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OCULAR GRAFT-VERSUS-HOST DISEASE

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INTRODUCTION

Chronic Graft versus host disease (cGVHD) is still the main complication of allogeneic hematopoietic stem cell transplantation (HSCT). GVHD prevention strategies should be established, the diagnosis promptly recognized, and treatment started as early as possible to minimize complications and risks. (Higman and Vogelsang, 2004) Recommendations and guidelines for the diagnostic assessment and treatment of GVHD proposed for this consensus were organized according to a system based on scientific evidence, ranked by the strength of recommendation and the quality of the evidence. (Guyatt *et al*., 2008)

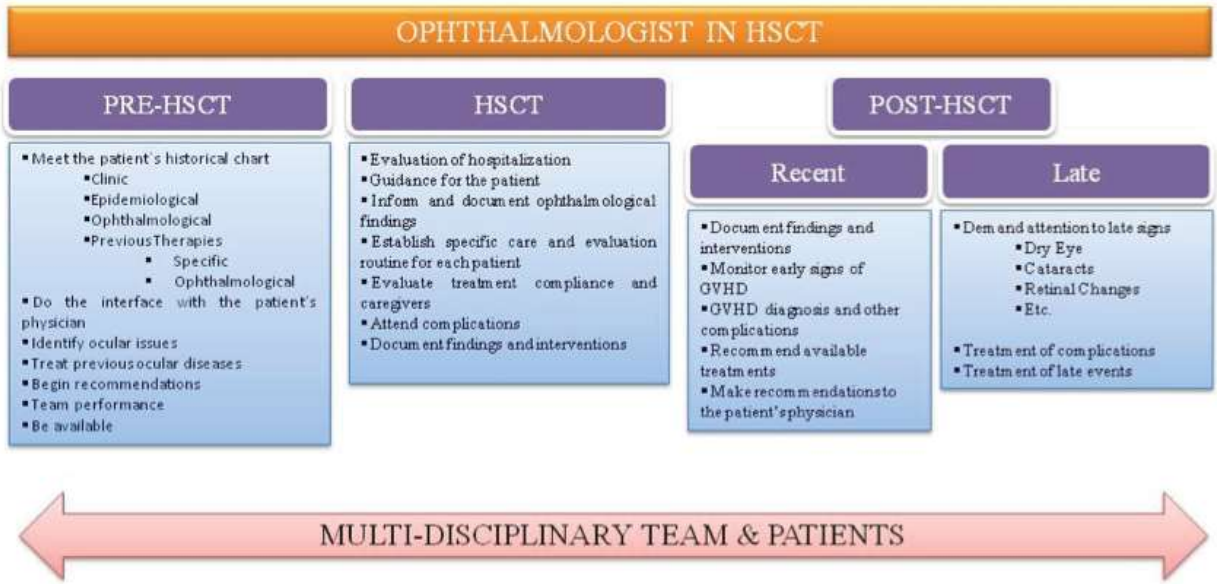
The most commonly clinical presentatiomn found in ocular GVHD is the dry eye disease, occurring, with varied intensity of clinical presentation, symptoms and involvement of the structures of the ocular surface and the tear film. However, it is a disease with complex pathophysiological mechanisms that involve loss of homeostasis of the ocular surface, changes in the composition of the tear film and glands, such as the main lacrimal gland and the meibomian glands. It constitutes a characteristic framework for the diagnosis of chronic GVHD, it occurs in most patients, typically 6 months after allogeneic HSCT. (Nassiri *et al.*, 2013)

The definition of Dry Eye Disease from the Dry Eye Workshop (DEWS) 2017 indicates that is a multifactorial disease of the tear and ocular surface that results in symptoms of discomfort, visual disturbances and instability of the tear film, with potential damage to the eye. It is accompanied by high osmolarity of the tear film and inflammation of the ocular surface, in which neurosensory changes also have an etiological role. (Craig *et al*., 2017) The pathophysiology of Dry Eye Disease related to GVHD is probably derived from the attack of T lymphocytes of the donor to receptor antigens, causing fibrosis and destruction of the conjunctiva, meibomian glands and the lacrimal gland, leading to a state of mixed dry eye, i.e, due to aqueous deficiency (lacrimal gland damage) and evaporative (lipid deficiency and meibomian gland dysfunction) which causes important damage to the ocular surface. (Shikari *et al*., 2013) There is a similarity between Sjögren's Syndrome (SS) and the dry eye secondary to GVHD since both have autoimmune inflammatory infiltration, although in GVHD the primary involvement is ductal and in Sjögren's Syndrome (SS) there is an immune-mediated inflammatory infiltrate affecting the glandular acinus. (Lee *et al.*, 2003) However, studies by Ogawa et al. demonstrated that there is more fibrosis in GVHD than in SS, and that the presence of the donor's fibroblasts in the ocular surface tissues of recipients with GVHD, such as in the lacrimal gland, may play a role in the pathophysiology of dry eye in chronic ocular GVHD. (Ogawa *et al.*, 2005)

Signs and symptoms of ocular GVHD occur according to the severity of tissue damage, compensatory mechanisms and stage of the disease from its inflammatory phase to the healing phase. Symptoms of fluctuating vision, foreign body sensation, irritation and red eye, photophobia and excessive tearing are described. Several complications, such as Meibomian glands dysfunction, pseudomembranous conjunctivitis, punctate and filamentary keratitis, cataracts secondary to the use of corticosteroids, narrowing and corneal perforation, secondary infection to ocular surface are in the published reports. (Rocha *et al*., 2000)

Ophthalmological evaluation must be performed before HSCT in order to assess the occurrence of previous ocular surface disease, proper identification of other risk factors and education of the patient regarding ocular symptoms after the procedure. Figure 1 shows the main aspects to be considered in the ophthalmological follow-up of patients undergoing HSCT.

FIGURE 1 - Ophthalmological Follow-up in HSCT



INCIDENCE AND RISK FACTORS FOR OCULAR GVHD

GVHD has an incidence of 25 to 70% of patients undergoing HSCT and the variability of rates reflects the adoption of new conditioning strategies, modalities of transplant and the lack of sensitive and specific markers for screening of this complication. The performance, on an increasing scale, of procedures with so-called unrelated donors, transplants in older patients, use of peripheral stem cells, adopted strategies of prophylaxis, among others, can explain different incidence rates. (Lee and Flowers, 2008, Lee *et al.,* 2003)

Ocular involvement in chronic GVHD can affect 40 to 60% of transplant recipients. There are some well-known risk factors related to the occurrence of ocular GVHD such as: non-Caucasian recipient patients, recipients of donors with positive serology for Epstein-Barr Virus (EBV) and Diabetes Mellitus. The severity of chronic GVHD and the number of organs involved, as well as previous dry eye, are also related to a higher incidence of ocular GVHD. (Nassiri *et al.*, 2013) In addition to the classic risk factors mentioned, it is also important to consider the occurrence of acute GVHD, use of peripheral stem cells, types of conditioning and prophylaxis. (Munir and Aylward, 2017)

The severity of chronic GVHD and the number of organs involved, as well as previous eye changes, such as signs and symptoms of dry eye prior to the procedure, are also related to a higher incidence of the ocular form of the disease. (Na et al., 2015) (Inamoto et al., 2019) (Giannaccare *et al.,* 2017). Table 1 summarizes the main risk factors associated to ocular GVHD

TABLE 1. Risk factors for ocular GHVD

Related to Recipient	Related to the Procedure
Age: older recipients	Use of Antithymocyte Globulin
Non-caucasian	Use of Total Body Irradiation
Diabetes Mellitus type 2	Donors with Incompatibilities
Previous ocurrence of acute GVHD	Donors with positive serology for Epstein-Barr Virus
Chronic GVHD GII to IV	Use of Peripheral Stem Cells
More than two organs involved in GVHD	Unrelated Donors
Previous Dry Eye Disease	Female donor for male donor

DIAGNOSTIC CRITERIA FOR OCULAR GVHD

The diagnosis of dry eye and ocular surface disease secondary to ocular GVHD is essentially clinical. It is important to quantify associated symptoms (standardized questionnaires as the OSDI - Ocular Surface Disease Index), to evaluate the tear volume (Schirmer's test and meniscometry), and tear stability (measure of the tear film break-up time and assessment of meibomian gland), osmolarity, conjunctival hyperemia and integrity of the ocular surface with the vital staining with 1% Green Lissamine, 1% Bengal Rose and 2% Sodium Fluorescein. In addition, a complete ophthalmological assessment including visual acuity, intraocular pressure, biomicroscopy and funduscopy should be performed on every patient prior and after allogeneic HSCT. Some diagnostic criteria have been developed and applied such as the NIH Consensus (Jagasia *et al*., 2015) and the International Chronic Ocular Graft-Versus-Host Disease Consensus Group (ICOGCG). (Ogawa *et al*., 2013)

The 2005 NIH Consensus established a standardized-criteria for the diagnosis of chronic GVHD and rating of disease severity through a scoring system, considering its impact on daily life activities. (Filipovich *et al*., 2005) In 2015, NIH launched a report to clarify the controversies related to the minimum criteria for the diagnosis of chronic GVHD (Table 2) and to refine the definition of the subcategories of chronic GVHD and the score of the specific gravity of the organ (Table 3). (Jagasia *et al*., 2015)

TABLE 2 – Signs and symptons of chronic GVHD according to NIH criteria (2015)

OrgAN Local	OR	DIAGNOSIS (Enough to establish the diagnosis for chronic GVHD)	DISTINCT (Seen in chronic GVHD, but insufficient individually for the diagnosis of chronic GVHD)		OTHER CHARACTERISTICS OR NON-CLASSIFIED ENTITIES*	COMMON (present in both acute and chronic GVHD)
Eyes				Dry, sand feeling, or pain Conjunctival scarring Keratoconjunctivitis sicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	

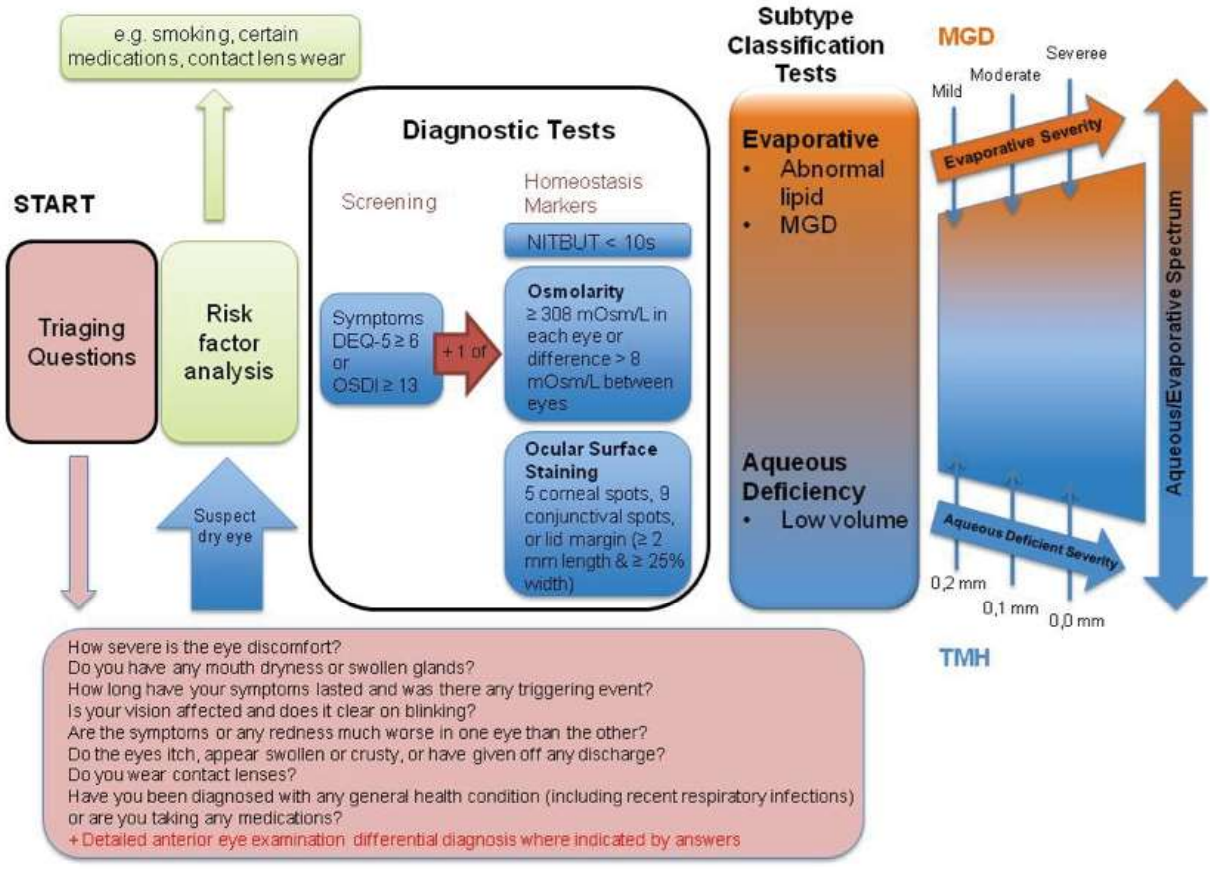
Source: Clinical Protocol and Therapeutic Guidelines, Immune suppression for Prophylaxis and Treatment of Acute and Chronic Graft-versus-host disease (GVHD) in Hematopoietic Stem Cell Transplants. (Jagasia et al., 2015)

TABLE 3 - Eyes Score for chronic GVHD according to NIH criteria (2015)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES Keratoconjunctivitis sicca, confirmed by the ophthalmologist: ☐ Yes ☐ No ☐ Not examined	☐ No symptoms	☐ Mild symptom of dry eye does not affect basic daily activities (it requires lubricant eye drops < 3 times a day)	☐ Moderate symptom of dry eye partially affects the daily activities (it requires lubricant eye drops > 3 times a day or tear duct ligature), without worsening visual acuity	☐ Severe symptoms of dry eye that significantly affect daily activities Or unable to work due to ocular symptoms Or vision loss due to keroconjunctivitis sicca.

Ocular symptoms of dry eye, foreign body sensation or recent onset of ocular pain; and the findings of conjunctival scarring; keratoconjunctivitis sicca; and confluent areas of punctate keratitis are defined as manifestations of chronic GVHD by the NIH report, while the manifestation of photophobia, periorbital hyperpigmentation and blepharitis (erythema of the eyelids with edema) are considered as unclassified manifestations. (Filipovich *et al.*, 2005) (Arai *et al.*, 2011) According to the NIH 2015 report, there are no specific diagnostic criteria for the eyes and dry eye is insufficient in itself to establish a diagnosis of chronic GVHD. Alterations of ocular surface and lacrimal gland are not considered diagnostic of chronic GVHD, as they may have other causes, e.g. secondary infections, medications or total body irradiation. Based on the NIH classification system, the diagnosis of ocular GVHD cannot be made in the absence of systemic GVHD. (Jagasia *et al.,* 2015)

According to the latest Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS II), Dry Eye diagnosis is considered if presence of symptoms and at least 1 positive test of homeostasis markers (such as tear film parameters, ocular surface staning or tear osmolarity). The investigation of dry eye starts with symptom evaluation through questionnaires, such as DEQ-5 or OSDI, followed by diagnostic tests of tear film stability (tear film break-up time) and tear volume, osmolarity and ocular surface staining with fluorescence and green lysamine (observing the cornea, conjunctiva and palpebral margin) (Figure 2). (Wolffsohn *et al.*, 2017) In the initial diagnosis, it is important to exclude conditions that can mimic dry eye such allergy and toxicity and, with the help of screening questions, evaluate risk factors, such as environmental exposure, medication in use and associated symptoms. Dry eye symptoms in the absence of clinical signs can suggest neuropathic pain. Meibomian gland evaluation is important and may be perfomed by quantification of expressibility and secretion pattern, tear lipid layer thickness and dynamics Tear volume is an important parametres measured by Schirmer test or tear meniscus height. Such parameters evaluate severity and classifiy subtypes as evaporative (associated to melbomian glands dysfunction, reduction of the lipidic layer and lacrimal instability) or aqueous deficiency (associated to lacrimal gland dysfunction and low tear volume) or mixed form. (Wolffsohn *et al.*, 2017)



In order to provide a stronger definition, rating, assessment and staging of ocular GVHD, the International Chronic Ocular Graft-Versus-Host Disease Consensus Group (ICOGCG) has launched a set of criteria that might help include ocular GVHD as a sufficient diagnostic signal itself for the diagnosis of chronic GVHD. (Ogawa *et al.,* 2013) The proposed diagnostic criteria for ocular GVHD include: (1) OSDI (Ocular Surface Disease Index) symptom questionnaire, (2) score for Schirmer I test (without anesthesia), (3) staining with corneal fluorescein and (4) conjunctival injection. Table 4 shows the scores for ocular criteria and the sum of the points obtained must be checked as to the presence or absence of systemic GVHD as shown in Table 5. A study compared the usefulness of the diagnosis between the 2005 NIH criteria and the ICOGCG criteria and showed that the stricter ICOGCG criteria better differentiated ocular GVHD (Pathak *et al.,* 2018).

TABLE 4 - Chronic ocular GVHD severity scale - ICOGCG.

Severity	Schirmer ITest	Corneal fluorescein staining	OSDI	Conjunctival Hyperemia
0	15 >	0	< 13	None
1	11-15	< 2	13-22	Mild/moderate
2	6 -10	2-3	23-32	Severe
3	£ 5	£ 4	> 33	

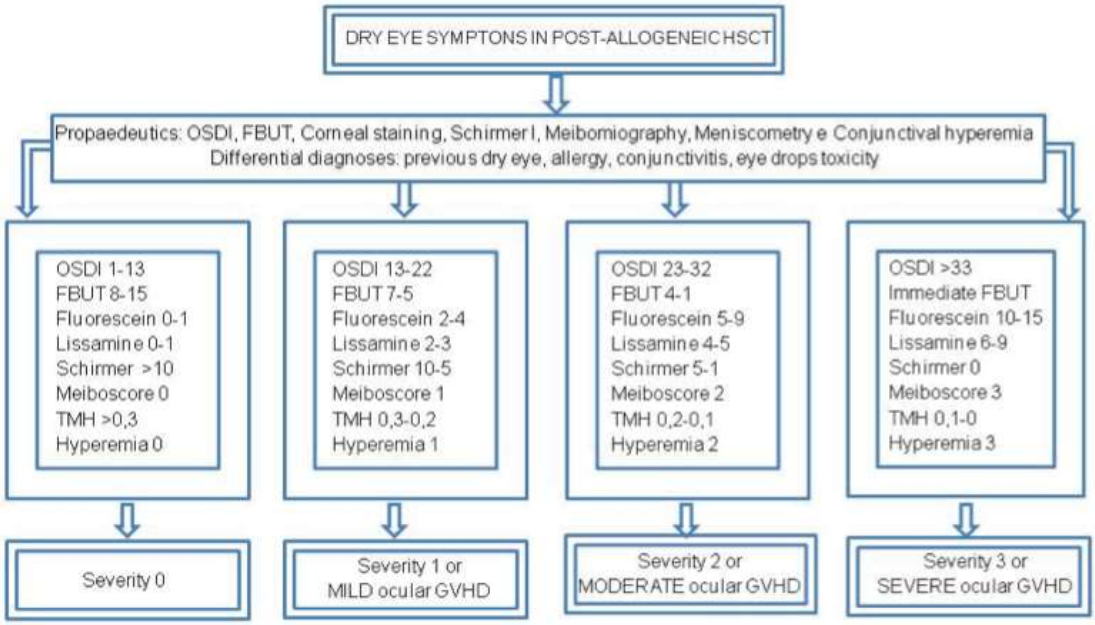
TABLE 5 - Diagnostic criteria of Chronic ocular GVHD – ICOGCG.

	Negative	Probable GVHD	Definitive GVHD
Systemic GVHD (-)	0-5	6-7	≥ 8
Systemic GVHD (+)	0-3	4-5	≥ 6

Diagnosis of chronic ocular GVHD: total score (Schirmer Test + corneal fluorescein staining+ OSDI + conjunctival hyperemia) = Negative: 0-4; Mild/moderate: 5-8; Severe: 9-11 and presence or not of systemic GVHD.

Figure 3 shows diagnostic criteria and severity scores for the investigation of ocular GVHD.

FIGURE 3 - Severity scores of ocular GVHD



TREATMENT

Treatment of ocular GVHD can be a challenge due the great diversity of clinical presentations, intensity of symptoms and potential complications. (Flowers and Martin, 2015) The main objectives of the treatment for chronic ocular GVHD refer to the reduction of symptoms, control of disease activity and prevention of permanent tissue damage and complications. Whenever possible, it should be monitored carefully and periodically by an ophthalmologist. (Inamoto *et al.,* 2019) Although topical therapy is usually enough to control the eye disease, systemic immune suppression should be considered in cases of moderate and severe disease.(Wolff *et al.*, 2010) (Dietrich-Ntoukas *et a*l., 2012)

The use of artificial lubricants is often the first step to treat dry eye secondary to GVHD, improving not only eye discomfort, but also visual quality. Distinct composition of eye drops regarding to viscosity, active compomnents and presence or quality of preservatives. Autologous serum eye drops, a biological tear substitute, presents characteristics in addition to its lubricating properties, due to its anti-inflammatory and epitheliotrophic characteristics, since it has epithelial growth factors, cytokines and supplement factors. The effectiveness of its use to improve symptoms has been extensively described in the literature. (Inamoto *et al.,* 2019) (Munir and Aylward, 2017)

Topical anti-inflammatory mediators such as corticosteroids, immunosuppressives and tetracycline derivatives contribute to better control of symptoms, in addition to slowing or preventing deterioration of ocular tissues. (Inamoto *et al.,* 2019) The use of topical corticosteroids, one of the main therapeutic choices, must be done with caution due to the important side effects that may result from its prolonged use. Numerous complications can be caused by its improper use, such as damage in the re-epithelialization, infections, corneal defect, cataract and secondary glaucoma. (Dietrich-Ntoukas *et al*., 2012) Some studies showed satisfactory results with the use of 0.05 to 0.1% cyclosporine and 0.05% tacrolimus as an alternative to prolonged use of corticosteroids. (Sall et al., 2000) (Abud et al., 2016) Acetylcysteine 5 to 10% may also be useful in treatment due to its mucolytic effects, although its effectiveness has not been investigated in clinical studies. (Dietrich-Ntoukas *et al.,* 2012)

Several other therapeutic modalities related to local and environmental eye care were evaluated as treatment options for ocular GVHD. Lacrimal punctum occlusion, either by temporary plug or permanent cauterization, is an option for patients with moderate symptoms. The use of soft or scleral contact lenses is also effective to improve symptoms of discomfort. Other options include application of warm compresses, hygiene and control of eyelid changes, as well as avoiding places with low humidity and hazardous environment exposure. Blepharitis must be addressed with warm compresses and eye drops or antibiotic and anti-inflammatory ointment, although some studies also suggest that oral therapy with tetracycline or doxycycline for 3 to 6 weeks reduces local inflammatory processes, improve lipid secretion of the Meibomian gland and lipid layer of the tear film. (Dietrich-Ntoukas *et al.,* 2012) (Frucht-Pery *et al*., 1993) Oral omega-3 supplementation may improve tear film stability and has been used in recent years, although randomized studies do not show its effectiveness. (Deinema *et al.,* 2017)

Surgical procedures may be necessary in specific and refractory cases. Options as tarsorrhaphy, grafting and transplants of the limbus and amniotic membrane may be performed. In severe cases, corneal damage and perforation may occur, with a potential risk of vision impairment. (Peris-Martinez *et al*., 2001) (Meller *et al.,* 2009)

Tables below show the recommendations for the assessment and treatment of ocular GVHD (Table 6), criteria used for strength of recommendation (Table 7) and the level of scientific evidence (Table 8). And in Figure 4 a flow chart with treatment recommendations for ocular GVHD.

TABLE 6 - Recommendations for GVHD as to ophthalmologic manifestation and recommendation score.

Recommendations for assessment and treatment of ocular GVHD	Levels of recommendation and evidence
Ophthalmologic Assessment Before transplantation From 3 to 6 months after transplantation In the diagnosis of chronic GVHD in any organ of the body	 a-3 a-2 a-3
First-line systemic treatment for ocular GVHD Corticosteroids	 a-1
Second-line systemic treatment ou subsequent treatment for ocular GVHD Extracorporeal Photophoresis Rituximab Sirolimus Mycophenolate mofetil	 c-2 c-2 c-2 c-2
Topic treatment Preservative-free artificial tears Artificial tears/viscous ointment Cyclosporine 0,05% - 0,1% Tacrolimus Plugs for lacrimal punctum occlusion Corticosteroids Heated compresses and eyelid hygiene Scleral Lenses Mucin secretagogue eye drops Occluding glasses Antibiotics eye drops and ointment Autologous serum eye drops Platelet-derived eye drops Partial Tarsorrhaphy Superficial epithelial debridement Amniotic membrane transplantation Limbo-keratoplasty stem cell transplantation	 a-2 a-2 b-1 b-1 b-2 b-2 b-2 b-2 b-2 b-2 b-3 c-2 c-2 c-2 c-3 c-3 c-3
Other treatmentss Low-dose oral tetracyicline/doxycycline Oral omega-3 supplement	 b-2 c-1

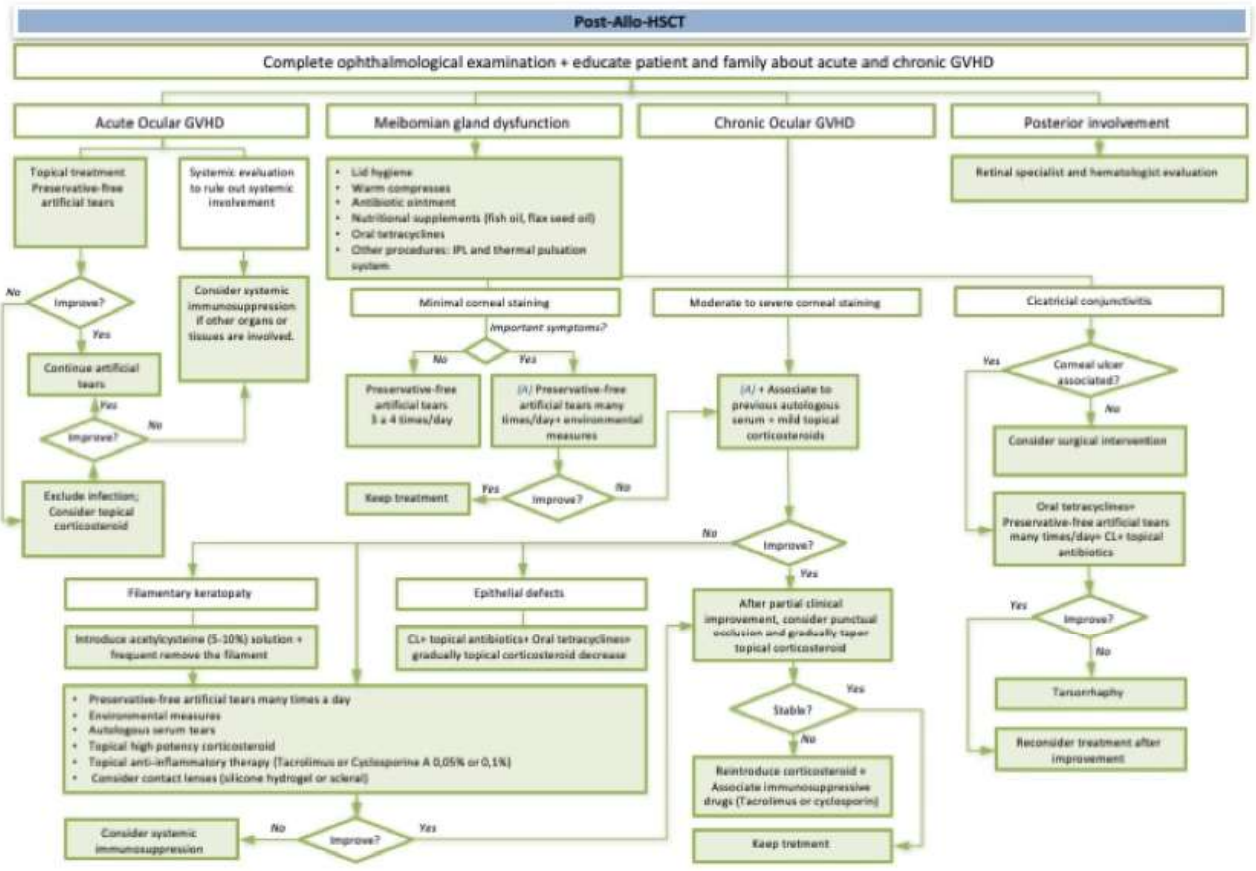
TABLE 7 - Assessment of the level of recommendation for treatment modalities

Strength of recommendation	
Strength of level of recommendation	Definition of the level of recommendation
A	It should always be offered
B	It should always be offered
C	The evidences of effectiveness are not enough to support or to be against; or the evidences may not compensate the adverse consequences or the cost of approach. Optional.
D	Moderate evidence that prove the lack of effectiveness or adverse results support a recommendation against the use. It shouldn't usually be offered.

TABLE 8 - Assessment of scientific evidence level

Quality of evidence for the recommendation	
Quality of evidence	Definition of level of evidence
I	Evidence of ≥ 1 controlled and appropriately randomized trial
II	Evidence of ≥ 1 well-designed clinical trial without randomization, from cohort or case-controlled analytical studies or from various time series or results from uncontrolled experiments
III	Evidences from opinions of respected authorities based on clinical experience, descriptive studies or expert committee report
III-1	Various reports of retrospective evaluations or small uncontrolled clinical trials
III-2	Only one small uncontrolled clinical trial, or retrospective evaluations
III-3	Only case reports available

FIGURE 4 - Ophthalmologic Treatment Flowchart



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