10th Evolving Practice Of Ophthalmology Middle East Conference
EPOMEC
EXPANDING VISION

Stepwise Approach for management of ocular chronic graft versus host disease patients

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Introduction

Graft versus host disease (GVHD) is an immune mediated disease due to complex interaction between donor (lymphoid tissue) and recipient's immunity occurring after transplantation.

Procedures with risk of GVH disease

- HSC Transplantation (hematopoietic stem cell transplantation)
  - Bone marrow transplantation.
  - Umbilical cord blood.
  - PBSC (peripheral blood stem cell) transplantation.

- Solid organ transplantation
  (esp. organs containing rich lymphoid tissue)
  - Kidney transplantation.(rare)
  - Liver transplantation.
  - Heart transplantation .

- Transfusion of unirradiated blood products.

- It can also be caused by whole blood transfusion in patients with severe combined immunodeficiency.

Immunological warfare:

- **Preconditioning regimen:**

in which the patient's own bone marrow—and, accordingly, immune system—is depleted through intensive chemotherapy, with or without radiation therapy.

- The transplanted donor cells repopulate the recipient's marrow and reconstitute the patient's hematologic profile, including the immune system.

- **GVHD** occurs when the donor-derived graft cells, mediated by **the donor $CD4^+$ and $CD8^+$ T cells** identifies the recipient's own histocompatibility antigens(HLA) as foreign and mount an immunological reaction against them.

- Despite improvements in immunosuppressive therapies and better human leukocyte antigen (HLA) typing

- **GVHD** remains a common complication, occurring in 30% to 70% of patients.

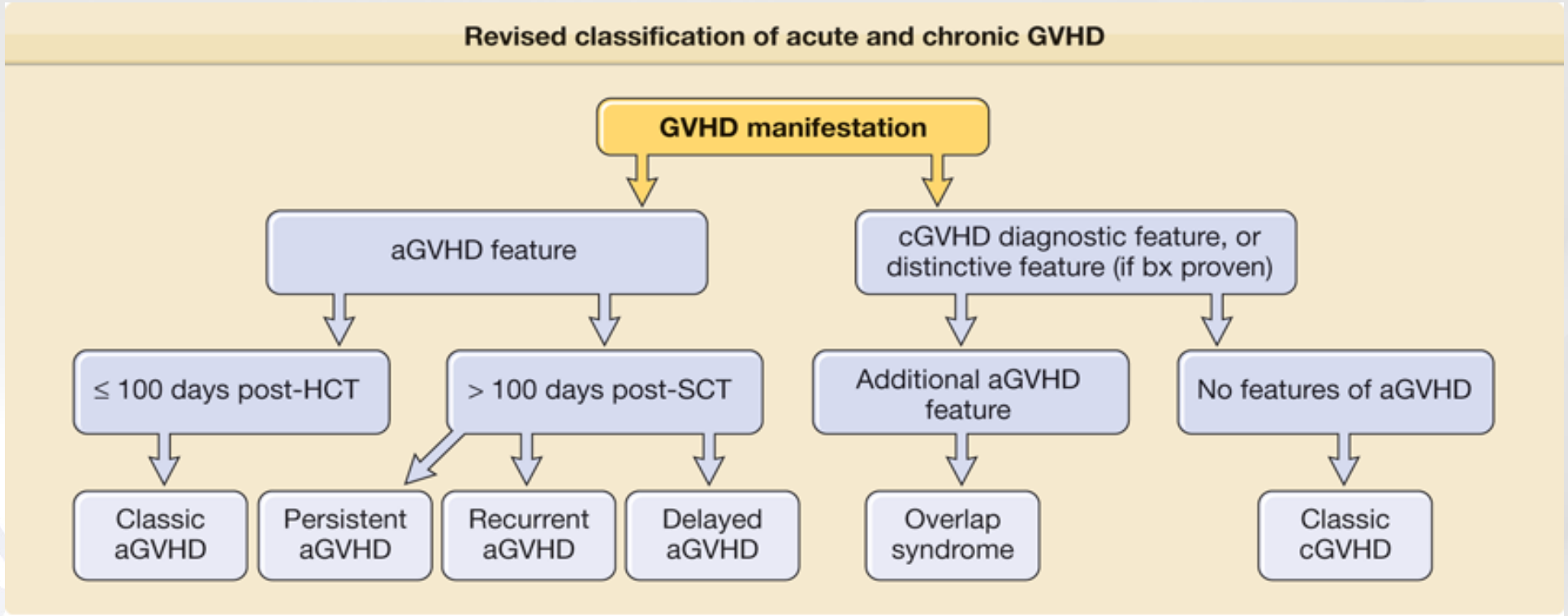
Pathophysiology

- ✓Immune-competent T cells transplanted into immune-compromised host.
- ✓Host cannot reject the graft due to decreased immunity. But graft T cells perceive the recipient's tissue as foreign and react against it.
- ✓This leads to activation of CD4 and CD8 T cells ultimately causing inflammation and killing of host cells.
- ✓Other studies suggested the contribution of B-cells to the pathogenesis of GVHD.

Types of GVHD

Acute GVHD = a GVHD
occur within 100 days of HSCT.

Chronic GVHD = c GVHD
occurs 100 or more days after HSCT



Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

Ocular manifestations of GVHD

- It is important for clinicians to keep ocular GVHD in mind when treating patients who have had BMT.

- The ocular disease may be overlooked, particularly if the patient has severe or life-threatening systemic conditions; and a delay in diagnosis and treatment can lead to increased morbidity due to corneal scarring and decreased vision.

The recommended screening schedule for ocular GVHD:

1) a baseline ophthalmological workup including the Schirmer test before HSCT
2) a screening examination at day 100–200 after HSCT
3) an ophthalmological assessment in case of ocular symptoms or any other manifestation of GVHD

The advantages of this screening protocol :

1. to provide a baseline examination to detect progressive KCS earlier,
2. to be able to diagnose ocular cGVHD earlier (eg, decrease in Schirmer scores, inflammation of the conjunctiva),
3. to allow an early start with treatment to prevent excessive inflammation and scarring processes and sight-threatening complications and improve symptoms and quality of life

- Ocular GVHD can present with a wide array of signs and symptoms affecting all layers of the eye including:

✓the eyelids,

✓lacrimal gland,

✓conjunctiva,

✓cornea,

✓Sclera,

✓ vitreous, retina and choroid.

Clinical Symptoms of Ocular cGVHD

- dry eye : grittiness, foreign body sensation, burning
- irritation,
- itchiness,
- epiphora (excessive tearing),
- photophobia,
- blurred vision
- pain, redness (being also a subjective feature),

In rare cases, pain and redness can be related to scleritis

OSDI

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?.	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?.	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?.	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?. . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

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Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
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Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

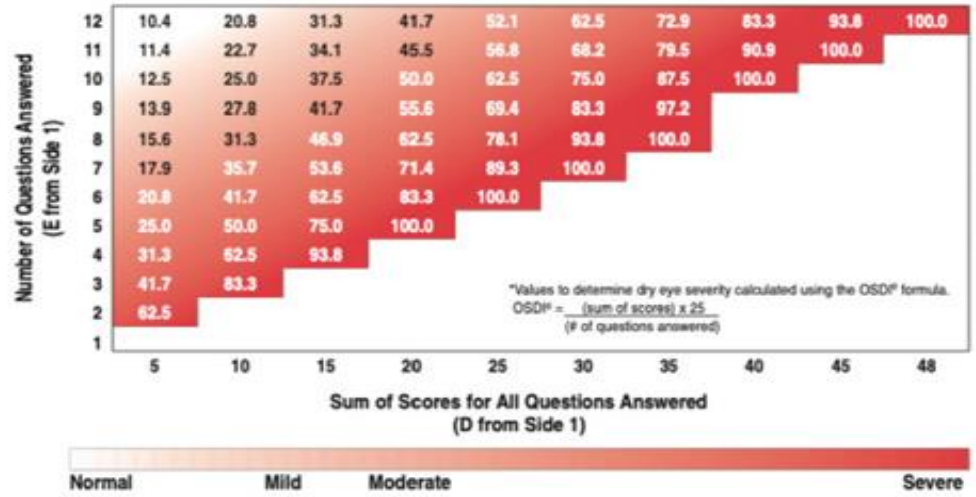
Please turn over the questionnaire to calculate the patient's final OSDI® score.

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



Patient's Name: _____ **Date:** _____

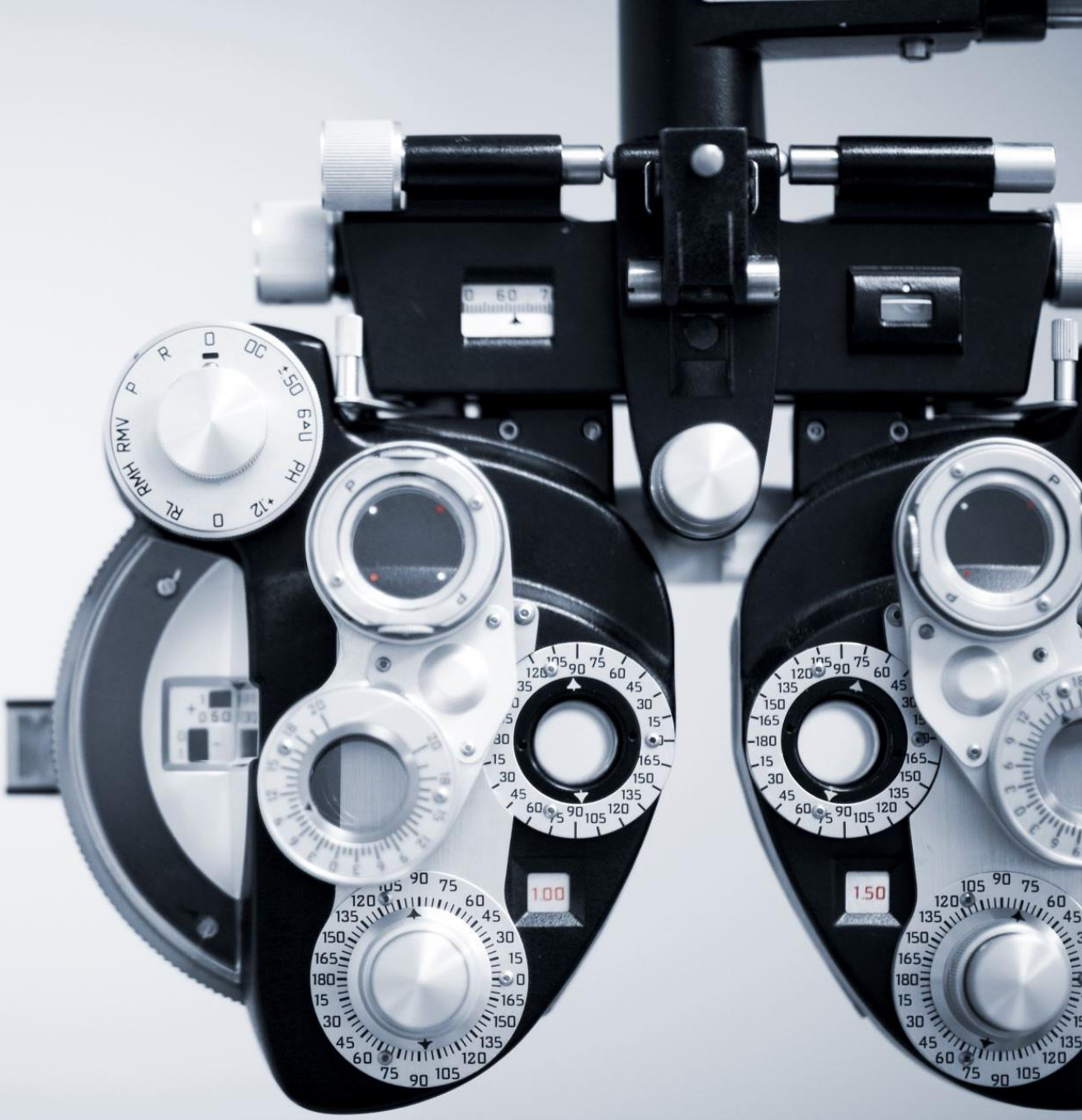
How long has the patient experienced dry eye disease? _____

Eye Care Professional's Comments: _____

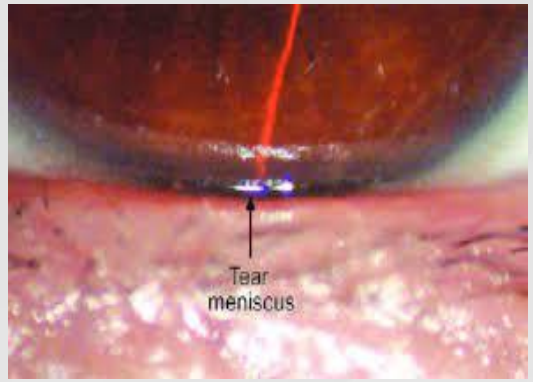
1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Ophthalmological Workup:

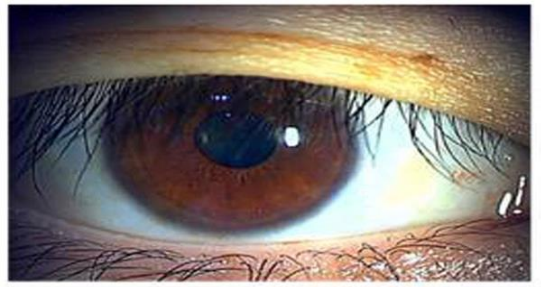
- visual acuity test
- slit-lamp examination using vital dyes (eg, fluorescein)
- subtarsal inspection,
- tear film breakup time (BUT)
- Schirmer test.
- IOP
- OSDI.



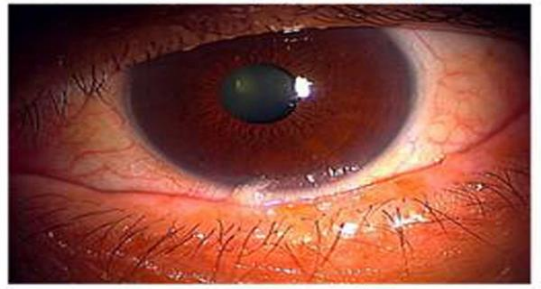
Slit-lamp exam to evaluate the tear film:



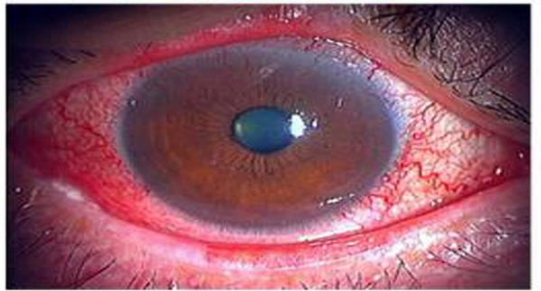
Conjunctival injection grading.



Grade 0



Grade 1



Grade 2

Grading systems for conjunctivitis in acute and chronic ocular GVHD, summarized

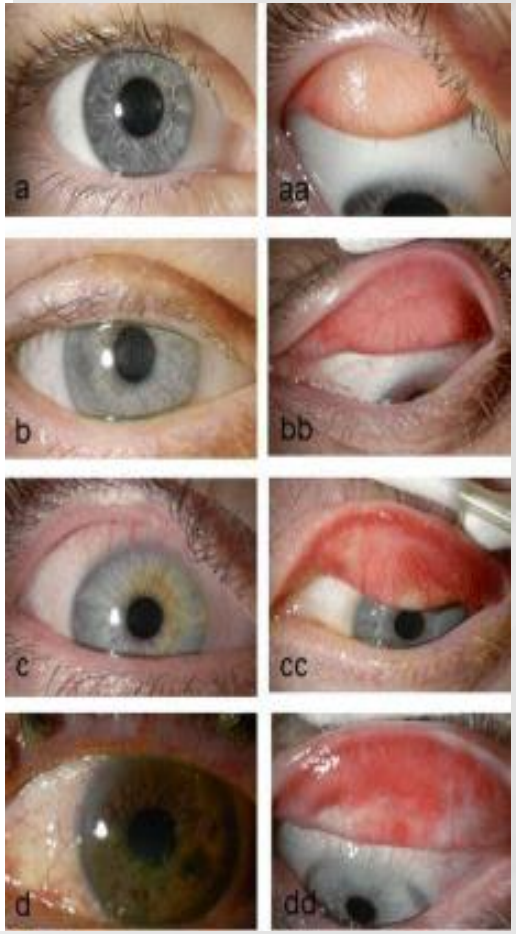
Conjunctival Grading in Acute and Chronic GVHD

Classification of Conjunctivitis in Acute GVHD[66]

0. None
1. Hyperemia
2. Hyperemia with serosanguinous discharge
3. Pseudomembranous conjunctivitis
4. Pseudomembranous conjunctivitis with corneal epithelial sloughing

Classification of Conjunctivitis in Chronic GVHD[135]

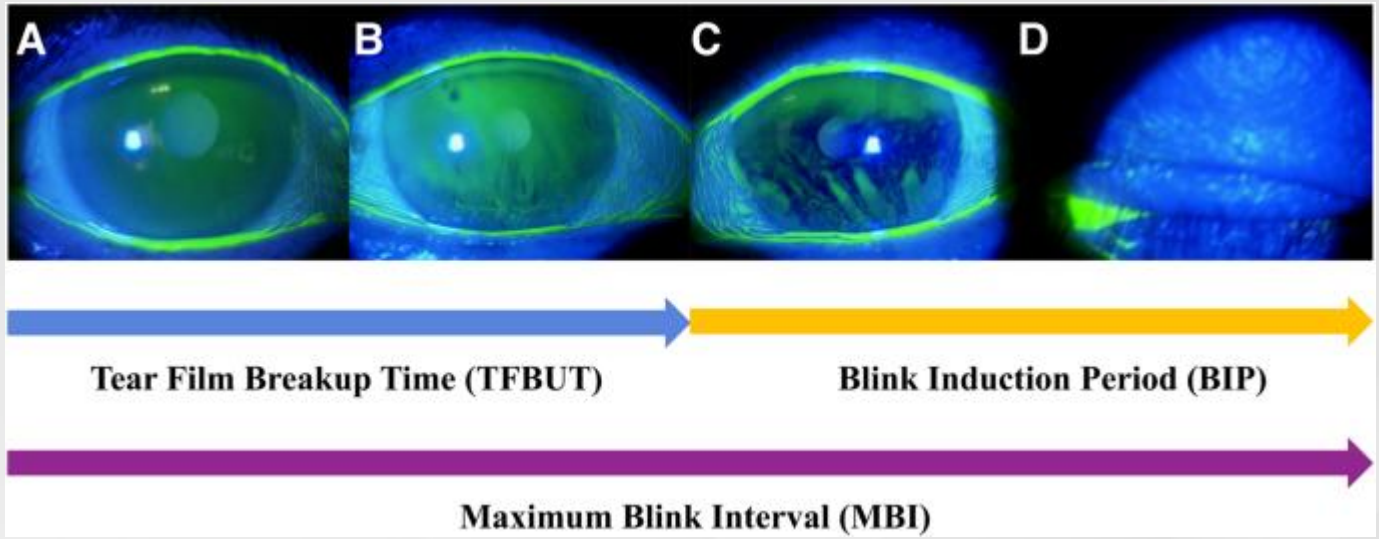
0. None
1. Hyperemia
2. Palpebral conjunctival fibrovascular changes with or without epithelial sloughing
3. Palpebral conjunctival fibrovascular changes involving 25–75% of total surface area
4. Involvement of >75% of total surface area with or without cicatricial entropion

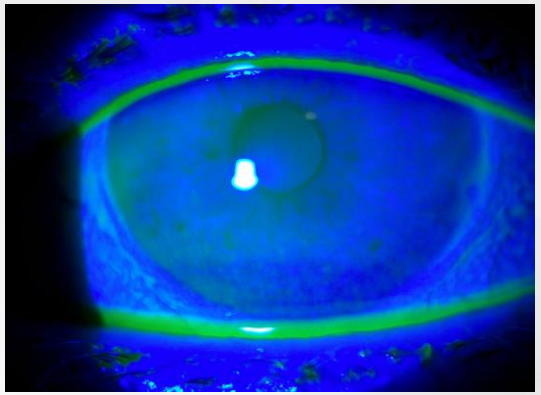


- Hasanain S, Joseph H. Reza D, MD et al. A Review Ocular Graft versus Host Diseaseare principally for patients with acute GVHD. SURVEY OF OPHTHALMOLOGY , 2013 , 58(3)

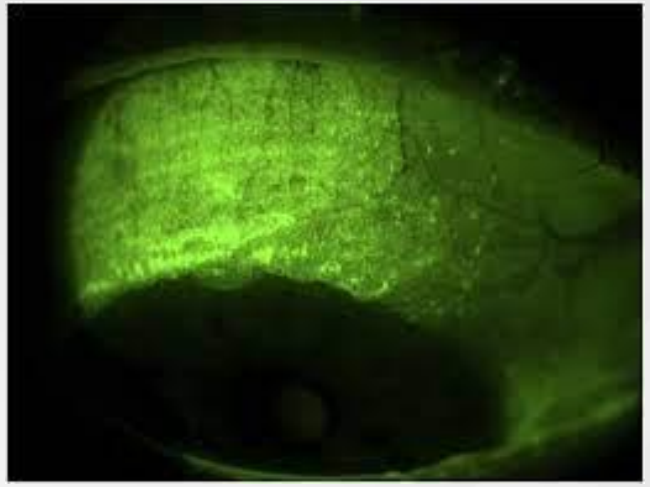
Fluorescein staining:

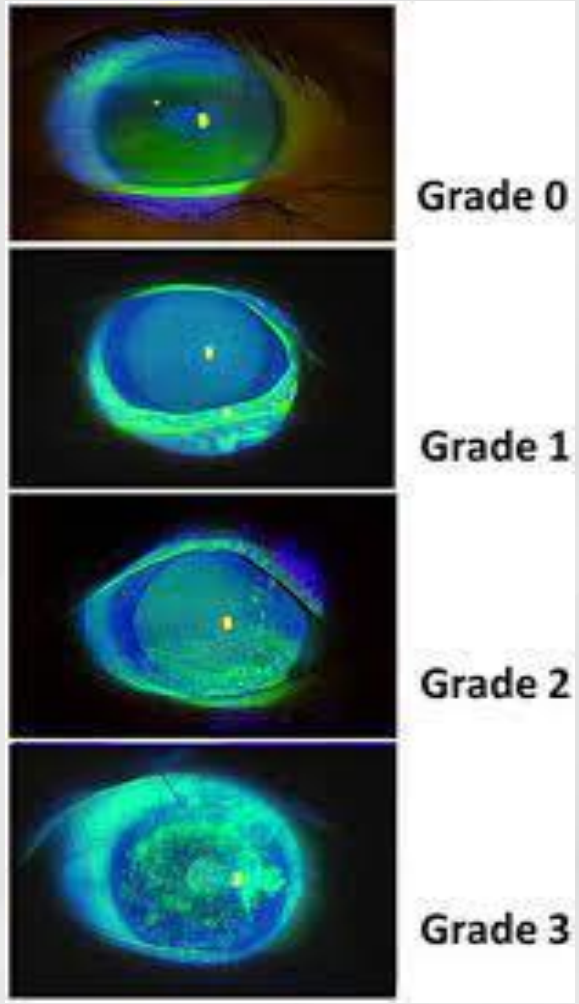
- tear film breakup time(tBUT)
- tear meniscus thickness.
- tear clearance in front of the ocular surface





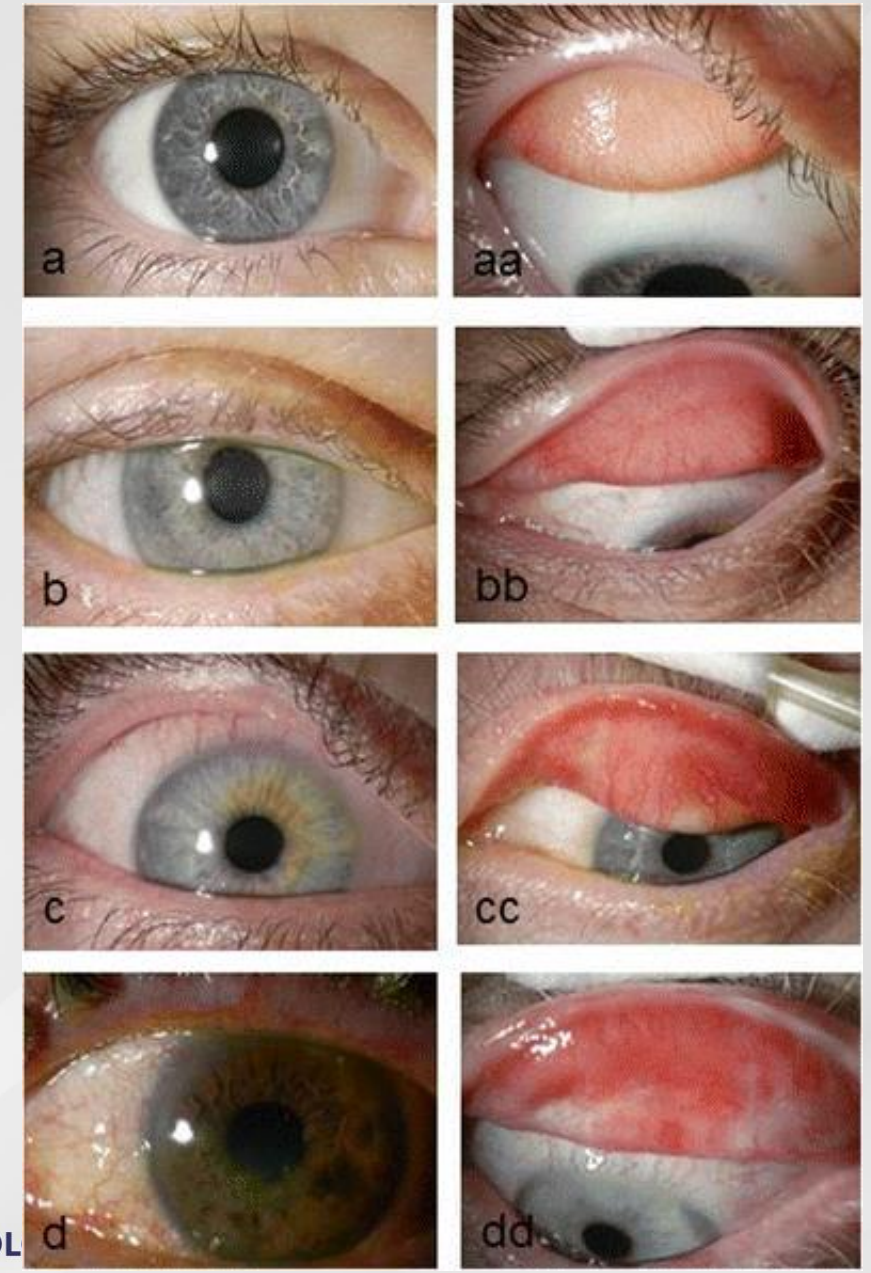
- Corneal Fluorescein Staining (CFS)
- Conjunctival staining





Don't forget :

Evert the eyelids



Management

- The main therapeutic aim in the management of ocular GVHD is the treatment of inflammation and dryness to relieve patients' symptoms and to maintain ocular integrity and function

Systemic treatment.

- Management of ocular GVHD begins with systemic treatment, usually tailored to the individual patient by the hematologist/oncologist, and may include corticosteroids in combination with other immunosuppressant therapies.

- These treatments should improve ocular manifestations when combined with local measures.

- New therapeutic approaches such as **extracorporeal photopheresis** seem to improve ocular involvement in cGVHD although controlled prospective studies are required

Local treatment.

- 4 main supportive goals for the treatment of ocular GVHD:
  - Lubrication.
  - decrease in ocular inflammation.
  - control of drainage.
  - control of evaporation.

I. Increase Lubrication

- **A. Preservative-free artificial tears.**

should be offered to all patients for ocular GVHD.

Different brands may need to be tried to maximize benefit.

- **B. Viscous ointment.** To be used at bedtime.

- **C. Hydroxypropyl methylcellulose pellets (Lacrisert).**

May be helpful for patients who use artificial tears often.

- **D. Oral cevimeline or pilocarpine.**

Has been shown to improve sicca symptoms in Sjögren syndrome. Drug interactions and effects on other disease processes such as angle-closure glaucoma must be reviewed.

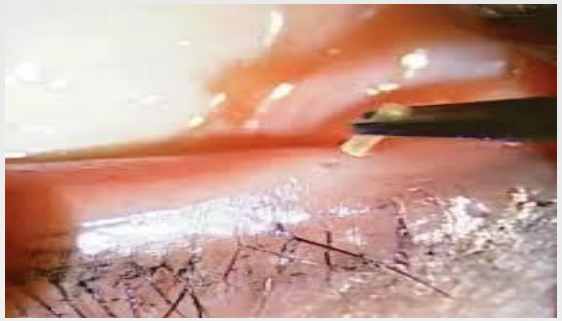
- **E. N-Acetylcysteine (5-10%)(mucolytic).**

If multiple corneal filaments are present

Decreases tear drainage:

Punctal occlusion:

✓Consider use in all chronic GVHD patients



✓Schirmer scores <5/5 mm, punctal occlusion—if necessary of all 4 puncta.

✓Thermal cauterization may be necessary if plugs are frequently dislodged.

II. Decrease Ocular Inflammation

- **A. Topical steroids.**

✓Valuable, but should be continued only for a limited time as needed during acute ocular GVHD exacerbation.

✓ Can be used while systemic steroids are being tapered.

✓ Chronic use of topical steroids can lead to infection, cataracts, and increased IOP.

B. Topical cyclosporine (Restasis).

- (cyclosporine ophthalmic emulsion 0.05%)

✓Topical CsA acts by inhibiting T-cell proliferation and the production and release of lymphokines from activated T-cells in the conjunctiva.

✓CsA has also been shown to increase goblet cell density and epithelial cell turnover in the conjunctiva.

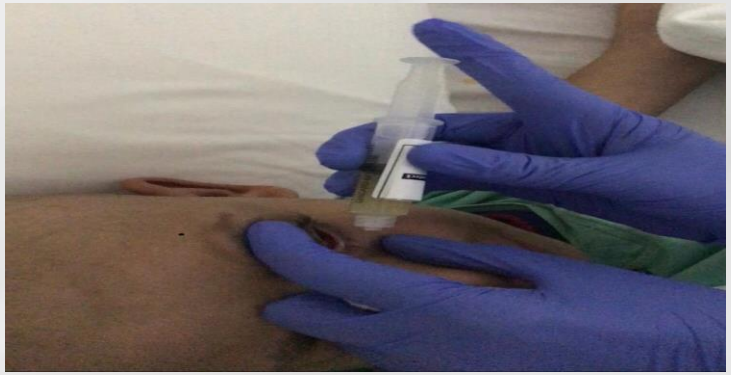
✓As well as other calcineurin-inhibitors, tacrolimus ointment.

• C. Autologous serum eye drops.

✓Can be started if there is progression despite use of methods above.

✓Contains growth factors and vitamins that support the health of the ocular surface.

✓Treatment with autologous serum eye drops must be performed according to the local legal regulations for drugs and transfusions and is therefore limited to specialized centers.



- **C. Lifitegrast ophthalmic solution (Xiidra).**

Down regulates T-cell–mediated inflammatory reactions

- **E. Topical anakinra 2.5%.**
- Interleukin 1 receptor antagonist now being studied to reduce inflammation and treat dry eye disease.
- Has shown good results in initial trials and case reports.

III. Treat Meibomian Gland Disease (MGD)

- **A. Lid hygiene.** Helps to clear blockages and restore normal flow.
- regular application of warm compresses (2–3) per day for 10 minutes.
- **B. Topical antibiotics** (eg, doxycycline, tetracycline **ointment or azithromycin e.d.).** Can help reduce meibomian gland blockage .

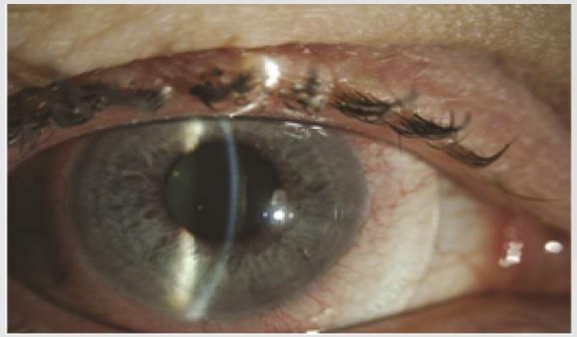
- **C. Fish oil or flaxseed oil (omega-3) dietary supplementation.**

Helps to improve the quality and consistency of the meibomian gland secretions.

- **D. Oral doxycycline or minocycline.** These drugs have anti-inflammatory and antibiotic effects and used if MGD is severe and there are no systemic contraindications.

- Coordinate use of doxycycline with patient's hematologist/oncologist to avoid potential drug interactions.

IV. Provide Surface Protection

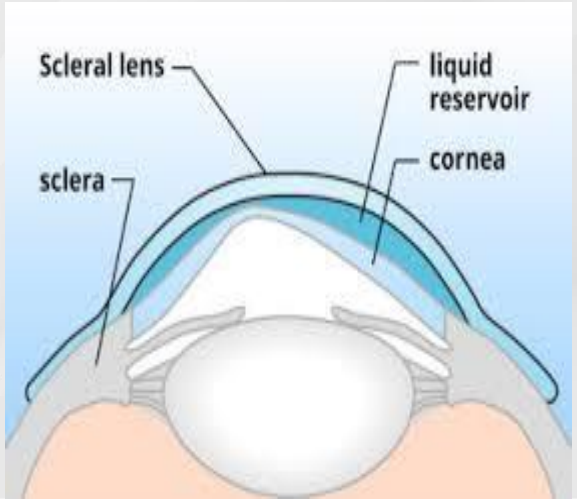


- **A. Scleral contact lenses (e.g., PROSE).**

A Prosthetic Replacement of the Ocular Surface Ecosystem

- Provide symptomatic relief with improved vision and comfort in patients with epithelial damage.

- Help to protect the cornea,
- maintain fluid on the cornea,
- promote healing,
- reduce evaporation.



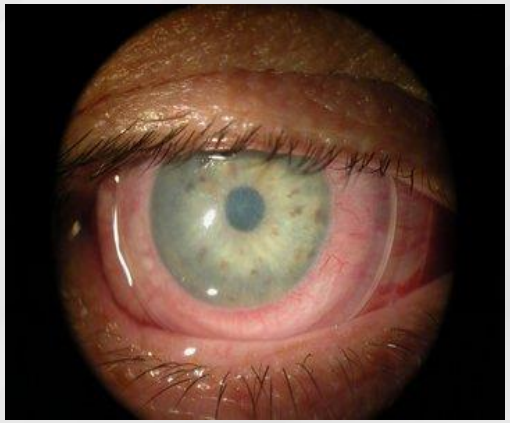
- **B. Amniotic membrane devices**

1. Prokera ocular bandage device.

Consists of amniotic membrane tissue stretched over a ring, which is inserted like a contact lens without sutures.

2. Ambio disk:

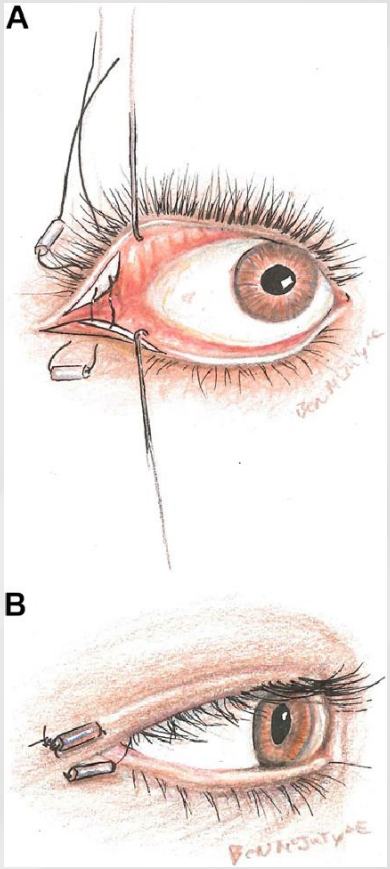
Amniotic membrane disk; may be held in place with sutures, tissue adhesive, or contact lens.



V. Consider Surgical Options

- **Tarsorrhaphy:**

Protects the cornea and decreases dryness/evaporation if significant corneal ulceration is present.



Prevention of Infectious Disease:

- In cases of epithelial defects, topical antibiotic agents are mandatory; if possible, preservative-free antibiotic eye drops with low epithelial toxicity are preferred (eg, ofloxacin).

- Some authors recommend anti-herpetic therapy as prophylaxis for herpes simplex–seropositive patients under topical immunosuppressive treatment.

Management of Complications

Multilayeramniotic membrane transplantation.

treatment for severe dry eyes and calcareous corneal degeneration with or without perforation also helps to prevent symblepharon formation.

Superficial debridement in filamentary keratitis, can improve epithelial healing.1

Excision or removal of pseudomembranes may be beneficial for epithelial recovery In cases of pseudomembranous conjunctivitis1

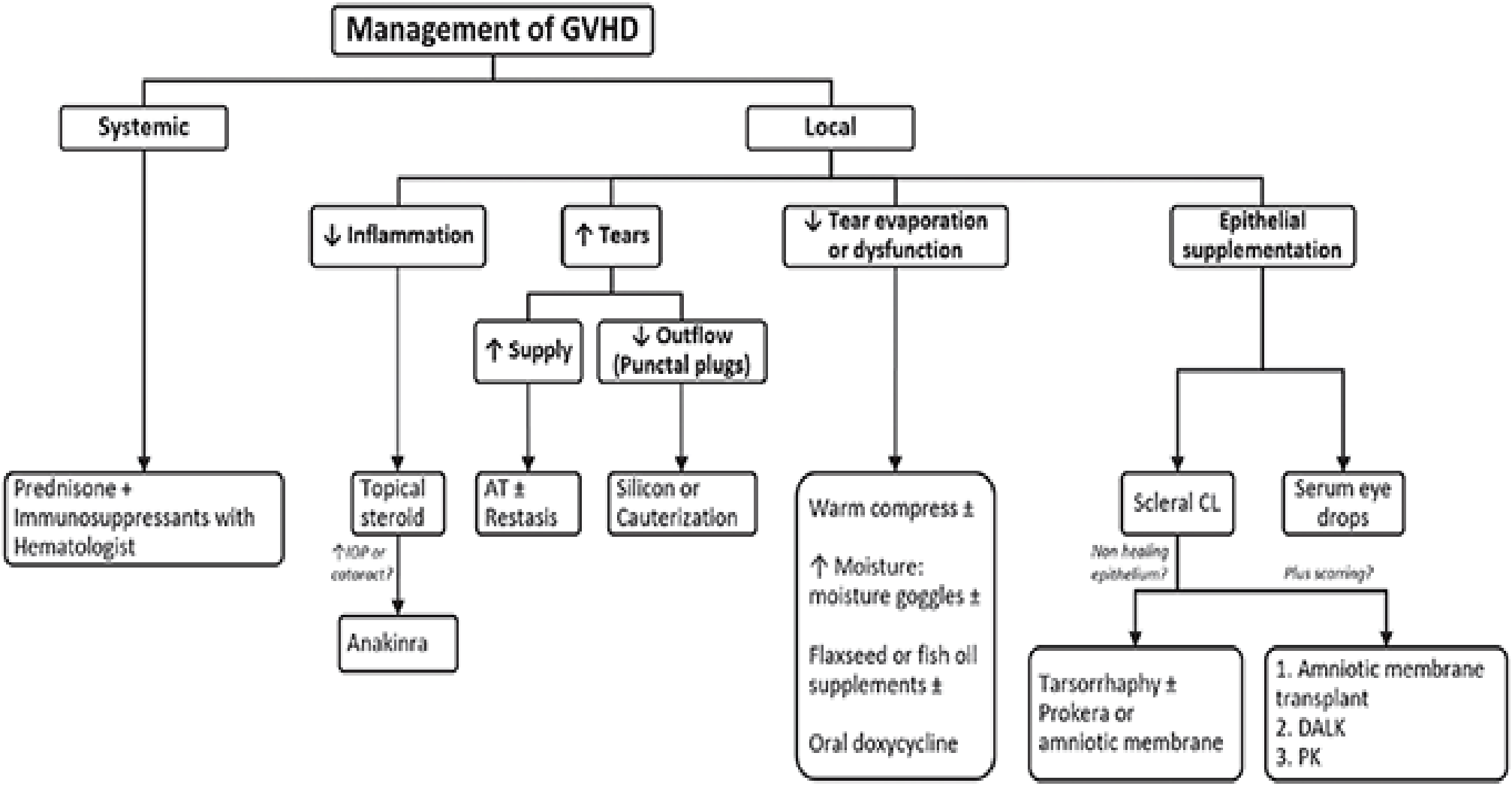
Lysis of membranes and symblepharon.

Helps prevent lid ectropion and lagophthalmos and subsequent conjunctival scarring.

Deep anterior lamellar keratoplasty or penetrating keratoplasty.

May be performed in very advanced cases of ocular GVHD if there is descemetocele formation or corneal perforation.

Flowchart for Management of Ocular GVHD



Take home message

- Ocular involvement in cGVHD is common in the long-term follow-up of patients after HSCT and is frequently related to morbidity and significant reduction in quality of life.

- Therefore, prevention, diagnosis, treatment, and supportive care of ocular cGVHD are important components of multidisciplinary post-HSCT management.

Thank you