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Updates in the Management of Thyroid Eye Disease

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Introduction: *Thyroid eye disease (TED) is an extrathyroidal manifestation of autoimmune thyroid diseases such as Graves' disease (GD) and Hashimoto's thyroiditis. TED frequently causes severe, sight-threatening symptoms requiring prompt medical or surgical intervention. Recent therapeutic advances are revolutionizing TED treatment, prompting an updated review on TED management.*

Epidemiology and Classification: *The estimated incidence of TED is 4.2/100,000 population/year, with a female-to-male ratio of 3.7:1. Risk factor control includes maintaining euthyroid function, smoking cessation and steroid prophylaxis following radioactive iodine therapy. The European Group on Graves' Orbitopathy (EUGOGO) denotes TED severity, whereas the clinical activity score (CAS) describes disease activity.*

Medical and Surgical Management: *Mild TED is treated conservatively using ophthalmic lubricants, selenium supplementation, cold compresses, and head elevation. Intravenous glucocorticoids are first-line for sight-threatening and moderate-to-severe TED with low activity, and for patients experiencing pain and discomfort with moderate-to-high activity, without sight-threatening symptoms. Newer targeted therapies for moderate-to-severe TED, such as teprotumumab, have promising outcomes, although exact therapeutic indications require further investigation. Surgery is indicated in refractory hyperthyroidism, sight-threatening keratopathy, optic neuropathy, and fibrotic disease. Interventions include total thyroidectomy, orbital decompression, strabismus correction, eyelid surgery, and aesthetic considerations. Patients require close follow-up with reclassification of CAS and EUGUGO severity at each visit to address refractory disease early.*

Conclusions: *TED is a severe extrathyroidal manifestation of autoimmune thyroid diseases, requiring precise disease stratification and longitudinal monitoring for optimal outcomes. Continued refinement of treatment algorithms is essential to improving long-term outcomes. Real-world data on emerging treatments will be critical in determining the future management of patients requiring intervention.*

Introduction

Thyroid eye disease (TED), also known as Graves' ophthalmopathy or Graves' orbitopathy, is an extrathyroidal manifestation of the autoimmune thyroid diseases such as Graves' disease (GD) and Hashimoto's thyroiditis.[1] The autoantibodies in GD and HT bind to thyroid-stimulating hormone receptors (TSHR) and insulin-like growth factor-1 receptors (IGF-1R).[2,3] Both TSHR and IGF-1R are also found on orbital fibroblasts, which are activated in TED, leading to the clinical sequelae of TED such as soft tissue inflammation, fat deposition, extraocular muscle enlargement and inflammation, and fibrotic remodelling of the orbit.[2–4] The disease can present both unilaterally and bilaterally. TED frequently causes severe, sight-threatening symptoms which require prompt medical and/or surgical intervention. Until recently, glucocorticoids served as the foundation of TED management, with adjunctive therapies and off-label, non-specific biologics providing alternative options in refractory cases.[5] However, advances in monoclonal antibody research are revolutionizing TED treatment, leading to the Health Canada regulatory approval of the selective IGF-1R antagonist teprotumumab in 2025.[6] On account of the recent treatment advances and

potentially sight-threatening nature of TED, we provide an updated review of the optimal management of TED.

Epidemiology And Risk Factors

The overall incidence of TED is estimated to be 4.2/100,000 population/year, with an approximate female-to-male ratio of 3.7:1.[1,7] A meta-analysis from 2020 calculated the pooled prevalence of TED in patients with GD to be 40%.[8] Incidence peaks in two similar age groups for each gender; 45–49 and 65–69 years in men, and 40–44 and 60–64 years in women.[9] TED can be further subdivided by severity, with a recent review in The Lancet reporting that mild, moderate, and sight-threatening disease occur in 77%, 22%, and 1% of patients, respectively.[10] Risk factors for the development and severity of TED include older age, male sex, cigarette smoking, cannabis usage, high serum thyroid-stimulating immunoglobulin, hyper- and hypothyroidism, radioactive iodine therapy, vitamin D deficiency, selenium deficiency, dyslipidemia, and diabetes.[1,5,10–12] Evidence-based prevention strategies and mitigation of disease severity include control of underlying thyroid hormone abnormalities, smoking cessation, and steroid prophylaxis in patients undergoing radioactive iodine therapy.[5,10,13,14]

Natural History and Classification

The natural history of TED was first described by F.F. Rundle in 1957 using "Rundle's curve", which demonstrated that TED is characterized by an 18–24 month period of activity with three stages–an initial inflammatory phase related to a pathogenic cascade caused by orbital fibroblast activity, a static stabilization phase with no change in inflammation, and finally an inactive phase with cessation of inflammation and incomplete restoration of orbital anatomy and fibrotic sequelae.[15] Indeed, this self-limiting pattern of disease activity is most applicable to mild forms of TED, which typically only require conservative management.[16] However, various risk factors and individual variation in presentation of the disease may result in more severe clinical presentations of TED, which require medical or surgical intervention to prevent sight-threatening complications.

The most widely endorsed guidelines for grading the severity of TED are the 2021 European Group on Graves' Orbitopathy (EUGOGO) severity scale, which classifies TED into mild, moderate-to-severe, and sight-threatening.[16] Mild TED includes lid retraction of <2 mm, mild soft-tissue involvement, exophthalmos of <3mm, intermittent diplopia, and corneal exposure responsive to lubricants. Moderate-to-severe TED involves greater lid retraction, soft-tissue involvement, and exophthalmos, with inconstant or constant diplopia. Finally, sight-threatening TED involves dysthyroid optic neuropathy and/or corneal breakdown.

TED activity is separately scored through classification systems such as the clinical activity score (CAS). The CAS initially predicts the level of inflammation according to a 1–7 score; **1-** painful, oppressive sensation on or behind the globe, during the last four weeks, **2-** pain on attempted up, side, or down gaze, during the last four weeks, **3-** eyelid(s) redness, **4-** diffuse conjunctival redness, covering ≥1 quadrant, **5-** swollen eyelid(s), **6-** chemosis, and **7-** swollen caruncle.[17] Additional scores during 1–3 month follow-up include **8-** increased proptosis ≥2 mm, **9-** decreased eye movements in any direction ≥5°, and **10-** decreased visual acuity of ≥1 line(s) on the Snellen chart using a pinhole.[17]

In addition to the EUGOGO severity scale and the CAS, additional classification systems such as the VISA and NO SPECS classifications provide valid methods of grading disease activity and/or severity. The VISA classification is an acronym for assessing disease severity using four categories, which include vision, inflammation, strabismus, and appearance.[18] Disease activity is determined by longitudinally assessing for worsening signs and symptoms within any of these four categories.[18] Similarly, the NO SPECS classification is an acronym for assessing disease severity, including **0- N**o physical signs or symptoms, **I- O**nly signs (eyelid retraction), **II- S**oft-tissue involvement, **III- P**roptosis, **IV- E**xtraocular muscle signs, **V- C**orneal involvement, and **VI- S**ight loss.[18] However, NO SPECS does not assess clinical activity.

Medical Management

Mild TED

Mild TED is the most common form of the disease, representing 77% of all TED cases.[10] On account of the self-limiting nature of mild TED, it is typically managed conservatively with local, supportive treatment.[16] Patients with mild TED often develop dry eye, necessitating artificial tears

during the day (preferably preservative-free), whereas ophthalmic lubricating gels/ointments can be used at night for more robust corneal protection to prevent exposure keratopathy.[16] Additionally, 100 mg twice daily of sodium selenite supplementation has been shown to improve quality of life and reduce disease progression.[19] Some patients may anecdotally report benefit from at-home interventions such as head elevation during sleep and cold compresses.

Moderate-to-severe TED

Management of moderate-to-severe TED is primarily guided by disease activity as per the CAS. Treatment of relatively inactive disease (CAS 1-2) involves supportive therapy similar to mild TED.[16,20] In cases of mild-to-moderate activation, such as CAS 3-4, intravenous (IV) glucocorticoids such as methylprednisolone remain the first-line therapy for disease inactivation.[16,20] Various studies have demonstrated superior efficacy of IV glucocorticoids compared with oral glucocorticoids through larger reductions in disease activity and greater improvements in markers of disease severity, such as visual acuity and chemosis.[21,22] IV glucocorticoids have also been shown to have higher treatment response rates and a more favourable safety profile compared to oral glucocorticoids, such as reduced risk of weight gain and development of Cushingoid features.[21-23] Glucocorticoids have a broad mechanism of action, which involves altered distribution, trafficking, and survival of leukocytes, interference of B- and T-lymphocyte function, and impaired recruitment of monocytes and macrophages to orbital tissue.[24] The most common dosing regimen is 500 mg weekly for 6 weeks followed by 250 mg weekly for 6 weeks, which is relatively well-tolerated in most patients, although major adverse events such as hepatotoxicity can occur at cumulative doses beyond 8000 mg.[16] Disease activity is reduced in 58–83% of patients.[5] However, glucocorticoids mainly reduce soft-tissue inflammation, while only achieving a modest reduction in proptosis and diplopia.[25] Additionally, 20–40% of patients can experience treatment failure.[5]

IV glucocorticoids can be combined with adjunctive therapies such as orbital radiotherapy or other immunosuppressive agents, such as mycophenolate, to reduce steroid exposure or increase efficacy of therapy.[5,20] Although this practice may persist in areas with limited access to biologics, teprotumumab is increasingly preferred as a targeted therapy for patients with TED with CAS 3-4.[26] Additionally, in patients with moderate-to-severe TED with CAS ≥4, teprotumumab is now being considered as a potential first-line therapy over IV glucocorticoids.[26,27] Teprotumumab is a selective IGF–1R antagonist, which is thought to prevent communication between IGF-1R and TSHR in orbital fibroblasts, significantly reducing the level of orbital inflammation.[28] Health Canada approved teprotumumab in 2025 as per the findings from the landmark TED01RV (phase II) and OPTIC (phase III) trials, which found a pooled proptosis improvement in 77% of treated patients, and improvements in all secondary outcomes, including CAS, diplopia, and quality of life score.[6,29–31] Serious adverse events are rare, with the most prominent being hyperglycemia and hearing loss.[29,30] It is administered as an IV infusion every 3 weeks, with the first dose at 10 mg/kg body weight and the following doses at 20 mg/kg.

Although teprotumumab may achieve similar results to glucocorticoids in less active TED, the high cost and lack of coverage as a newly approved therapy in Canada mean broad use is not currently feasible for many patients. There is also limited data on the efficacy of teprotumumab in patients with CAS <4 since the major clinical trials which led to regulatory approval only included patients with CAS ≥4.[29,30] A study conducted on the durability of teprotumumab following the TED01RV, OPTIC, and OPTIC extension studies found that among CAS responders, 90.7% maintained CAS reductions at week 72.[32] Additionally, three new patients became responders at week 72.[32] However, rates vary between studies, with a recent retrospective case series of 21 patients reporting only 33% of patients maintaining treatment response over two years.[33]

Teprotumumab is contraindicated in patients who are pregnant and carries a significant warning in patients with inflammatory bowel disorder.[5] Patients with pre-existing diabetes or hearing loss should be closely observed due to the risk of further hearing loss and hyperglycemia.[29,30] Some patients may experience treatment failure on teprotumumab, in which case tocilizumab and rituximab have previously been shown to be effective.[16,20] Tocilizumab is an interleukin-6 (IL-6) antagonist which prevents activation of orbital fibroblasts, adipogenesis, and production of pro-inflammatory cytokines and autoantibodies.[34] Rituximab inhibits activation of B-lymphocytes

through antagonism of the CD20 antigen, which prevents autoantibody formation.[35] Both agents are used off-label, and most studies agree that they achieve a modest effect in CAS reduction with little impact on proptosis.[16,20] A multicenter, randomized controlled trial was recently completed comparing IV tocilizumab to methylprednisolone in moderate-to-severe TED, which may provide further support for its use as a first-line therapy.[36]

Sight-threatening

In patients with severe, sight-threatening forms of TED as per the EUGOGO criteria, high-dose IV glucocorticoids remain the first-line therapy over newer therapies such as teprotumumab and tocilizumab.[16] Sight-threatening TED is characterized by serious complications such as compressive optic neuropathy and exposure keratopathy, requiring timely management to prevent permanent vision loss. Evidence supporting the use of teprotumumab in such cases is scarce, and glucocorticoids offer a more rapid anti-inflammatory effect than any other available therapy. Therefore, these patients should receive 500–1000 mg IV methylprednisolone for three consecutive days or more, or every second day for 1–2 weeks to reduce the risk of steroid-related adverse events.[16] According to the EUGOGO guidelines, if TED is refractory to high-dose glucocorticoids with deterioration of visual acuity or visual fields, urgent orbital decompression surgery is mandatory.[16] Significant keratopathy with risk of corneal melt also requires urgent surgery and antibiotic prophylaxis to avoid an open globe and sight-loss.[16]

Targeted Therapies

Novel TED therapies under investigation were identified by conducting a search of the World Health Organization International Clinical Trials Registry Platform, the European Union Clinical Trials Information System, and the United States National Institutes of Health Ongoing Trials Register. The search identified 24 unique targeted therapies under investigation for TED. The drug names, current status, and reference trial numbers are provided in **Table 1**.

Surgical Intervention

Surgical management of TED involves several interventions for sight-threatening complications, persistent functional impairment, and corrective surgery for aesthetic complications with severe psychosocial impacts. While mild TED is typically managed conservatively, facial appearance and quality of life may be affected with even subtle degrees of proptosis, eyelid retraction, or periorbital fat prolapse necessitating surgical intervention.[37] For moderate-to-severe disease, surgery is generally reserved for the inactive phase to correct changes in orbital anatomy following stabilization of inflammatory activity and achievement of euthyroidism.[5] In the setting of multiple surgeries, it was traditionally thought that a 3-step approach beginning with orbital decompression, followed by strabismus surgery, and finally eyelid surgery, would result in superior outcomes.[38,39] However, a recent systematic review found that the clinical benefit of this approach is minimal, further suggesting that a single combined surgery may achieve comparable outcomes while increasing efficiency.[40]

Although most patients with TED do not require surgical intervention, patients with hyperthyroidism refractory to medical therapy, compressive symptoms from a large goiter, and suspicious or malignant nodules may benefit from total thyroidectomy followed by lifelong thyroid hormone replacement therapy.[41,42] Orbital decompression may also be indicated in patients with dysthyroid optic neuropathy (DON), exposure keratopathy, or disfiguring/progressive proptosis.[43] Decompression alleviates elevated intraorbital pressure by expanding the orbital compartment through either removal of orbital walls, resection of orbital fat, or both. While decompression effectively improves visual function and reduces proptosis, complications may include new-onset diplopia, sensory disturbances, and sinus-related issues.[44]

Restrictive strabismus arises from fibrotic extraocular muscle involvement and may be exacerbated by prior decompression. Surgical correction is considered once ocular deviation has been stable for at least 4–6 months.[45] The goal of surgery is to restore or expand binocular single vision, most commonly through recession of affected rectus muscles.[45] Adjustable sutures may improve postoperative alignment, though residual diplopia may persist in severe cases, necessitating prism correction.[5]

Drug	Current Status	Registration Trial Number(s)
IBI311	Approved in China	-
Tocilizumab	Phase 2	NCT04876534
MHB018A	Phase 3	NCT06989918
Satralizumab	Phase 3	NCT05987423, NCT06106828
Teprotumumab	Approved in Canada	-
Linsitinib	Phase 2b	NCT05276063
Lu AG22515	Phase 1	NCT06557850
LASN01	Phase 2	NCT06226545
Rilzabrutinib	Phase 2	NCT06984627
IMVT-1402	Phase 2b	NCT07018323, NCT06727604
BHV-1300	Phase 1	NCT06980649
MER511	Phase 1	NCT07305818
Batoclimab	Phase 3	NCT05524571
CFZ533	Phase 2	NCT02713256
GenSci098	Phase 1	NCT06569758
Veligrotug	Pending FDA approval	NCT05176639, NCT06021054
AMG 732	Phase 1/2	NCT06401044
VV-14305	Phase 1/2	NCT07404111
ZL-1109/VRDN-003	Phase 3	NCT07211776
SCTT11	Phase 1/2	NCT06769984
Kamuvudine-9	Phase 1	NCT06467435
TOUR006	Phase 2	NCT06088979
ZB001	Phase 1	NCT05776121
Lonigutamab	Phase 1/2	NCT05683496

Table 1. Current Status of Novel Drugs Under Investigation for Treatment of Thyroid Eye Disease; *courtesy of Syed Ahmad, BSc, Abdelrahman Abuosba, BSc, and Ahsen Hussain, MD, FRCOphth.*

In addition to functional outcomes, oculoplastic surgeons should also consider aesthetic/cosmetic changes in the periocular region. Eyelid surgery may be indicated in patients with TED for Graves' associated upper eyelid retraction (GAUER), lagophthalmos, and periorbital fat prolapse, and is typically performed after decompression or strabismus correction.[5] GAUER is the most common indication and results from levator dysfunction and compensatory mechanisms, while lower eyelid retraction may require spacer grafts.[46] A recently published scoping review found that Botulinum Toxin A was the most effective non-surgical intervention to correct GAUER.[47] However, surgeries targeting the levator-Müller complex, including anterior levator disinsertion and Müllerectomy, represented the greatest average reduction in GAUER.[47] In cases of severe retraction or fibrosis, spacer grafting may be the most effective intervention.[47]

Although medical therapies reduce disease activity and anatomical severity in some patients, surgery remains essential for those with fibrotic disease, those refractory to medical therapy, or for acute sight-threatening complications.[5] Optimal outcomes are achieved through individualized surgical planning within a multidisciplinary TED care model.

Follow-up

In TED, longitudinal follow-up is essential due to the disease's variable clinical course and potential for irreversible vision loss. Follow-up strategies should be individualized based on disease severity, activity, and treatment modality. Patients with active TED should be reviewed at regular intervals, depending on severity and risk of progression, with more frequent follow-up in moderate-to-severe or sight-threatening disease. Most patients with mild TED require observation and symptomatic management; for these patients, follow-up every 3–6 months is generally sufficient unless symptoms worsen or new features develop.[5] If the activity of the disease is unclear or progression is suspected, a repeat assessment in 4–6 weeks is recommended to clarify the disease course.[5] Refractory disease requires reassessment of disease activity, treatment adherence, and modifiable risk factors. Indicators of clinical progression when managing TED include a rising EUGOGO severity or CAS score, and/or new/worsening symptoms. Failure to control TED with first-line therapy should prompt consideration of alternative treatments, referral to a specialized TED center, or surgical intervention as appropriate.

At each visit, assessment should include standardized evaluation of disease activity and severity using measures such as the CAS and EUGOGO classification.[48] A comprehensive ophthalmic examination should also be performed, including best-corrected visual acuity, colour vision, pupillary responses (including subjective and objective RAPD), IOP, ocular motility and diplopia assessment, exophthalmometry, corneal evaluation for exposure-related disease and optic nerve assessment. Visual fields, optic nerve imaging (such as ganglion cell and retinal nerve fibre layer analysis) and electrodiagnostic tests can be utilized to affirm the presence of optic neuropathy.[49-51] Orbital imaging is not routinely required in stable disease; however, noncontrast computed tomography (CT) may be used to assess disease severity via extraocular muscle size or optic neuropathy according to optic nerve and intraorbital changes.[52,53] Preoperative assessment for acutely indicated orbital decompression may also be conducted using non-contrast CT, as it is a fast and readily available imaging modality.[52] If contrast imaging is required, CT should be avoided due to the risk of developing Wolff-Chaikoff or Jod-Basedow phenomena, with possible worsening of thyroid eye disease.[54] Instead, gadolinium-enhanced magnetic resonance imaging (MRI) offers a safer alternative.[54] MRI also offers higher resolution of soft tissue changes and demonstration of compressive optic neuropathy, allowing TED to be differentiated from other orbital pathologies and to evaluate disease activity with T2 relaxation times.[52,55]

A summary flowchart of the proposed management for TED is provided in **Figure 1**.

Conclusion

TED is a complex extrathyroidal manifestation of autoimmune thyroid disease with the potential for significant morbidity. Whilst glucocorticoids remain foundational to TED treatment in many cases, recent advances in biologic therapies such as teprotumumab are revolutionizing the management of moderate-to-severe TED. There are ongoing clinical trials and advances in therapies which will impact future care, with approved therapies requiring further scrutiny in clinical practice. Optimal TED outcomes largely

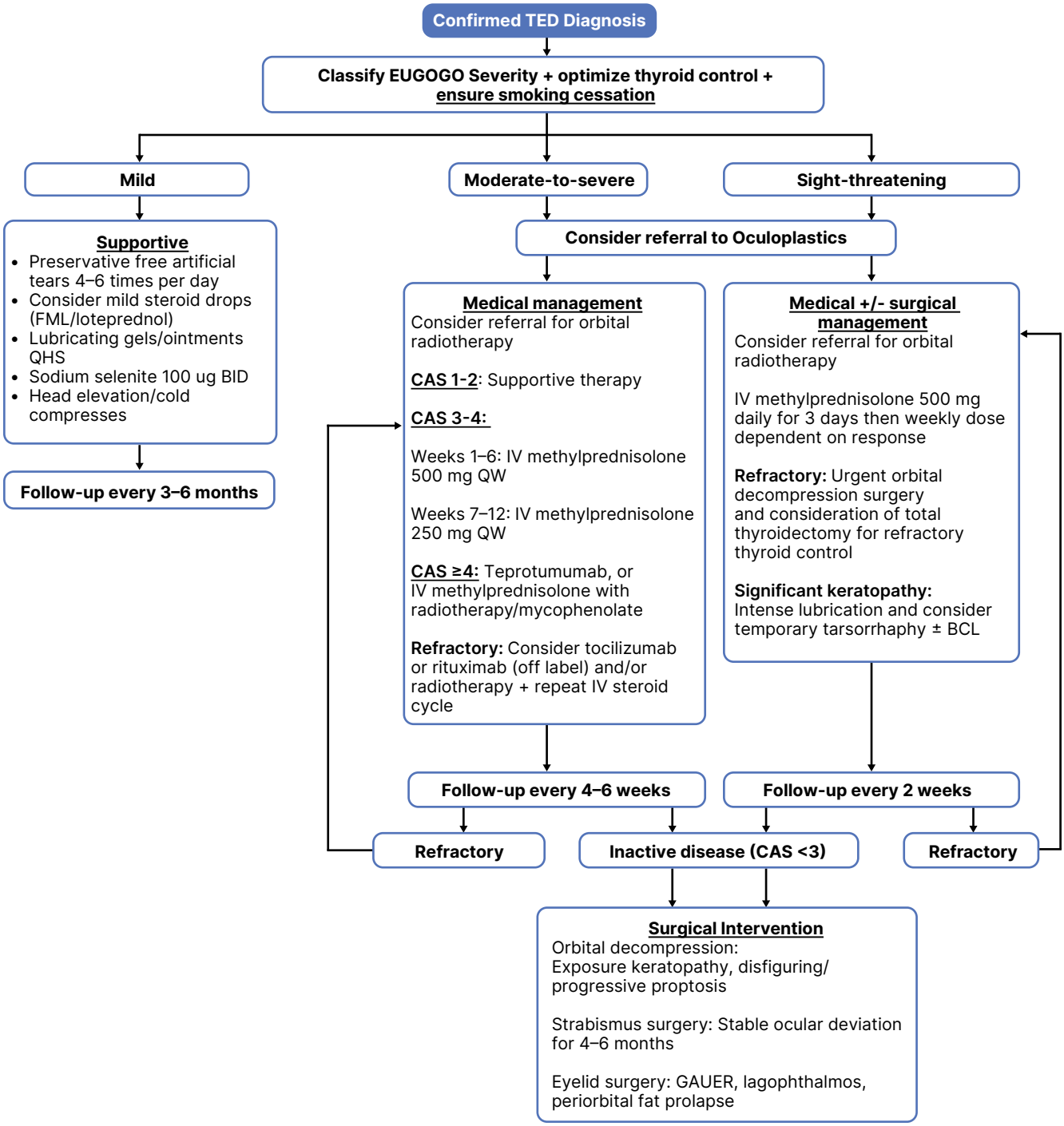

Figure 1. Summary flowchart for the management of thyroid eye disease*; *courtesy of Syed Ahmad, BSc, Abdelrahman Abuosba, BSc, and Ahsen Hussain, MD, FRCOphth.*

*Patients should always be counselled regarding the risks and benefits of treatment, and should be routinely monitored for adverse events when administering any of the recommended steroid, biologic, immunosuppressive, and/or radiation therapies. Incidence of severe complications should prompt immediate discontinuation of the offending therapy and consideration of alternative management strategies.

Abbreviations: BCL: bandage contact lens; **BID:** twice daily; **CAS:** clinical activity score; **EUGOGO:** European Group on Graves' Orbitopathy; **FML:** Fluorometholone; **GAUER:** Graves' associated upper eyelid retraction; **IV:** intravenous; **QHS:** nightly; **QW:** weekly; **TED:** thyroid eye disease

depend on accurate disease stratification, close longitudinal monitoring, and coordinated multidisciplinary care. Certain challenges remain, such as the long-term durability of biologic therapy, identifying predictors of treatment response, and clarifying the role of newer agents in less active or chronic disease. As therapeutic options continue to advance, refinement of individualized, evidence-based treatment algorithms will be essential to improving long-term outcomes for patients with TED.

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