# THYROID EYE DISEASE: Navigating Diagnosis and Treatment

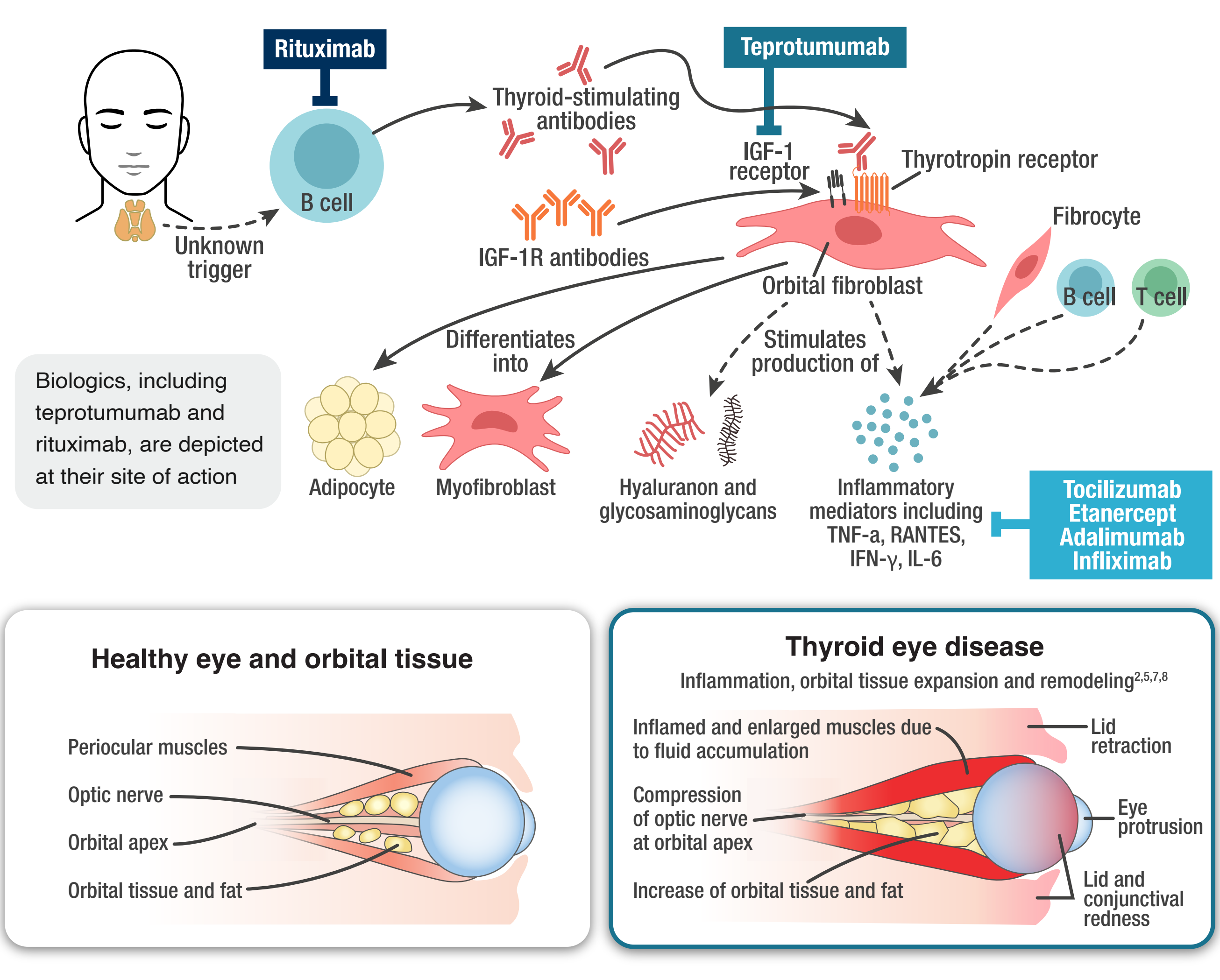
## Introduction

Thyroid eye disease (TED) is an autoimmune disorder that presents with heterogeneous symptoms and is frequently misdiagnosed. Differential diagnosis as well as early diagnosis and treatment can help limit the risk of progression to more severe forms of the disease, including disfigurement and vision loss. This infographic highlights some of the keys to diagnosis and treatment of TED to improve the overall care and management of patients with this disease.

## TED symptoms are driven by inflammation and tissue expansion

The pathophysiology of Graves—disease-associated thyroid dysfunction and TED is driven by an inflammatory response triggered by activation of the TSH/IGF-1 receptor complex on orbital fibroblasts.[1-5]

### SIMPLIFIED PATHOPHYSIOLOGY OF TED[6]


Rituximab
B cell
Unknown trigger
Thyroid-stimulating antibodies
Teprotumumab
IGF-1 receptor
Thyrotropin receptor
IGF-1R antibodies
Fibrocyte
B cell
T cell
Orbital fibroblast
Differentiates into
Stimulates production of
Adipocyte
Myofibroblast
Hyaluranon and glycosaminoglycans
Inflammatory mediators including TNF-a, RANTES, IFN-γ, IL-6
Tocilizumab
Etanercept
Adalimumab
Infliximab
Healthy eye and orbital tissue
Periocular muscles
Optic nerve
Orbital apex
Orbital tissue and fat
Thyroid eye disease
Inflammation, orbital tissue expansion and remodeling2,5,7,8
Inflamed and enlarged muscles due to fluid accumulation
Compression of optic nerve at orbital apex
Increase of orbital tissue and fat
Lid retraction
Eye protrusion
Lid and conjunctival redness

Biologics, including teprotumumab and rituximab, are depicted at their site of action

IGF = insulin-like growth factor; IL = interleukin; RANTES = regulated on activation, normal T cell expressed and secreted; TED = thyroid eye disease; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone.

1. Hodgson NM, Rajaii F. *Ophthalmol Ther.* 2020;9(1):21-33.
2. Pritchard J, et al. *J Immunol.* 2003;170(12):6348-6354.
3. Smith TJ. *J Neuroophthalmol.* 2020;40(1):74-83.
4. Smith TJ, Hegedus L. *N Engl J Med.* 2016;375(16):1552-1565.
5. Smith TJ, Hoa N. *J Clin Endocrinol Metab.* 2004;89(10):5076-5080.
6. Yu CY, et al. *Indian J Ophthalmol.* 2022;70(7):2335-2345.

## TED involves both modifiable and nonmodifiable risk factors

### MODIFIABLE RISK FACTORS

**Smoking**

2- to 8-fold increased risk of TED with smoking[1-3]

Proportional to the number of daily cigarettes[3]

**Radioactive iodine therapy[4]**

Risk for new-onset or worsening TED is ≈20% after radioactive iodine treatment

**Thyroid dysfunction**

Hyperthyroidism negatively influences TED and amelioration is associated with restoration of euthyroidism[7]

### NONMODIFIABLE RISK FACTORS

**Sex[5,6,7]**

Women are at higher risk, but men have elevated risk for more-severe TED

Incidence in women ranges from 2.7 to 16/100,000 population per year and from 0.54 to 2.9/100,000 in men

**Age**

Peaks between the ages of 40 and 70 years[6,7]

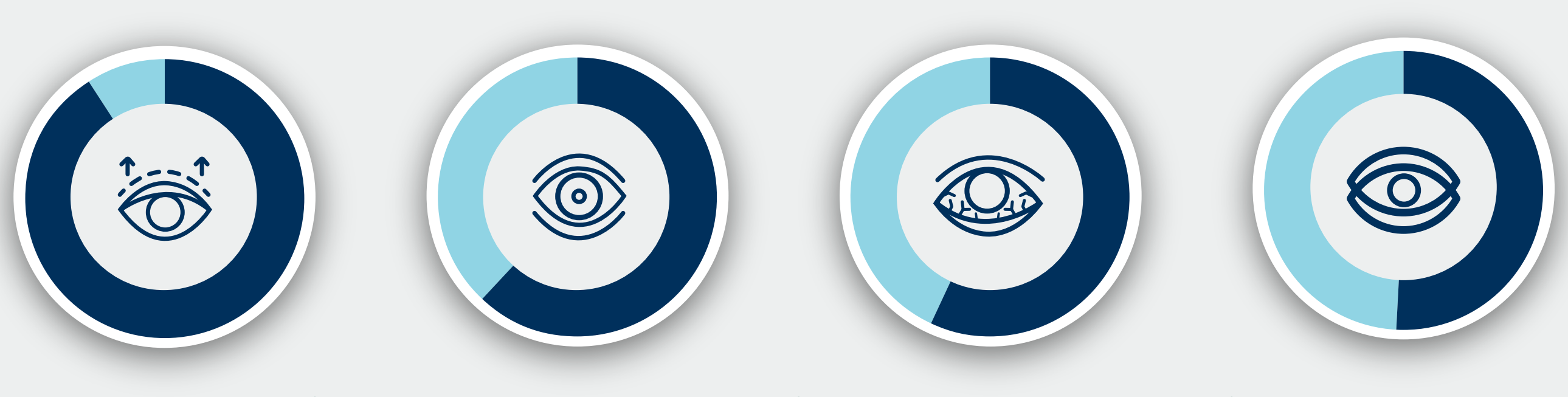
Odds of TED increase by 17% with each decade of age progression[3]

**Genetics**

Genetic contribution to clinical phenotype remains unclear[7]

1. Prummel MF, et al. *JAMA.* 1993;269(4):479-482.
2. Manji N, et al. *J Clin Endocrinol Metab.* 2006;91(12):4873-4880.
3. Khong JJ, et al. *J Clin Endocrinol Metab.* 2016;101(7):2711-2720.
4. Ponto KA, et al. *Thyroid.* 2010;20(7):785-793.
5. Perros P, et al. *Clin Endocrinol* (Oxf). 1993;38(4):367-372.
6. Bartley GB. *Trans Am Ophthalmol Soc.* 1994;92:477-588.
7. Bartalena L, et al. *Front Endocrinol* (Lausanne). 2020;11:615993.

## Common signs and symptoms of TED



**91%** have eyelid retraction | **62%** have proptosis (bulging of the eyes) | **57%** have eye dryness/grittiness | **51%** have diplopia (double vision)

**Other symptoms may include:**

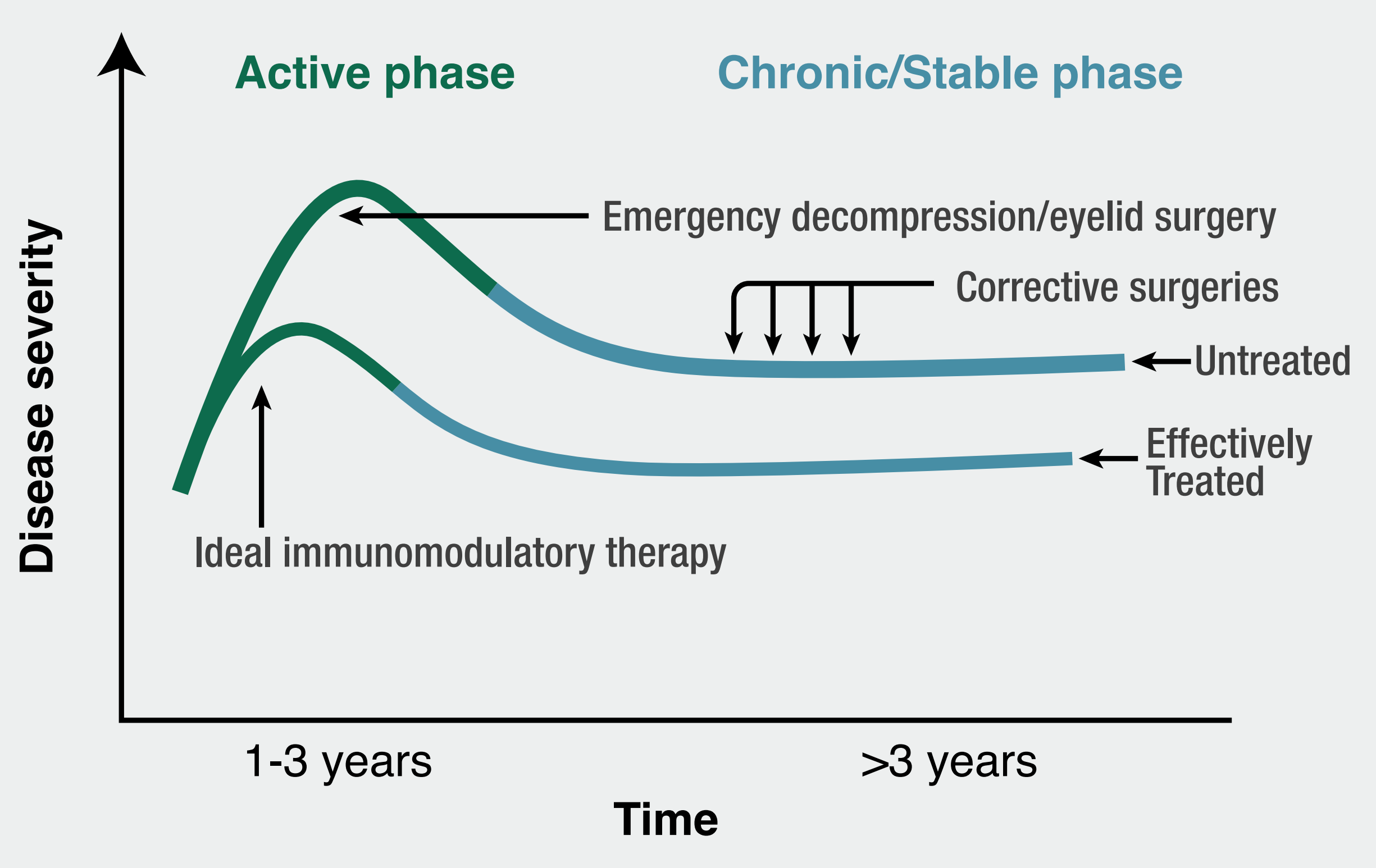
- Redness, swelling
- Excessive tearing
- Photophobia
- Pressure and/or pain behind the eyes

1. Bahn RS. *N Engl J Med.* 2010;362(8):726-738.
2. Patel A, et al. *Am J Ophthalmol.* 2019;208:281-288.

## TED is considered a biphasic disease

- TED is clinically biphasic, with an **active inflammatory phase** followed by a **chronic/stable phase**
- The **active stage** of TED usually persists for 1 to 3 years but can be longer at a subacute level
- Symptoms may wax and wane during the **active phase**, after which it transitions to a more **stable phase**; some patients have low disease activity and long-duration TED
- TED can be viewed as a chronic, long-term, symptomatic disease

### RUNDLE'S CURVE



Adapted from Rundle FF, et al. *Clin Sci.* 1945;5(3-4):177-194 and Liaboe CA, et al. EyeRounds.org. Updated January 17, 2020. Accessed February 14, 2024. https://webeye.ophth.uiowa.edu/eyeforum/patients/thyroid-eye-disease.htm

## The Clinical Activity Score (CAS) is a tool designed to evaluate TED disease activity

### TED: CLINICAL ACTIVITY SCORE ELEMENTS

| | Elements | Each Visit | Score |
|---|---|---|---|
| 1 | Spontaneous retrobulbar pain | X | 1 |
| 2 | Pain on attempted up or lateral gaze | X | 1 |
| 3 | Redness of the eyelids | X | 1 |
| 4 | Redness of the conjunctiva | X | 1 |
| 5 | Swelling of the eyelids | X | 1 |
| 6 | Chemosis (conjunctival edema) | X | 1 |
| 7 | Inflamed caruncle (flesh body at medial angle of eye) and/or plica | X | 1 |
| 8 | Increase in proptosis ≥2 mm | C | 1 |
| 9 | Decreased eye movements ≥5 degrees in any direction | C | 1 |
| 10 | Decreased visual acuity ≥2 lines on Snellen chart | C | 1 |

**Initial score**
The 7-point CAS describes whether a patient is in the active phase of TED.

**Follow-up score**
Patients seen 1 to 3 months later can be assessed out of 10 with additional criteria.

CAS <3 = stable/inactive TED

CAS ≥3 = active TED

C = compared with previous visit.

1. Smith TJ, Hegedus L. *N Engl J Med.* 2016;375(16):1552-1565.
2. Data from Burch HB, et al. *Thyroid.* 2022;32(12):1439-1470.
3. Bartalena L, et al. *Eur J Endocrinol.* 2021;185(4):G43-G67.

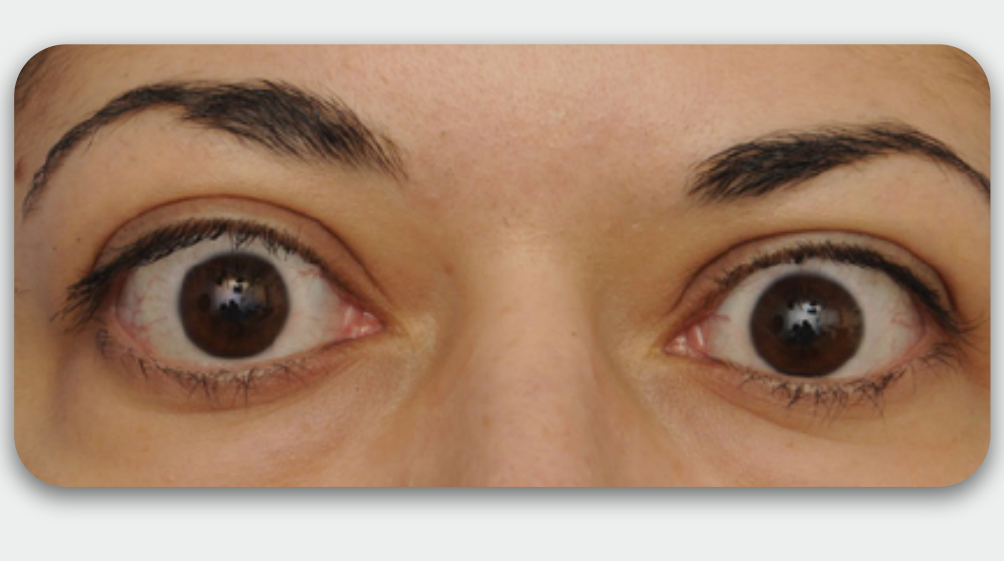
## Suspected TED can be clinically evaluated in a number of ways

- Risk-factor assessment
- Thyroid function (TSH, free T4, T3) and antibody panel (TRAb, TSI)
- Conjunctiva and cornea (inflammation)
- Gross examination and proptosis measurement
- Eyelids
- Extraocular muscles
- Visual function

Actively spotting the more "subtle" or early signs of TED (at onset or in chronic disease) is essential:

- Dry eyes and grittiness
- Pain/discomfort
- Light sensitivity
- Facial changes

Patient exemplifying the most common signs of TED.



T3 = triiodothyronine; T4 = thyroxine; TRAb = TSH receptor binding antibody; TSI = thyroid-stimulating immunoglobulin.

1. Bartalena L. In: Feingold KR, et al., eds. *Endotext* [Internet]. Updated February 20, 2018. Accessed February 14, 2024. https://www.ncbi.nlm.nih.gov/books/NBK285551/?report=classic
2. Novaes P, et al. *Clin Diabetes Endocrinol.* 2016;2:19.

## TED management involves an individualized approach

**TED management is individualized based on:**

- Disease activity (active phase vs inactive phase)
- Severity (mild vs moderate-to-severe vs sight-threatening)
- Duration
- Impact on daily living
- Treatment goals
- Patient age
- Comorbidities
- Preferences

**MILD TED**

| Treatment Goals | Active phase | | | Inactive phase |
|---|---|---|---|---|
| | Preferred therapy | Acceptable therapy | | Surgical |
| QOL/promote remission | Watchful monitoring<br>Selenium | Oral glucocorticoids | | Corrective procedures |

**MODERATE-TO-SEVERE TED**

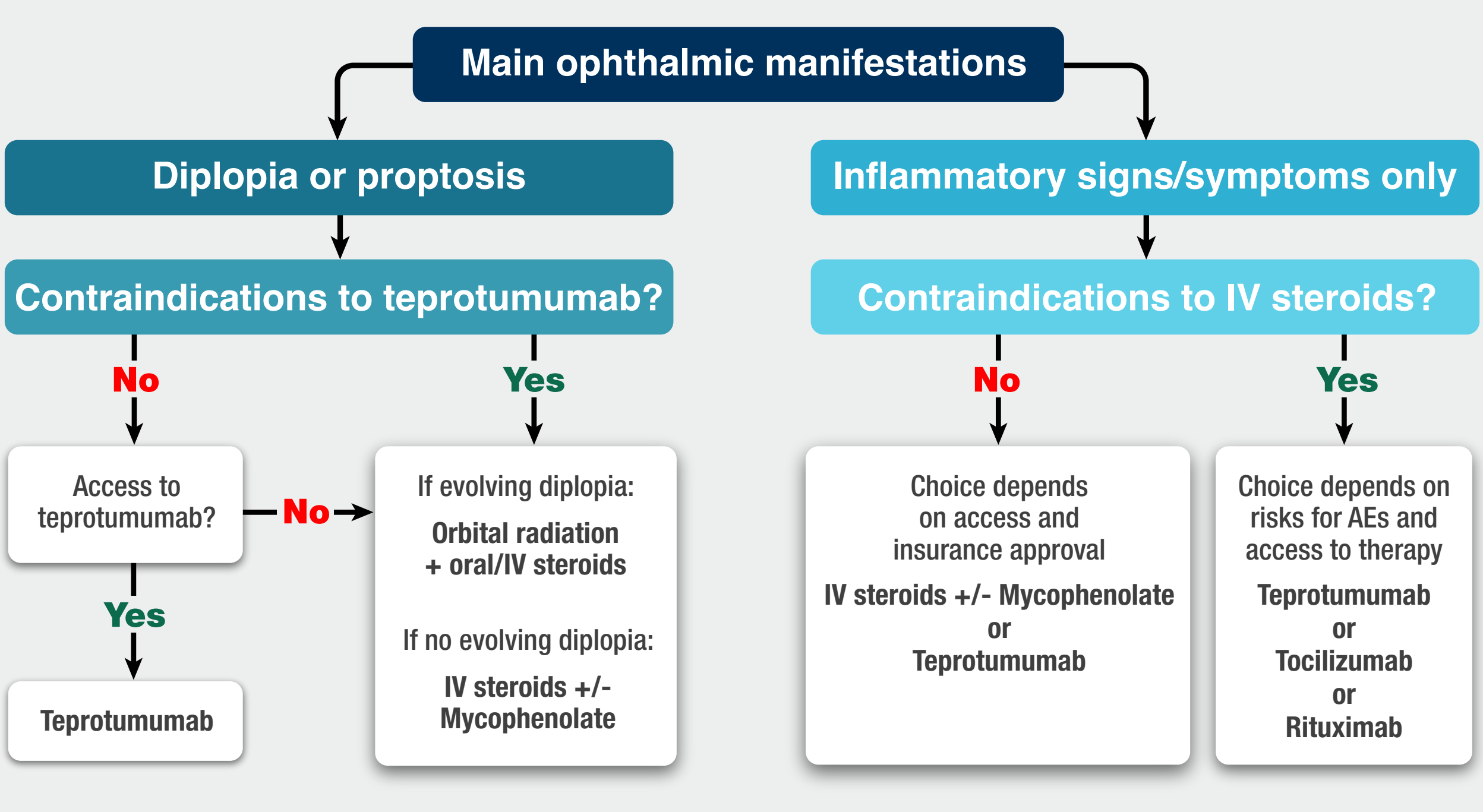
| Treatment Goals | Preferred therapy | Acceptable therapy | Other interventions | Surgical |
|---|---|---|---|---|
| Disease inactivation Reduction of soft tissue involvement | IV glucocorticoids | Radiation +/- IV/PO Glucocorticoids<br>Teprotumumab | | Orbital decompression<br>Blepharoplasty |
| Disease inactivation & diplopia | Teprotumumab | Radiation +/- IV/PO Glucocorticoids | | |
| Reduction of proptosis | Teprotumumab | | | Orbital decompression |
| Improve eye motility | IV glucocorticoids<br>Radiation +/- IV/PO Glucocorticoids<br>Teprotumumab | | Selective ocular occlusion<br>Adhesive prisms | Strabismus surgery<br>Permanent prisms |
| Reduction of lid aperture | | | Botulinum toxin<br>Tarsorrhaphy | Eyelid correction |

IV = intravenous; PO = oral; QOL = quality of life.
Modified from Burch HB, et al. *Thyroid.* 2022;32(12):1439-1470.

## Management of active moderate-to-severe TED

Treatment decisions need to be individualized, with consideration paid to each patient's main eye symptoms, efficacy of treatment, risk for different AEs, as well as access to various treatments.

### TREATMENT ALGORITHM: ACTIVE MODERATE-TO-SEVERE TED



Main ophthalmic manifestations

Diplopia or proptosis

Contraindications to teprotumumab?

No: Access to teprotumumab?
- Yes: Teprotumumab
- No: see next box

Yes: If evolving diplopia: Orbital radiation + oral/IV steroids. If no evolving diplopia: IV steroids +/- Mycophenolate

Inflammatory signs/symptoms only

Contraindications to IV steroids?

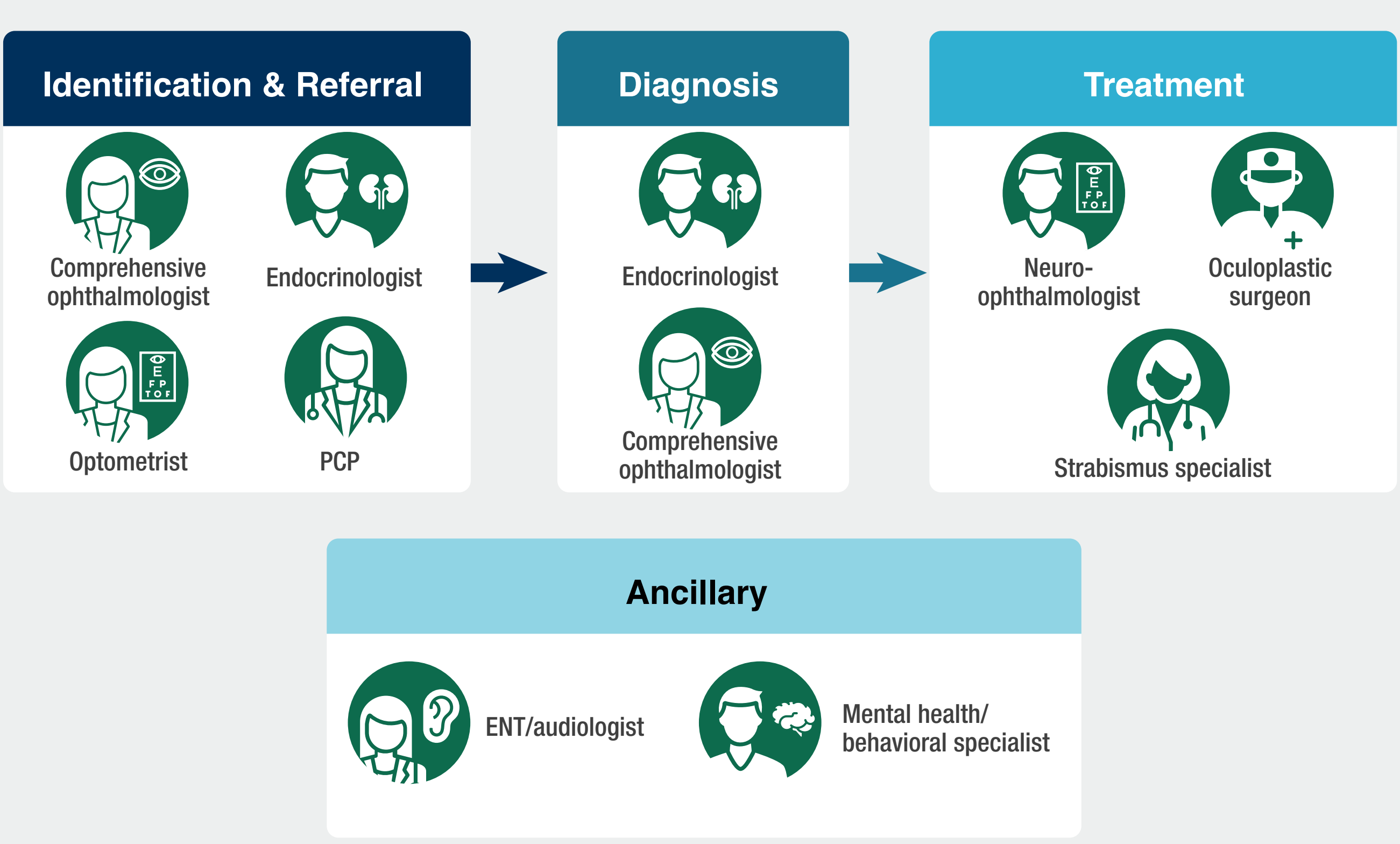
No: Choice depends on access and insurance approval. IV steroids +/- Mycophenolate or Teprotumumab

Yes: Choice depends on risks for AEs and access to therapy. Teprotumumab or Tocilizumab or Rituximab

AE = adverse event.
Kossler AL, et al. *J Clin Endocrinol Metab.* 2022;107(Supplement 1):536-546.

## Key takeaway: The TED patient journey from diagnosis to treatment is often complex

- Clear patient communication on disease and treatment course is key
- Timely access to care is critical in TED
- Effective treatment of TED requires a multidisciplinary team
- Referral is vital to successful TED management and is based on patient status, medical history, and clinical priorities



**Identification & Referral**
Comprehensive ophthalmologist
Endocrinologist
Optometrist
PCP

**Diagnosis**
Endocrinologist
Comprehensive ophthalmologist

**Treatment**
Neuro-ophthalmologist
Oculoplastic surgeon
Strabismus specialist

**Ancillary**
ENT/audiologist
Mental health/behavioral specialist

ENT = ear, nose, and throat doctor; PCP = primary care physician.

1. Bartalena L, et al. *Eur Thyroid J.* 2016;5(1):9-26.
2. Estcourt S, et al. *Eur J Endocrinol.* 2009;161(3):483-487.

## Additional resources

**CAS TOOL:**
Scan this QR code for a link to the CAS tool

**EDUCATIONAL TOOLS:**
Scan this QR code for a full listing of additional resources available through Vindico Medical Education, or please visit: www.vindicocme.com/educational tools

This educational resource is provided by VINDICO medical education

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