

# Thyroid Eye Disease

## A Summary of Information for Patients

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September 1, 2016; updated January 9, 2017

### Introduction

Thyroid eye disease (TED) is an inflammatory disease of the eye and the surrounding tissues. The inflammation is due to an autoimmune reaction - the body's immune system is attacking tissues within and around the eye socket. TED is sometimes referred to by other names, such as Graves' ophthalmopathy, Graves' orbitopathy, thyroid-associated ophthalmopathy, and/or thyroid orbitopathy.

About 90% of TED patients also have Graves' disease, an autoimmune disorder that causes excess thyroid hormone production (hyperthyroidism). However, 10% of patients with TED have either a normal-functioning or under-functioning thyroid (e.g. Hashimoto's thyroiditis). While control of systemic thyroid hormone levels is crucial in patients with TED, the ocular disease course and severity does not always correlate with thyroid hormone levels.

Most patients with TED have signs and/or symptoms in both eyes, however the severity can differ between the eyes. Some of the most common manifestations of TED are

- Swelling in and around the eye socket
- Retraction (tightening) of the eyelids
- Strabismus (the eyes are not in alignment with each other) and diplopia (double vision)
- Dry, irritated, red eyes

More severe ocular effects from TED are rare, but can occur and include vision loss from damage to the optic nerve and breakdown/infection of the cornea (the transparent, outermost layer of the eye that we see through).

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*Figures 1 and 2 - These patients have some of the classic signs and symptoms of TED. Note the swelling around the eye, retraction of the eyelid, and injection of the conjunctiva.*



### Epidemiology

- TED is the most common cause of both orbital disease and exophthalmos (external protrusion of the eyeball from the socket) in North America and Europe.
- TED occurs more frequently in women than in men, with both sexes having two age ranges in which TED is most likely to be diagnosed.
  - Females
    - 16 per 100,000 (0.016%) females have TED
    - Most diagnoses occur between 40-44 and 60-65 years old
  - Males
    - 3 per 100,000 (0.003%) males have TED
    - Most diagnoses occur between 45-49 and 65-69 years old
- Risk factors for the development of TED include the following
  - Age (see above age ranges)
  - Sex (females more likely to be diagnosed with TED)
  - Ethnicity (higher incidence among people of black and Asian/Pacific Island ethnicity, [JAMA. 2014;311:1563-1565])
  - Family history of TED or other thyroid disorders
  - Smoking, or exposure to tobacco smoke

- The signs, symptoms, and severity of TED can be worsened by both genetic and environmental factors.
  - Smoking or exposure to cigarette smoke
    - Smokers are twice as likely to develop Graves' disease
    - Smokers with Graves' disease are over 7x more likely to develop TED, when compared to nonsmokers
    - Smokers tend to have a longer duration of the active phase of TED (2-3 years for smokers, compared to 1 year for nonsmokers)
  - Low blood levels of selenium (see [Selenium](#))
  - Increased stress levels (see [Stress reduction](#))

## Mechanism of TED

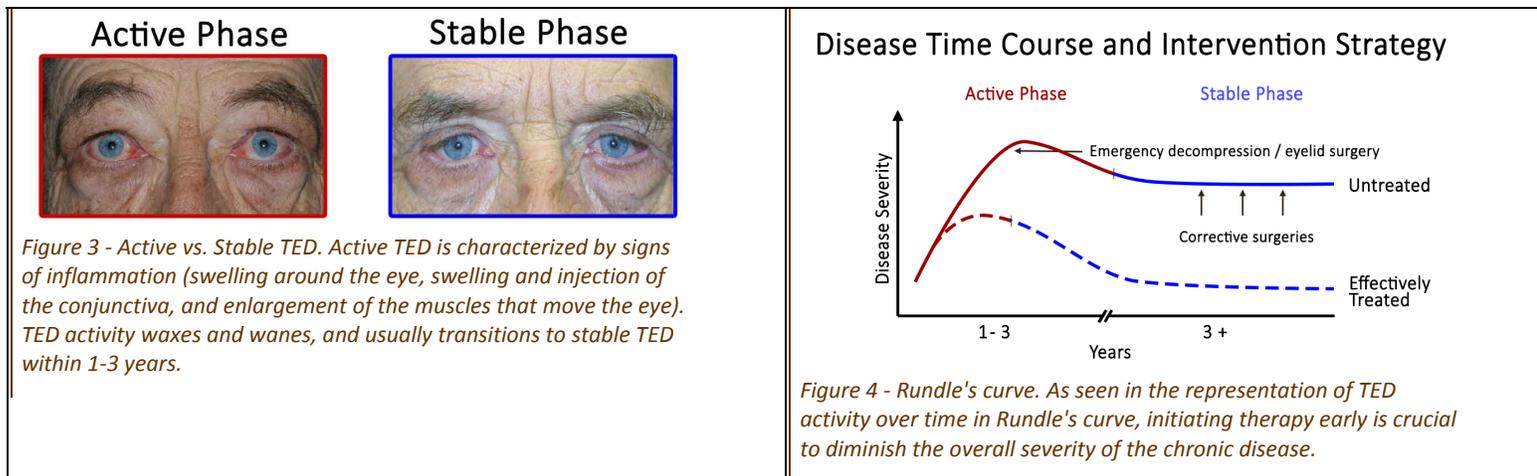
TED is caused by an inflammatory response involving the tissues in and around the eye socket.

- TED patients produce autoantibodies (proteins of the immune system that aberrantly react against the body's own cells) that bind to fibroblast cells within the eye socket
- When these antibodies bind, they cause the fibroblast cells to produce and release chemical signals and biologic materials that lead to swelling and congestion in and around the eye socket
- The main autoantibody produced by TED patients is known as Thyroid Stimulating Immunoglobulin (TSI), and this autoantibody can be measured in the blood to help monitor disease activity
  - The amount of TSI present in a TED patient correlates with TED severity
  - However, sometimes TED can occur without TSI formation

## Clinical Presentation of TED

About 90% of patients with TED also have some thyroid dysfunction - usually the thyroid is overactive (i.e. Graves' disease), but occasionally the thyroid is underactive (e.g. Hashimoto's thyroiditis). Most times, the diagnosis of TED and diagnosis of a thyroid dysfunction occur within the same year. Patients who are diagnosed with TED but have no known thyroid dysfunction should see their primary care physician for an evaluation of their thyroid function.

The disease course for TED involves 2 phases - active and stable. In the active phase there is active swelling and inflammation. This presents as redness in and around the eye, eye pain with or without eye movement, as well as swelling around the eyes and eyelids. The active phase of TED involves a waxing/waning period of these symptoms, and can last months to years. On average, the active phase of TED lasts about 1 year for non-smokers, and 2-3 years for smokers (or patients exposed to smoke). The active phase of TED spontaneously transitions to the stable phase, but can recur. Active TED has a recurrence rate of about 5-10%, but is less likely to recur after 18 months in the stable phase.



Many patients with TED present to a physician with similar complaints. The most common signs and symptoms associated with TED are

- Upper and/or lower eyelid retraction - the eyelid is pulled away from its normal resting position
  - Affects up to 90% of TED patients, and can affect one or both eyes

- On exam, there is a larger palpebral fissure (the space between the upper and lower eyelids) and the eyes have a characteristic "startled/surprised" appearance
- In cases of severe retraction, it may become difficult to close the eyelids at rest, leading to dry eyes, which can lead to tearing, foreign body sensation, and blurred vision
  - It is important to treat dry eyes, starting with liberal use of preservative-free eye drops, in addition to eye ointment at night



*Figure 5 – Eyelid retraction is the most common presenting sign of TED, and is the result of many factors associated with TED.*



*Figure 6 – Lagophthalmos is the inability of the eyelid to fully close. It typically presents as dry eye, tearing, foreign body sensation, and blurred vision.*



*Figure 7 – Temporal flare. Note the elevation of the outer portion of the normal eyelid.*

- Exophthalmos/Proptosis - bulging of the eyeball out of the eye socket
  - Affects up to 60% of TED patients
  - Most commonly leads to dry eye and excessive tearing
    - It is important to treat dry eyes, starting with liberal use of preservative-free eye drops, in addition to eye ointment at night
  - In severe cases, damage to the cornea can result
    - This can be treated with the dry eye therapy listed above in addition to decreasing the palpebral fissure (distance between the upper and lower eyelids) with surgery to close the outer and/or inner corners of the eyelids (tarsorrhaphy), lowering the upper lid, raising the lower lid, or orbital decompression surgery (See Below)
  - In rare cases, proptosis can cause globe subluxation, which is a displacement of the eye out of the eye socket
    - This is an eye emergency, and needs to be addressed immediately



*Figure 8 – Exophthalmos, also known as "proptosis," is when the eyeball is displaced out of the eye socket. This is an eye emergency – the cornea is at risk of drying out, and the optic nerve is at risk of irreversible damage.*

- Restrictive extraocular myopathy - swelling of the muscles that control eye movement resulting in inadequate mobility of the eyes

- Affects up to 40% of TED patients
- One or both eyes are restricted in how far they are able to move
- In more severe instances, the eye muscles can be affected at rest leading to misalignment of the eyes
  - This can cause strabismus (i.e. "crossed eyes"), which is a cause of diplopia (double vision).
- Permanent correction of restrictive myopathy is not typically performed until the patient has been in the stable phase of TED for several months.
  - Temporary correction can be undertaken with adding prism lenses to the patient's glasses
  - When the patient has been in the stable phase of TED for several (typically at least 6) months, surgical correction of strabismus can be considered
- Pain with eye movement
  - Affects about 30% of TED patients
  - Characterized as a dull, deep orbital pain
  - Can usually be managed with over-the-counter NSAIDs
- Optic nerve dysfunction / compressive optic neuropathy
  - Affects about 6% of TED patients
  - The eye is encased in a confined, bony eye socket. With progressive inflammation and swelling of the muscles and tissues surrounding the eye, the pressure within the eye socket can increase, leading to damage of the optic nerve
    - Warning signs include
      - Decrease or change in color vision
      - Decreased peripheral vision
      - Decreased crispness of central vision
  - This is an eye emergency, and needs to be addressed urgently by an ophthalmologist



Figure 9 – Hypotropia is when an eye is deviated downwards in comparison to the other eye, when looking straight ahead. This misalignment is due to an enlarged and restricted orbital muscle.



Figure 10 – Esotropia is when an eye is deviated inward in comparison to the other eye, when looking straight ahead. This misalignment is due to an enlarged and restricted orbital muscle.



Figure 11 – Chemosis is swelling within the conjunctiva.



Figure 12 – Conjunctival injection is caused by the dilation of the vessels within the conjunctiva. (larger image not available)

## Evaluating the Activity and Severity of TED

When examining patients with TED, it is important to document both the current activity and severity of disease. This helps both the patient and physician track the course of the disease as well as monitor for signs and symptoms of "flare-ups" or disease recurrence. In addition, management is based on both the activity and severity of disease, making proper disease categorization of great importance in determining proper treatment strategies.

To assess the activity level of TED, the Clinical Activity Score (CAS) can be used

- At the initial visit, patients are given a CAS score of 1-7 (one point for each of the following signs or symptoms)
  - Spontaneous pain in or around the eye in the past 4 weeks (pain without eye movement)
  - Eye pain associated with eye movement in the past 4 weeks
  - Swelling of the eyelids
  - Redness of eyelids
  - Conjunctival injection (redness of the actual eyeball)
  - Chemosis (swelling of the eyeball)
  - Swelling of the caruncle (the red prominence at the inner corner of the eye)

Figure 13 - Clinical Activity Score

Initial Visit (1 point each)	Follow-up Visit (1 point each)
1. spontaneous orbital pain in last 4 weeks 2. Gaze-evoked orbital pain in last 4 weeks 3. Eyelid swelling 4. Eyelid erythema 5. Conjunctival injection 6. Chemosis 7. Inflammation of caruncle or plica semilunaris  CAS $\geq 3 \rightarrow$ "Active"	- Criteria 1-7  8. Increase $\geq 2$ mm proptosis 9. Decrease in uniocular motility in any one direction of $\geq 8^\circ$ 10. Decrease in visual acuity equivalent to 1 Snellen line  CAS $\geq 4 \rightarrow$ "Active"

- At subsequent follow-up visits, the 3 following criteria are added for a potential CAS score of 10
  - Increase in proptosis/exophthalmos (bulging of the eye out of the eye socket) of the eye (by at least 2mm)
  - Decrease in motility of an eye in one direction (by at least  $8^\circ$ )
  - Decrease in vision (by at least 1 line on the Snellen chart)
- TED is considered "active" if the CAS  $\geq 3$  at the initial visit, or  $\geq 4$  at follow-up visits

To grade the severity of TED, many indices are used, two of which are mentioned below

- NOSPECS
  - Class 0: **N**o signs or symptoms
  - Class 1: **O**nly signs (upper lid retraction)
  - Class 2: **S**oft tissue involvement (swelling of the eye or tissues surrounding the eye)
  - Class 3: **P**roptosis (bulging of the eye out of the eye socket)
  - Class 4: **E**xtraocular muscle involvement (usually with strabismus)
  - Class 5: **C**orneal involvement (severe dry eye from inability to adequately close the eye)
  - Class 6: **S**ight loss (due to optic nerve involvement)

- The European Group of Graves' Orbitopathy (EUGOGO) classifies TED severity into three categories
  - Mild
    - Only a mild impact on daily life
    - Insufficient signs/symptoms to justify immunosuppressive drugs or surgical treatment
    - One or more of the following
      - Minor lid retraction (<2mm)
      - Mild soft tissue involvement
      - Proptosis (bulging of the eye out of the eye socket) <3mm above normal for race and gender
      - Transient or no diplopia (double vision)
      - Dry eye symptoms responsive to lubricants/ointments
  - Moderate-to-severe
    - Non sight-threatening, but has sufficient impact on daily life to justify immunosuppression or surgical intervention
    - One or more of the following
      - Lid retraction  $\geq$  2mm
      - Moderate or severe soft tissue involvement
      - Exophthalmos  $\geq$  above normal for race and gender
      - Transient or constant diplopia
  - Sight-threatening
    - TED patients with optic neuropathy and/or corneal breakdown
    - Warrants immediate intervention

Finally, both activity and severity of TED can be assessed with the VISA analysis, which evaluates Vision, Inflammation, Strabismus, and Appearance. (SEE VISA CHART BELOW)

The VISA chart is a comprehensive form for tracking patient progress. It includes fields for patient name, age, sex, and date. The main body is divided into five primary sections: Vision, Inflammation, Strabismus, and Appearance, each with a 'Program' and 'Target' row. Under 'Vision', there are sub-sections for 'Visual acuity' and 'Visual symptoms'. 'Inflammation' includes 'Signs of inflammation' and 'Symptoms of inflammation'. 'Strabismus' covers 'Signs of strabismus' and 'Symptoms of strabismus'. 'Appearance' includes 'Signs of appearance' and 'Symptoms of appearance'. Each section contains specific clinical parameters and a severity scale from 0 to 4.

Figure 14 - VISA chart – see readable resolution version at end of article

## Treatment

First and foremost, patients with TED should maintain good general health and well-being. In addition, it is important to achieve normal systemic thyroid hormone levels, especially in patients who undergo thyroid treatment (e.g. radioactive iodine ablation, thyroidectomy, etc.) Smoking cessation is extremely important in TED patients - it will help maintain stable thyroid hormone levels, as well as decrease the duration of the active phase of the disease. As previously mentioned, smokers are twice as likely to develop Graves' disease and 7x more likely to develop TED compared to nonsmokers. Additionally, smoking reduces the effectiveness of many treatments used for TED.

It is important to initiate treatment for TED at the time of diagnosis in order to decrease the final severity of the disease. Early initiation of treatment has been shown to be most effective at decreasing the final severity of the disease. Early intervention during the active phase allows for correction of inflammation and swelling within the eye and its surrounding tissues, which decreases the degree of permanent tissue scarring.

The majority of patients with TED have mild to moderate disease, and require mostly "supportive care" including

- Dry eye management with preservative-free drops and ointments (topical cyclosporine can be added if symptoms persist)
- Lifestyle modifications such as
  - Smoking cessation
  - Sodium restriction (reduces water retention in the tissues surrounding the eyes)
  - Sleeping with the head of the bed elevated (to decrease swelling around the eyes)
  - Sunglasses (decreases dryness and helps with light sensitivity)
  - Mineral supplementation with Selenium (taken regularly) has been shown to significantly benefit patients with mild TED in Europe (see *Selenium*)

- Oral NSAIDs for eye pain
- Prism lenses (may be used long term or as a temporary measure until surgical correction can be considered) for patients with strabismus (misalignment of the eyes)
- Selenium
  - When taken regularly for one year, selenium has been shown to exert significant benefits in patients with mild, non-inflammatory orbitopathy in Europe where the soil is selenium deficient
  - The benefits of selenium supplementation from non-selenium-deficient populations is not known
- Stress reduction
  - Recently, studies have been conducted to evaluate the role of stress in patients with thyroid disorders, including TED.
    - Specific hormones are released in response to stress, and these hormones affect thyroid hormone levels, thus impacting TED.
    - While the current research is not strongly evidenced-based and mostly circumstantial, many clinical studies have observed an association of stress and the severity (or recurrence) of TED.

## Disease Time Course and Intervention Strategy

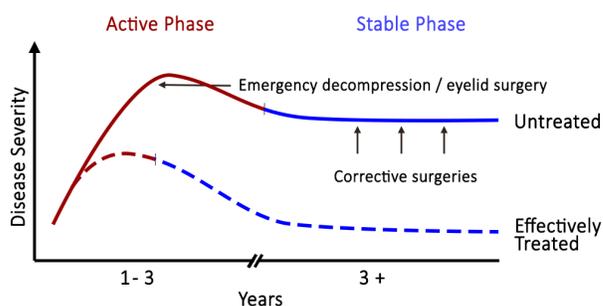


Figure 15 – Rundle's curve. As seen in the representation of TED activity over time in Rundle's curve, initiating therapy early is crucial to diminish the overall severity of the chronic disease.

## Medical Treatment Options, A brief overview

Please realize that each TED patient has a unique presentation, requiring different treatment regimens.

- Corticosteroid Therapy
  - Steroids have many beneficial properties in treating TED
    - They prevent and reduce inflammation, leading to decreased swelling of tissue in and around the eyes
    - They down-regulate the immune system, which limits TED (an autoimmune disease)
  - However, many patients do not respond completely (or at all) to steroid treatment, and some patients have their symptoms recur when weaning off or discontinuing the steroids.
  - Treatment with oral steroids (e.g. prednisone) is most common
    - Patients typically start with a high dose, and then slowly taper over the course of several months
    - The overall mean effectiveness rate for oral steroids is about 60%
    - Drawbacks and side effects include
      - Partial response, or no response at all
      - Relapse of signs/symptoms with tapering or discontinuing therapy
      - Cushing syndrome
      - Weight gain
      - Increased risk of infection
      - Worsening of diabetes, hypertension (high blood pressure), and osteoporosis

- Treatment with high-dose intravenous (IV) steroids has been shown to be more effective (about 70% success rate) than oral steroids, however this form of therapy requires weekly clinic visits
  - Treatment usually lasts 12 weeks, with treatment administered once per week
  - With high-dose IV steroids, there is greater risk for toxicity but this decreases with lower IV doses
    - Frequent monitoring of electrolytes, liver function, and blood pressure is required
    - A low risk of liver toxicity, electrolyte disturbances, and arrhythmias exists
- Orbital Radiotherapy (ORT)
  - ORT is commonly used in conjunction with corticosteroids
  - ORT works by decreasing the autoimmune response of TED, as well as preventing the congestion and swelling of tissue in and around the eye socket, including the extraocular muscles responsible for moving the eye
  - ORT reduces the amount of inflammation in TED patients, especially with patients who have experienced compressive optic nerve damage, tissue inflammation around the eye, and restrictive extraocular myopathy
  - Risks associated with ORT
    - Increased inflammation initially post treatment
    - Increased incidence of retinal damage
      - Patients with diabetic and/or hypertensive retinopathy are at an increased risk of retinal damage
    - Increased risk of cataract formation
    - Theoretical risk of causing a secondary cancer

About 20% of patients with TED require some sort of surgical intervention, with 13% undergoing eyelid surgery, 9% undergoing strabismus surgery, and 7% undergoing orbital decompression (for compressive optic nerve damage and/or proptosis).

Most surgical intervention occurs after the patient has been in the stable phase of TED for at least 6 months, with the exception of urgent orbital decompression for compressive optic neuropathy or eyelid surgery such as a tarsorrhaphy for exposure keratopathy (destruction of the cornea due to severe dry eye). By waiting for disease stability, the treating physician is reassured that the disease is unlikely to recur and that the signs and symptoms are unlikely to progress further. In general, surgery is not advised while the patient's thyroid is dysfunctional - thus it is important to attain normal thyroid hormone levels during the initial management.

- Orbital Decompression Surgery
  - Occasionally required if excess pressure on the optic nerve leads to vision loss that is rapidly progressive
  - The procedure relieves pressure (on the optic nerve and blood supply) in the eye socket by removing bone, allowing excess tissue to expand/decompress from the confined bony socket.
  - There are many different approaches to orbital decompression surgery and different parts of the eye socket can be decompressed
- Correction of Eyelid Retraction
  - There are both surgical and non-surgical approaches to treating eyelid retraction
  - Non-surgical approaches focus mainly on injections into the eyelids
    - Fillers commonly used to restore facial volume and minimize wrinkles can be injected to promote extension of the eyelid via mass effect
    - Botulinum toxin (i.e. Botox™) can be injected into the muscles that control the eyelid, helping them relax and lower from their retracted position
    - Both filler and botulinum toxin injections are temporary measures, and are used most often in patients who are currently in the active phase of TED, or for patients who are poor surgical candidates or not interested in surgery
  - There are many surgical approaches available to correct eyelid retraction
    - The muscles that control the eyelids can be surgically altered to relieve tension of the eyelids (e.g. a "blepharotomy" is a surgical procedure in which the eyelid is cut in order to help lengthen the eyelid from its retracted position)
    - Eyelid "weights" or spacer material (i.e. ear cartilage, hard palate from the mouth, sclera, or synthetic material) can be implanted into the upper eyelid to help the eyelid descend from its retracted position

- Correction of Strabismus
  - TED can cause swelling and tightening of the muscles that control eye movements (restrictive extraocular myopathy), leading to strabismus (crossed eyes), and diplopia (double vision).
  - Most TED patients with diplopia do not require surgical intervention, but can be managed with prism lenses until the disease enters the stable phase
  - If diplopia persists in the stable phase, or if strabismus leads to abnormal head positioning, surgery can be considered.
    - Surgery involves repositioning the muscles that control eye movement
  - For patients who are unable to be treated with prism lenses, and are poor surgical candidates, botulinum toxin (i.e. Botox™) injections into the extraocular muscles can be considered.

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Liaboe CA, Clark TJ, Shriver EM. Thyroid Eye Disease: A Summary of Information for Patients. *EyeRounds.org*. September 1, 2016; Available from: <http://eyerounds.org/patients/thyroid-eye-disease.htm>

## APPENDIX

| *Figure 14 - VISA chart, next page*

**VISA FOLLOW-UP FORM**

Date:

Visit #:

Patient Label:

Date of birth:

Age:

Gender:

**ORBITOPATHY**

Symptoms:

**THYROID**

Symptoms:

Progress:

Status:

Therapy:

Therapy:

**GENERAL**

Smoking:

Meds:

QOL:



SUBJECTIVE	OBJECTIVE	OD	OS	
<p><b>VISION</b></p> <p>Vision: n / abn</p> <p>Color vis: n / abn</p> <p><b>Progress: s / b / w</b></p>	<p>Central vision: sc / cc / ph</p> <p>with manifest</p> <p>Color vision plates (HRR) / 14</p> <p>Pupils (afferent defect)</p> <p>Optic nerve: Edema Pallor</p> <p>Macular/ lens pathology</p>	<p>20/___</p> <p>20/___</p> <p>y / n</p> <p>y / n y / n y / n</p>	<p>20/___</p> <p>20/___</p> <p>y / n</p> <p>y / n y / n y / n</p>	<p><b>Refractions</b></p> <p>Wearing _____ + _____ X _____</p> <p>_____ + _____ X _____</p> <p>Manifest _____ + _____ X _____</p> <p>_____ + _____ X _____</p>
<p><b>INFLAMM<sup>n</sup>/ CONGESTION</b></p> <p>Retrobulbar ache</p> <p>At rest (0-1)</p> <p>With gaze (0-1)</p> <p>Lid swelling: y / n</p> <p>Diurnal variation: (0-1)</p> <p><b>Progress: s / b / w</b></p>	<p>Caruncular edema (0-1)</p> <p>Chemosis (0-2)</p> <p>Conjunctival redness (0-1)</p> <p>Lid redness (0-1)</p> <p>Lid edema Upper (0-2) Lower (0-2)</p>			<p><b>Inflammatory Index (worst eye/eyelid)</b></p> <p>Caruncular edema (0-1):</p> <p>Chemosis (0-2):</p> <p>Conj redness (0-1):</p> <p>Lid redness (0-1):</p> <p>Lid edema (0-2):</p> <p>Retrobulbar ache (0-2):</p> <p>Diurnal Variation (0-1):</p> <p><b>Total: (10):</b></p>
<p><b>STRABISMUS/ MOTILITY</b></p> <p>Diplopia:</p> <p>None (0)</p> <p>With gaze (1)</p> <p>Intermittent (2)</p> <p>Constant (3)</p> <p>Head turn/ tilt: y / n</p> <p><b>Progress: s / b / w</b></p>	<p>Ductions (degrees):</p> <p>Restriction &gt; 45° 30-45° 15-30° &lt; 15°</p>	<p>0 1 2 3</p>	<p>0 1 2 3</p>	<p>Prism Measure:</p>
<p><b>APPEARANCE/EXPOSURE</b></p> <p>Lid stare y / n</p> <p>Light sensitivity y / n</p> <p>Bulging eyes y / n</p> <p>Tearing y / n</p> <p>Ocular irritation y / n</p> <p><b>Progress: s / b / w</b></p>	<p>Upper lid position: MRD</p> <p>Scleral show (upper) (lower)</p> <p>Levator function</p> <p>Lagophthalmos</p> <p>Exophthalmometry (Base: mm)</p> <p>Corneal erosions</p> <p>Corneal ulcers</p> <p>IOP -straight -up</p>	<p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mmHg</p> <p>mmHg</p>	<p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mm</p> <p>mmHg</p> <p>mmHg</p>	<p>Fat prolapse and eyelid position:</p>
<p><b>DISEASE GRADE</b></p> <p>V (optic neuropathy)</p> <p>I (inflammation/congestion)</p> <p>S (diplopia)</p> <p>(restriction)</p> <p>A (appearance/exposure): normal - severe</p>	<p>y / n</p> <p>0-10</p> <p>0-3</p> <p>0-3</p> <p>normal - severe</p>	<p><b>Grade</b></p> <p>/ 1</p> <p>/ 10</p> <p>/ 3</p> <p>/ 3</p> <p>/ 3</p>	<p><b>Progress / Response</b></p> <p>s / b / w</p>	<p><b>DISEASE ACTIVITY</b></p> <p>Active</p> <p>Quiescent</p>

**MANAGEMENT**

**FOLLOW-UP INTERVAL:**