitivities suggested). Topical quinolones can also be toxic to the ocular surface.\textsuperscript{23}

[NB: Drug toxicity is a high probability when initial clinical improvement changes to worsening and the upper bulbar conjunctiva appear noncongested compared to the lower bulbar and fornix.\textsuperscript{24}]
Treatment for symptomatic relief (minimize ocular irritants)
All preserved therapy wherever possible, should be stopped. Meibomian gland dysfunction should be treated with warm compresses, lid massage and hygiene and use of matrix metalloproteinases (MMP) inhibitors like low dose tetracyclines or macrolides azithromycin. NSAIDs should be avoided due to their epithelial toxicity and the risk of corneal melt.25

Use of ocular lubricants
Tear substitutes help in epithelialization and dilution of proinflammatory mediators. Unpreserved lubricants should be prescribed. Carboxymethylcellulose agents are cytoprotective, and hyaluronate have anti-inflammatory properties in addition to facilitating epithelial wound healing.26,27

Role of serum eye drops
Enriched in many growth factors and tear components, such as EGF, vitamin A, transforming growth factor-β, fibroblast growth factors, platelet-derived growth factor, neurotrophic factors like SP, IGF-1 and NGF helps restoration of ocular surface integrity in patients with NK. Umbilical cord serum also has same properties and effective in NK treatment.28 Platelet-rich plasma (PRP) Which is abundant in growth factors gives better results than autologous serum.

Prevention of stromal lysis
Proteolytic enzymes from inflammatory cells activate clotting and kinin cascades that induce further inflammation and stromal loss. MMP inhibitors (oral tetracyclines, doxycycline and topical acetylcysteine) restrict neutrophil collagenase and epithelial gelatinase gene expression, suppress alpha-1 antitrypsin degradation and scavenge reactive oxygen species.29,30

Use of Biologics
These agents target mediators of inflammation and helps in wound healing. Murine NGF, Substance P and Insulin-like growth factor were the first mediators to show encouraging results.31,32 Recently some novel treatment modalities have emerged and are available for clinical use which include recombinant human NGF (rhNGF, cenefermin ), lifitegrast 5% (lymphocyte function-associated antigen-1 (LFA-1) antagonist), ReGenaTing Agent (RGTA) – matrix therapy agent, Cacicol20, Thymosin beta 4, Coenzyme Q10, Substance P, Netrin-1 (protein help in axon guidance and cell migration) and Nexagon® (an antisense oligonucleotide that downregulates expression of gap junction protein Cx43), in conditions with persistent epithelial defects where it is upregulated.33,34 Cenefermin 20 μg/ml (Oxervate®) is a pro-peptide, identical to human NGF recently granted by European Medicines Agency, 2017 for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) NK and is the first approved specific therapy for this.

Non-surgical interventional therapy
Eyelid closure- helps to protect against external insults as well blink related trauma. Nonsurgical methods include eyelid closure with tape, pressure patching, and botulinum toxin injection induced ptosis.

Therapeutic Contact lenses - Silicone hydrogels and rigid gas permeable are commonly used to protect the ocular surface with secondary visual improvement. Prosthetic replacement of the ocular surface ecosystem (PROSE) device is a special lens which form a vault over cornea to bathe therapeutic agents for prolonged time. But its use should be with extreme caution and with prophylactic use of topical non-preserved antibiotics.35

Punctal Occlusion -Punctum can be closed temporarily or permanently by thermal cautery to increases the retention of natural tears enhancing the healing process.
Surgical intervention
Severe refractory NK (grade 2/3) often require surgical intervention along with medical therapy.

- Permanent tarsorrhaphy- Should be done in all cases of refractory PED.\textsuperscript{36} If healing started, the tarsorrhaphy opening may be enlarged after a few weeks, but prematurely/permanent removal mostly results in a recurrence in complete corneal anaesthesia.

- Debridement of epithelium –Removal of the swollen rounded epithelium around persistent defect may stimulate healing response.\textsuperscript{37}

- Role of Amniotic Membrane Transplantation (AMT)- In NK, it is used to support epithelial adhesion, growth, differentiation and prolongation of lifespan of epithelial progenitor cells.\textsuperscript{38} It also contains multiple growth factors, anti-angiogenic and anti-inflammatory factors that may help in the resolution of ulcers and decrease scarring.\textsuperscript{39} AMT can be used alone or combined with tarsorrhaphy in refractory cases.\textsuperscript{40}

- Role of Tissue glue – Small perforation (less than 2 mm) can be closed with glue. Cyanoacrylate glue polymerizes rapidly and has antibacterial activity against most gram-positive organisms.\textsuperscript{41} Fibrin glue polymerises very slowly and rapidly degrades so less effective in brisk leaks.

- Conjunctival Flap - A conjunctival flap may help to prevent progression of the epithelial defect to perforation, provide blood supply to aid in healing of resistant infections and provide serum-based growth factors.\textsuperscript{42}

- Other graft types- In severe cases of perforation methods that have been tried to maintain globe integrity include buccal mucous membrane grafts, split thickness dermal grafts, and tenon's capsule grafts.\textsuperscript{43-45}

- Corneal transplants – A tectonic corneal transplant is often the last resort but in background of NK they are at high risk of failure.\textsuperscript{46} Keratoprosthetics has emerged as an effective modality for visual rehabilitation in such patients. \textsuperscript{47,48}

- Direct neurotisation -Contralateral supraorbital and supratrochlear branches of trigeminal nerve has been transplanted in patients with unilateral facial palsy and anesthetic cornea.\textsuperscript{49} Recently sural nerve for this purpose has also been used which preserves ocular anatomy and cosmesis and restores function.\textsuperscript{50,51}

A Step-ladder approach should be followed in the management of NK as described by Dua et al in their recent publication\textsuperscript{9}

<table>
<thead>
<tr>
<th>Clinical grade</th>
<th>Therapeutic Options</th>
<th>Intervention Aim</th>
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</table>
| stage 1 /mild  | 1. Discontinuation of all preservative containing drops  
2. Evaluation of side effects of any systemic drugs.  
3. Treat concurrent ocular surface | To Improve epithelial quality and transparency.  
To Stabilise epithelium and |
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<th>Stage 2/Moderate</th>
<th>As per Stage 1 and:</th>
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<tr>
<td></td>
<td>1. Topical preservative free antibiotics.</td>
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<td></td>
<td>2. To prevent stromal melt if threatened with tetracycline / macrolides</td>
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<tr>
<td></td>
<td>3. Biologics-Recombinant Human (rh)NGF(Cenegermin), Q10 co-enzyme, Cacicol 20 / RGTA.</td>
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<td></td>
<td>4. Serum eye drops, PRP</td>
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<td></td>
<td>5. Corneal or scleral therapeutic contact lenses.</td>
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<tr>
<td></td>
<td>7. Debridement of ’rolled’ edges of epithelial defect.</td>
</tr>
<tr>
<td></td>
<td>8. Tarsorrhaphy.</td>
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<tr>
<td></td>
<td>9. AMT Conjunctival flaps.</td>
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<tr>
<td></td>
<td>Promote recurrence of the epithelial breakdown</td>
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<td></td>
<td>Prevent progression to grade 3</td>
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<th>Stage 3/severe</th>
<th>As per Stage 2 and:</th>
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<tr>
<td></td>
<td>1. Amniotic membrane, multilayer, can be combined with tarsorrhaphy.</td>
</tr>
<tr>
<td></td>
<td>2. Corneal grafts if perforation</td>
</tr>
<tr>
<td></td>
<td>3. Cyanoacrylate tissue adhesive in small perforation</td>
</tr>
<tr>
<td></td>
<td>Promote corneal healing.</td>
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<tr>
<td></td>
<td>Prevent further corneal stromal lysis and perforation.</td>
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For each grade, all interventions listed may not be required.

**Conclusion**

NK occurs because of partial or total impairment of trigeminal innervations, leading to a reduction or loss of corneal sensitivity, has complex etiopathogenesis and can be manifested symptoms in several ocular and systemic diseases. Recently new understanding about the NK has come like theories about dissociation of trophic and sensory nerve functions and the association of hyperalgesia with aberrant nerve re-generation. The aim of treatment is to treat the etiopathogenesis, to promote epithelial healing and preventing the progression of corneal melt.

**References**


45. Reim, M., Overkamping, B., Kuckelkorn, R., 1992. [2 years experiences with Tenon-plasty]. Ophthalmologe 89, 524-530

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**Photogallery**

![Image of a patient with myasthenia gravis before and after Tensilon test](image)

Fig 1 a,b: Myasthenia gravis: before and after Tensilon test

*(note the disappearance of ptosis)*

Photo Courtesy: Chandana Chakraborti
IMMUNOSUPPRESSIVES AND BEYOND:
NEW ADVANCES IN TREATMENT OF UVEITIS

Avirupa Ghose

Ocular inflammatory disorders have a high propensity for visual morbidity if not managed properly. They account as the 4th cause for legal blindness in developed countries. Though corticosteroids have been the gold standard of treatment, with new modalities of therapy with immunosuppressive and biological agents, management has been revolutionised specially in recalcitrant and steroid dependant or intolerant cases. This review article focuses on these new modalities of therapy, their mechanism of action, their indications and side effects.

Keywords: Uveitis, immunosuppressive, cytokine, biological.

Ocular inflammatory disorders have potential for visual morbidity and visual loss. In one large series of patients with uveitis, 35% had visual loss to a level of worse than 20/60 in at least one eye with blindness in 20%. 1 Corticosteroids have been the mainstay of management in uveitis. However the systemic as well as ocular side effects of long term administration of steroids and failure to maintain adequate control of inflammation with steroids only warrants addition or change of the drug regimen. Here comes the role of immunosuppressives.

Indications of immunosuppressives
- Intolerance or contraindication to oral steroids.
- Failure to control inflammation with steroids.
- Chronic treatment with steroids for more than 3 months with 5-10 mg daily.
- Specific diseases like Behcet's uveitis, birdshot choroidopathy, serpiginous choroiditis, VKH syndrome, sympathetic ophthalmia.

Category of immunosuppressives

<table>
<thead>
<tr>
<th>Category</th>
<th>Name</th>
<th>Mechanism Of action</th>
<th>Expected onset</th>
<th>Dose</th>
<th>Lab test</th>
<th>Side effects</th>
<th>Comments</th>
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<tr>
<td>Antimetabolite</td>
<td>Azathioprine</td>
<td>Alters purine metabolism</td>
<td>1-3 months</td>
<td>1.3 mg/kg daily</td>
<td>CBC every 4-6 week, LFT every 12 weeks</td>
<td>Bone marrow suppression, hepatitis, g.i. upset</td>
<td></td>
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<td></td>
<td>Methotrexate</td>
<td>Inhibitor of dihydrofolate reductase</td>
<td>2 weeks to 3 months</td>
<td>7.5-25 mg weekly, titrated every month</td>
<td>CBC LFT every 6-8 weeks</td>
<td>Myelosuppression, hair loss, stomatitis, nausea, vomiting</td>
<td>Supplement with folic acid 1 mg daily</td>
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