

CONSENSUS STATEMENT

Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO

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Introduction

Graves' orbitopathy (GO) constitutes a major clinical and therapeutic challenge (1, 2). GO is an autoimmune disorder representing the commonest and most important extrathyroidal manifestation of Graves' disease, but it may occur in patients without current or prior hyperthyroidism (euthyroid or ophthalmic Graves' disease) or in patients who are hypothyroid due to chronic autoimmune (Hashimoto's) thyroiditis (3, 4). Although the pathogenesis of GO (5–9) is beyond the scope of this document, attention is drawn to the link between the orbit and thyroid, which has important clinical and therapeutic implications. Optimal management of GO requires a coordinated approach addressing the thyroid dysfunction and the orbitopathy (10, 11).

GO is often mild and self-limiting, and probably declining in frequency, with only 3–5% of cases posing a threat to eyesight (3, 4). The onset and progression of GO are influenced by factors that are potentially controllable such as cigarette smoking, thyroid dysfunction, and choice of treatment modalities for hyperthyroidism (12, 13).

Suboptimal management of patients with GO appears to be widespread (2). The objective of this document is to provide practical information for managing patients with GO, for both non-specialists and those with special interest and expertise in this condition, and thus

improve the outcomes of patients with GO. It is hoped that the document will also be useful to specialist nurses, orthoptists, and those involved in managerial roles, and that it will provide a focus for audit and research. Randomized clinical trials (RCTs) are infrequent in this field. The document should therefore be considered as a consensus statement rather than a guideline.

Methods

European Group on GO (EUGOGO) represents a multi-disciplinary consortium of clinicians from the European centers, who share a commitment to improving the management of patients with GO (www.eugogo.org). A working group was formed and met in November 2006. Subsequent discussions took place electronically and at a further meeting in May 2007. After revision, the document was posted on the European Thyroid Association (ETA) and the European Society of Ophthalmic Reconstructive and Plastic Surgeons websites for wider consultation. The document was presented at the ETA Annual Meeting in Leipzig, Germany, in September 2007. Relevant articles were identified by searching MEDLINE using the terms Graves' ophthalmopathy or orbitopathy, thyroid-associated ophthalmopathy or orbitopathy, and thyroid eye disease. The definition of the Types of Evidence and the Grading of Recommendations used follows that of the Agency for Health Care Policy and Research, now Agency for Healthcare Research and Quality (www.ahrq.gov), as set out in Table 1.

This article is also being published in the March issue of the journal *Thyroid*.

Table 1 Types of evidence and the grading of recommendations.

Level	Type of evidence
Type of evidence (based on Agency for Health Care Policy and Research (AHCPR 1992))	
Ia	Evidence obtained from the meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grade	Evidence levels	Description
Grading of recommendations (based on Agency for Healthcare Research and Quality (AHRQ 1994))		
A	Ia, Ib	Requires at least one randomized controlled trial as a part of the body of literature of overall good quality and consistency addressing the specific recommendation
B	IIa, IIb, III	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C	IV	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates the absence of directly applicable studies of good quality

√ Good practice point recommended by consensus development group.

Recommendations

Referral to combined thyroid eye clinics and initial assessment

- a. Should all patients with GO be referred to combined thyroid eye clinics (10)? (Box 1)
 - All patients with GO, except for the mildest cases, should either be managed by a physician with particular expertise in managing GO or better be referred to a combined thyroid eye clinics for further assessment and management.
 - Many patients with GO never reach combined thyroid eye clinics or are referred too late to benefit from treatments (2). This practice is undesirable and may result in a suboptimal outcome and sometimes loss of vision.
 - A simple tool for assessing patients by generalist is recommended (1) and is summarized in Box 1.

Management issues of GO that should be addressed by both non-specialists and specialists

Smoking and GO

- a. Is smoking related to the occurrence, severity, and progression of GO? (Box 2)
 - There is a strong and consistent association between smoking and GO (12–24).
 - Smokers suffer more severe GO (14, 15, 17) than non-smokers.
 - A dose–response relationship between the numbers of cigarettes smoked per day and the probability of developing GO has been demonstrated (21).
 - Smoking increases the likelihood of progression of GO after radioiodine therapy for hyperthyroidism (25–27).
 - Some evidence suggests that smoking either delays or worsens the outcomes of treatments for GO (28, 29).
 - There is some retrospective evidence that quitting smoking is associated with a better outcome of GO (19, 21).

Management of hyperthyroidism in patients with GO

- a. Is correction of thyroid dysfunction important for GO? (Box 3)
 - Patients with uncontrolled thyroid function (both hyper- and hypothyroidism) are more likely to have severe GO than patients with euthyroidism (30–32).
- b. Is there a relationship between the modality of treatment for hyperthyroidism and the course of GO?
 - Antithyroid drug (ATD) therapy (27, 30, 33) and thyroidectomy do not affect the course of GO (26, 34–36), although the role of the latter requires further investigation.
 - No particular ATD or regimen, nor any type of thyroidectomy (subtotal or total) has been demonstrated to have any advantages in terms of outcome of GO.
 - The few available RCTs on the effects of radioiodine therapy on GO show that a definite proportion of patients (~15%) develop new eye disease or experience the progression of pre-existing GO within 6 months after radioiodine therapy (25–27). In ~5% of patients, worsening persisted at 1 year and required additional treatment (25). This risk is almost eliminated by giving a short course (~3 months) of oral glucocorticoids (GCs) after radioiodine therapy (25, 27), and avoiding post-treatment hypothyroidism (32). Shorter administration of oral GCs (1–2 months) may be equally protective.

Box 1 Tools for referral of patients with GO to combined thyroid eye clinics

Primary-care physicians, general practitioners, general internists, and specialists, who have no particular expertise in managing GO, should refer patients with GO, except for the mildest cases, to combined thyroid eye clinics for further assessment and management (IV, C).

Assessments and criteria for referral recommended by EUGOGO (IV, C).

- **Patients with a history of Graves' disease, who have neither symptoms nor signs of GO, require no further ophthalmological assessments and need not be referred to a combined thyroid eye clinic.**
- **Patients with unusual presentations (unilateral GO or euthyroid GO) should be referred, however mild their symptoms or signs, in order to make an accurate diagnosis.**
- **All other cases should be screened according to the protocol below (IV, C), as recommended previously by Wiersinga et al. (1)**

Refer urgently if any of the following are present:

Symptoms

- Unexplained deterioration in vision
- Awareness of change in intensity or quality of color vision in one or both eyes
- History of eye(s) suddenly 'popping out' (globe subluxation)

Signs

- Obvious corneal opacity
- Cornea still visible when the eyelids are closed
- Disk swelling

Refer non-urgently if any of the following are present:

Symptoms

- Eyes abnormally sensitive to light: troublesome or deteriorating over the past 1–2 months
- Eyes excessively gritty and not improving after 1 week of topical lubricants
- Pain in or behind the eyes: troublesome or deteriorating over the past 1–2 months
- Progressive change in appearance of the eyes and/or eyelids over the past 1–2 months
- Appearance of the eyes has changed causing concern to the patient
- Seeing two separate images when there should only be one

Signs

- Troublesome eyelid retraction
- Abnormal swelling or redness of eyelid(s) or conjunctiva
- Restriction of eye movements or manifest strabismus
- Tilting of the head to avoid double vision

The reader is referred to [Table 1](#) for an explanation of the recommendations grading system.

- The risk of exacerbation of pre-existing GO following radioiodine therapy is negligible and steroid cover can be avoided in patients with inactive eye disease, as long as post-radioiodine hypothyroidism is avoided (37, 38), and other risk factors for GO progression, including smoking (28) and high thyrotrophin receptor antibody levels (> 7.5 IU/l) (39), are absent (40).

Other simple measures that may alleviate symptoms

- a. Are there worthwhile simple measures that can relieve some of the symptoms of GO? (Box 4)
 - The symptoms of corneal exposure (grittiness, watering, and photophobia) often accompany active GO, and may persist if lid retraction is severe. Such patients benefit from lubricants (3, 4).
 - Nocturnal ointment is of great benefit for incomplete eyelid closure provided the cornea is protected (3, 4). Otherwise, urgent intervention will be required.

- Prisms may control intermittent or constant diplopia, and sleeping with head up may reduce morning eyelid swelling. Diuretics are rarely useful.
- Botulinum toxin injection can reduce upper lid retraction (41), but this procedure should be carried out in specialist centers.

Management issues of GO, which should be addressed in specialist centers

Grading severity and activity of GO

- a. What protocol should be followed for detailed assessment of patients with GO in specialist centers? (Boxes 5 and 6)
 - Making treatment decisions for patients with GO requires detailed assessment of the eyes, understanding of the natural history of the disease, insight into the impact of GO on the individual patient (42), and appreciation of the efficacy and side effects of therapies.

Box 2 Smoking and GO

All patients with Graves' disease should be informed of the risks of smoking for GO (IV, C) emphasizing the detrimental effects of smoking on:

- Development of GO (IIb, B),
- Deterioration of pre-existing GO (IIb, B),
- Effectiveness of treatments for GO (IIb, B),
- Progression of GO after radioiodine treatment (Ib, A).

If advice alone is ineffective, referral to smoking cessation clinics, or other smoking cessation strategies should be considered (IV, C).

Box 3 Management of hyperthyroidism and GO

Euthyroidism should be restored promptly and maintained stably in all patients with GO (III, B).

Frequent monitoring of thyroid status (every 4–6 weeks) is imperative in the initial phases of treatment when changes in thyroid status are expected (IV, C).

Patients with active GO given radioiodine should be offered prophylactic steroid cover (commencing with 0.3–0.5 mg of prednisone/kg bw per day orally 1–3 days after radioiodine and tapering the dose until withdrawal ~ 3 months later) (Ib, A). Shorter periods of glucocorticoid therapy (1–2 months) may be equally protective (IV, C).

Patients with inactive GO can safely receive radioiodine without steroid cover, as long as hypothyroidism is avoided (IIb, B), particularly if other risk factors for GO progression, such as smoking, are absent (IV, C).

Box 4 Simple measures that may alleviate symptoms in GO

Lubricant eye drops during the day and/or lubricant ointments at night-time are recommended for all patients with GO, who have symptoms of corneal exposure (III, B).

Patients with symptomatic diplopia should be given prisms if appropriate (IV, C).

Botulinum toxin injection may be considered for upper lid retraction in centers that have experience and expertise in this technique (IV, C).

- b. Is it helpful to grade the severity of GO?
- Grading the severity of GO is fraught with difficulties; however, classifying patients into broad categories facilitates decision making (Fig. 1).
 - Careful assessment of the impact of GO on quality of life (QoL) by disease-specific questionnaire (GO-QoL) (42) is fundamental in deciding whether treatments used for moderate-to-severe GO (see below) are justified in patients with mild GO.
- c. Is it helpful to grade the activity of GO?
- Grading the activity of GO is also fraught with difficulties; however, classifying patients into active/inactive GO categories is frequently possible and greatly facilitates decision making (Fig. 1). The patients with a clinical activity score (CAS) $\geq 3/7$ should be considered as having active GO (43, 44).
- Management of sight-threatening GO**
- a. How can patients with sight-threatening GO be identified? (Boxes 7 and 8)
- Sight-threatening GO usually occurs in the context of dysthyroid optic neuropathy (DON).
 - The risk of corneal breakdown and perforation is significant when lagophthalmos is associated with poor Bell's phenomenon (45).
 - Sight can also be threatened in patients with GO in the following rare circumstances: eyeball subluxation, severe forms of frozen globe in the presence of lagophthalmos, choroidal folds, and postural visual obscuration (46).
 - The above clinical entities require recognition and prompt medical attention (1). Box 1 can be used to identify patients with sight-threatening GO.
- b. What is the treatment of choice for DON?
- DON can be treated by systemic GCs, surgery, or both.
 - Orbital radiotherapy is not recommended in the case of DON unless as an adjunct to proved therapies.
 - High-dose i.v. GCs administered in pulses are more efficacious and associated with fewer adverse

Box 5 Activity and severity assessments in GO

EUGOGO recommends the following assessments for patients with GO in specialist centers (IV, C), as reported previously by Wiersinga *et al.* (1):

(a) Activity measures based on the classical features of inflammation: clinical activity score (CAS) is the sum of all items present (43, 44)

- Spontaneous retrobulbar pain
 - Pain on attempted up or down gaze
 - Redness of the eyelids
 - Redness of the conjunctiva
 - Swelling of the eyelids
 - Inflammation of the caruncle and/or plica
 - Conjunctival edema
- A CAS $\geq 3/7$ indicates active GO

(b) Severity measures

- Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed, and with distant fixation)
- Swelling of the eyelids (absent/equivocal, moderate, severe; www.eugogo.org)
- Redness of the eyelids (absent/present; www.eugogo.org)
- Redness of the conjunctivae (absent/present; www.eugogo.org)
- Conjunctival edema (absent, present; www.eugogo.org)
- Inflammation of the caruncle or plica (absent, present; www.eugogo.org)
- Exophthalmos (measured in millimeter using the same Hertel exophthalmometer and same intercanthal distance for an individual patient)
- Subjective diplopia score (0=no diplopia; 1=intermittent, i.e. diplopia in primary position of gaze, when tired or when first awakening; 2=inconstant, i.e. diplopia at extremes of gaze; 3=constant, i.e. continuous diplopia in primary or reading position)
- Eye muscle involvement (ductions in degrees; www.eugogo.org)
- Corneal involvement (absent/punctate keratopathy/ulcer)
- Optic nerve involvement (best-corrected visual acuity, color vision, optic disk, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected)

Box 6 Severity classifications in GO

EUGOGO recommends the following classification of patients with GO (IV, C):

- 1. Sight-threatening GO: Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention.**
- 2. Moderate-to-severe GO: Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate-to-severe GO usually have any one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, inconstant, or constant diplopia.**
- 3. Mild GO: patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.**

effects than oral or retrobulbar steroids (3, 4, 47–51) (Table 2).

- Improvement of optic nerve function can be expected after high-dose i.v. GCs within 1–2 weeks (52).
- Relapse of DON may occur when systemic GCs are withdrawn too quickly (see Management of moderate-to-severe GO) (3, 4).
- Decompression surgery can lead to rapid resolution of DON with an acceptable adverse effect profile. However, GCs and squint surgery are frequently required, and occasionally further decompression surgery is necessary (53). Immediate decompression surgery as first-choice therapy

does not appear to result in a better outcome compared with i.v. GCs as first choice, nor does it obviate the need for subsequent GC therapy (54).

- c. What is the treatment of choice for sight-threatening corneal breakdown?
 - In severe, sight-threatening corneal breakdown when the cornea cannot be protected by the closed eyelid, hourly topical lubricants are indicated; however, this intervention alone may be insufficient to prevent ulceration, thinning, and perforation. In such cases, specific measures to improve eyelid closure are required.
 - A moisture chamber or temporary eye closure by blepharorrhaphy, tarsorrhaphy, or botulinum

toxin injections can help temporize until corneal healing occurs (55).

- The effect of GCs on severe corneal exposure has never been specifically addressed.
- Most of the studies on the effects of orbital decompression report a reduction in symptoms associated with exposure keratopathy; rarely severe corneal ulcers may be refractory to decompression surgery if lagophthalmos persists (56).

Management of moderate-to-severe GO

- Does every patient with moderate-to-severe GO require treatment? (Boxes 9 and 10)
 - Many patients in this category should be considered for treatment, with the exception of patients who are asymptomatic or unwilling to have treatment.
 - Patients with moderate-to-severe and active (CAS $\geq 3/7$) GO should be treated with immunosuppressive treatment modalities, while those with inactive GO may benefit from rehabilitative surgery (see below; Fig. 1).
- What are the non-surgical treatments of choice for moderate-to-severe GO?
 - *Glucocorticoids.* GC therapy has been used in the management of GO through oral, local

(retrobulbar or subconjunctival), or i.v. routes (35). *Oral GC* therapy (starting dose, 80–100 mg prednisone (or ~ 1 mg/kg bw) or equivalent) requires high doses for prolonged periods of time. No randomized, placebo-controlled studies have been performed. Open trials or randomized studies, in which oral GCs were compared with other treatments (47, 48, 50, 57–62), show a favorable response in ~ 33 –63% of patients, particularly for soft tissue changes, recent onset eye muscle involvement, and DON. The eye disease frequently flares up on tapering or withdrawing GCs. Side effects are frequent. Prolonged oral GC treatment is associated with a risk of osteoporosis (49), which may be decreased using bisphosphonates or other antiresorptive drugs (63, 64). *Retrobulbar or subconjunctival GC* therapy is less effective than oral GCs (65). *Intravenous GC pulse therapy* is more effective than oral GC (response rates $\sim 80\%$ vs $\sim 50\%$; Table 2) (3, 4, 47–51, 66). Evidence for the superiority of any of the different i.v. GC schedules is lacking (Table 2). Although i.v. GCs are tolerated better than oral GCs (47, 50), acute liver damage and a risk of life-threatening liver failure has been reported in association with very high cumulative doses (67, 68) in $\sim 0.8\%$ of patients (68). Intravenous

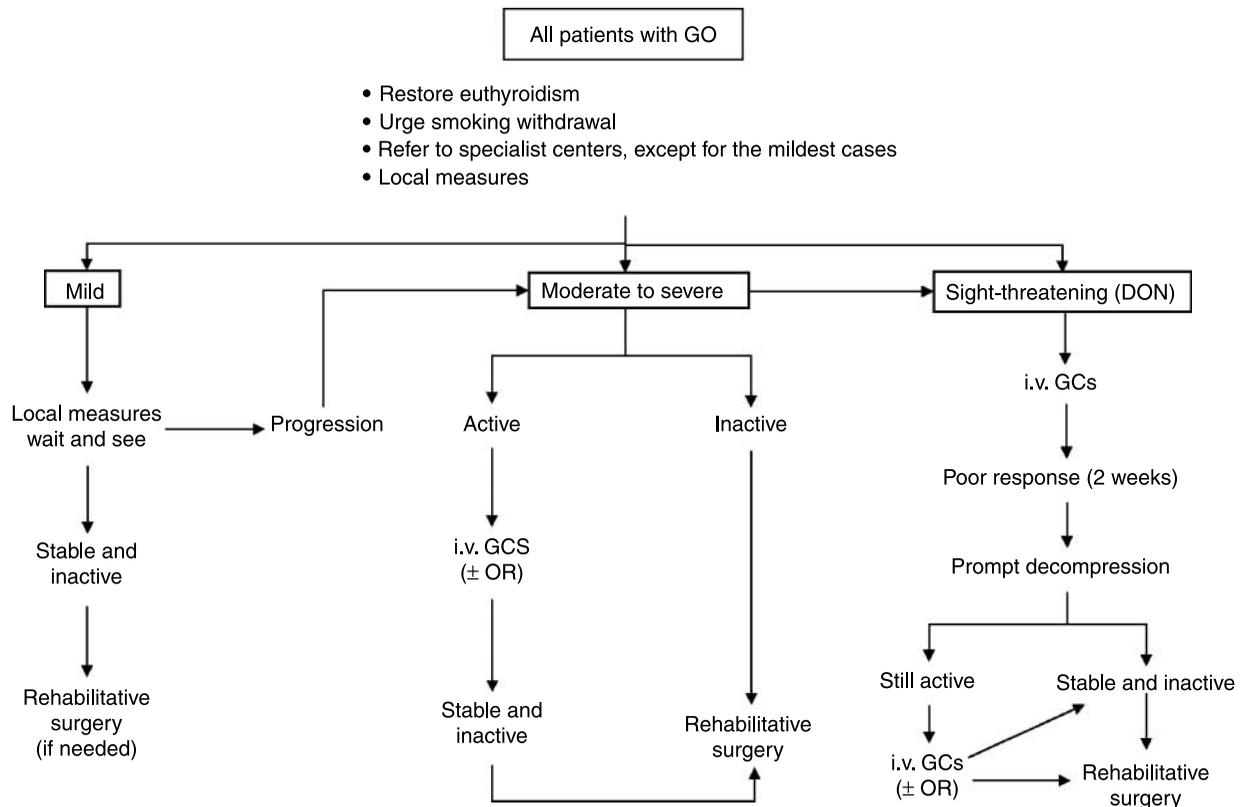


Figure 1 Management of Graves' orbitopathy. Rehabilitative surgery includes orbital decompression, squint surgery, lid lengthening, and blepharoplasty/browplasty. i.v. GCs, intravenous glucocorticoids; OR, orbital radiotherapy; DON, dysthyroid optic neuropathy. For the definitions of GO severity and activity, see text.

Box 7 Glucocorticoids and orbital decompression in DON

Glucocorticoids (GCs) and surgical decompression of the orbit are the only treatments proved to be effective in patients with DON (III, B).

High-dose i.v. GCs is the preferred first-line treatment for DON (III, B).

If the response to i.v. GCs is absent or poor after 1–2 weeks, or the dose/duration of steroid required induces significant side effects, prompt orbital decompression should be carried out (IV, C).

Orbital decompression should be offered promptly to patients with DON or corneal breakdown who cannot tolerate GCs (III, B).

Both i.v. GC therapy and orbital decompression surgery should only be undertaken in centers with appropriate expertise (IV, C).

GCs are safe if the cumulative dose is <8 g methylprednisolone in one course of therapy (69). Bisphosphonates should be considered for patients receiving i.v. GCs, although no RCTs have specifically addressed this issue.

- **Orbital radiotherapy.** The reported response rate to orbital radiotherapy (OR) in open trials is ~60% (3, 4, 66). A cumulative dose of 20 Gy per orbit fractionated in ten doses over a 2-week period is commonly used (70), but an alternative regimen of 1 Gy per week over a 20-week period was equally effective and better tolerated (71). Higher doses are no more effective (72). A lower cumulative dose of 10 Gy was found to be as effective as the standard 20 Gy regimen (71). The response to OR did not differ from oral prednisone in an RCT (60). Two recent RCTs have shown that OR is more effective than sham irradiation in improving diplopia and eye muscle motility (73, 74). Another RCT has questioned the efficacy of OR (75). OR is usually well tolerated, but may cause transient exacerbation of ocular symptoms, which is preventable with concomitant GC administration (3, 66). Data on long-term safety are reassuring (76–78), but theoretical concerns about carcinogenesis remain for younger patients, particularly those under the age of 35 years (70, 76–78). Although cataracts

can occur earlier after OR than naturally, they are easily treated by surgery. Retinal microvascular abnormalities have been detected in a minority of patients (79), mostly in those with concomitant severe hypertension or diabetic retinopathy, and these two comorbidities are considered absolute contraindications to OR (80, 81). It is possible that diabetes, even in the absence of retinopathy, represents a risk factor for the development of retinal changes after OR (78), but the evidence is less clear (77). Thus, diabetes without retinopathy may be regarded as a relative contraindication to OR (see also Box 12).

- **Combination of GC (either orally or locally) with OR** is more effective than either treatment alone (57, 82). It is unclear whether i.v. GCs with OR are more efficacious than i.v. GCs alone.
- **Treatments of marginal or unproven value** include somatostatin analogs (83–86), azathioprine (87), ciamexone (88), and i.v. immunoglobulins (62, 89). Two studies have shown the superiority of the combination of oral GCs and cyclosporine than either treatment alone (58, 59). The potential usefulness of immunomodulatory agents, such as rituximab (90) or etanercept (91), has been suggested by open studies, but no RCTs have been carried out as yet.

Box 8 Sight-threatening corneal breakdown in GO

Sight-threatening corneal breakdown should be managed as an emergency (IV, C).

The management of sight-threatening corneal breakdown includes:

Frequent topical lubricants (preservative-free topical lubricants for hyperallergic patients), moisture chambers, blepharorrhaphy, tarsorrhaphy, or other temporary measures until the cornea has healed (IV, C).

Consideration of systemic GCs or surgical decompression when the above measures alone are ineffective (IV, C).

In the event of corneal perforation/severe ulceration, appropriate antibiotics, and emergency glueing, amnion membrane as shield, or corneal grafting need to be considered (IV, C).

Once the corneal breakdown is brought under control, it is imperative that treatment is offered to improve lid closure and thus prevent further episodes of corneal breakdown (IV, C).

Table 2 Randomized clinical trials of i.v. methylprednisolone versus oral prednisone.

Treatment randomization		Response rate (%)			Reference
Group A	Group B	Group A (%)	Group B (%)	P value	
i.v. methylprednisolone ^a + radiotherapy ^b (n=41)	Oral prednisone ^c + radiotherapy ^b (n=41)	88	63	<0.02	Marcocci <i>et al.</i> (47)
i.v. methylprednisolone ^d (n=35)	Oral prednisone ^e (n=35)	77	51	<0.01	Kahaly <i>et al.</i> (50)

^a15 mg/kg⁻¹ for four cycles, then 7.5 mg/kg⁻¹ for four cycles; each cycle consisted of two infusions on alternate days at 2-week intervals.

^b20 Gy in ten daily doses of 2 Gy over 2 weeks.

^c100 mg daily for 1 week, then weekly reduction until 25 mg daily, and then tapering by 5 mg every 2 weeks.

^d500 mg once weekly for 6 weeks, 250 mg once weekly for 6 weeks, total treatment period: 12 weeks.

^e100 mg daily starting dose, tapering by 10 mg per week, total treatment period: 12 weeks.

c. Do non-surgical treatments reduce the subsequent need for rehabilitative surgery or do they adversely interfere with it?

- No RCTs have been performed to investigate specifically whether non-surgical treatments reduce the subsequent need for rehabilitative surgery, so this important question remains unanswered.
- The theoretical concern that radiation-induced fibrosis may reduce orbital compliance, and hence compromises subsequent therapies, is not supported by the available evidence (92, 93).

d. What is the role of surgery in moderate-to-severe GO?

- Rehabilitative surgery includes one or more of the following procedures: (a) orbital decompression (the usual indications being disfiguring exophthalmos, troublesome retroocular pain/discomfort, and/or grittiness associated with minor exposure keratopathy not amenable to topical therapies (94); (b) squint correction; (c) lid lengthening; and (d) blepharoplasty/browplasty.

If more than one procedure is required, the sequence should be as outlined above.

- Orbital decompression for disfiguring exophthalmos is best deferred until the orbitopathy has been inactive for at least 6 months. However, orbital decompression can be considered also in patients with active GO who are intolerant or non-responsive to GCs, if waiting for spontaneous inactivation of GO can potentially be hazardous for visual function.
- Almost all studies show the efficacy and relative safety of orbital decompression (46, 94–101); however, the available studies do not allow any meaningful comparison of the available techniques (93, 94, 100, 101).
- Eye muscle and lid surgeries are effective treatments for correcting diplopia and improving lid function and appearance.
- Rehabilitative surgery yields the best results when GO is inactive. Very long duration of GO is no contraindication to rehabilitative decompression (100).

Box 9 Treatment of moderate-to-severe GO that is ACTIVE

The treatment of choice for moderate-to-severe and active (CAS ≥ 3/7) GO is pulses of i.v. glucocorticoids (GCs) (Ib, A). This treatment should be undertaken in centers with appropriate expertise (IV, C).

The total cumulative dose of methylprednisolone should not exceed 8 g in one course of therapy (III, B).

Patients being treated with high-dose i.v. GC should be first screened for liver dysfunction, hypertension, history of peptic ulcer, diabetes, urine infection, and glaucoma, and then monitored for side effects (IV, C).

Bisphosphonates are recommended when long-term (> 3 months) oral GC therapy (average daily dose > 5 mg prednisone or equivalent) is used (Ia, A). It is reasonable to suggest the use of antiresorptive agents also when GCs are used i.v. (IV, C).

Orbital irradiation (OR) should be considered in patients with active disease who have diplopia or restricted motility (Ib, A). OR with lower cumulative doses (10 Gy) may be as effective as and better tolerated than OR with higher doses (20 Gy) (Ib, A). Doses > 20 Gy are not recommended (IV, C).

Caution should be exercised before administering OR to patients younger than 35 years; OR must be avoided in patients with diabetic retinopathy or severe hypertension (III, B).

The combination of oral GCs with OR is more effective than either treatment alone (Ib, A), but randomized clinical trials indicating that the combination of i.v. GCs with OR is better than i.v. GCs alone are lacking (IV, C).

Box 10 Timing and the order of surgery for GO

The timing and the order of surgical interventions should be carefully planned (IV, C).

Surgical management should proceed in the following sequence: orbital decompression, then squint surgery, and then lid lengthening with or followed by blepharoplasty/browplasty, since side effects of the preceding step can interfere with the step that follows (III, B).

Rehabilitative surgery should only be performed in patients who have had inactive GO for at least 6 months (III, B).

Rehabilitative surgery should only be undertaken in centers with appropriate expertise (IV, C).

e. Does orbital decompression compromise subsequent non-surgical therapy?

- In the rare event of reactivation of GO after rehabilitative surgery, systemic GCs, and/or OR can be used with the usual expected efficacy (99).

Management of mild GO

a. Are GCs and/or orbital radiotherapy indicated or useful in mild GO? (Box 11)

- Although GCs and OR are of potential value in mild disease (60, 73, 74), they are usually not recommended as the risks outweigh the benefits. Simple measures (Box 4) are usually sufficient.

b. Is a 'wait-and-see' strategy reasonable?

- GO is a self-limiting disease. In the absence of efficacious treatments with minimal side effects, watchful waiting is appropriate for the majority of patients with mild disease, especially those with a satisfactory QoL, as assessed by the EUGOGO questionnaire (www.eugogo.org).

c. How should mild eyelid retraction, soft tissue swelling, and exophthalmos be managed, and when in the course of the orbital disease?

- Sometimes even mild eyelid retraction, soft tissue swelling, or exophthalmos has a profoundly negative impact on psychosocial functioning and QoL, depending on the circumstances of the individual (102, 103).
- Treatment might be offered to these patients if careful consideration of risks and benefits favors intervention.

Special situations

a. How should a diabetic or hypertensive patient with moderate-to-severe or sight-threatening GO be treated? (Boxes 12 and 13)

- Systemic GCs can induce or exacerbate diabetes and/or hypertension. However, the indications for steroid use in patients with diabetes and/or hypertension are no different than in other patients. Close monitoring of glycemic control and blood pressure is important. Thiazide or loop diuretics should be used with caution during high-dose GC therapy to avoid hypokalemia. The same principle applies to surgical treatments.
- OR may increase the risk of retinopathy in diabetic and hypertensive patients (77, 78, 80, 81), at least using a 20 Gy cumulative dose.
- Diabetes and/or hypertension are not contraindications to surgical orbital decompression or other surgical treatments for GO.

b. What is the best therapeutic approach to GO in childhood?

- GO is rare in childhood because of the low incidence of Graves' disease in this age group (104, 105). The eye disease is usually milder in children than in adults and often stabilizes and eventually resolves without intervention (105).
- Achieving and maintaining euthyroidism are as important objectives as in adult patients.
- Exposure to smoking (active and, possibly, passive) is probably as detrimental as in adults (106–108).
- Because of the effects on growth, GCs should be avoided unless DON is present. OR is contraindicated in children. Somatostatin analogs have

Box 11 Management of mild GO

Glucocorticoids are rarely justified in mild GO as the risks outweigh the benefits (IV, C).

Watchful waiting is appropriate for the majority of patients with mild GO (IV, C).

In a minority of patients with mild disease, quality of life may be so profoundly affected as to justify using treatments as for moderate-to-severe disease (IV, C).

Box 12 Diabetes or hypertension and GO

Diabetes and/or hypertension should not be considered as contraindications to GC or surgical treatments for GO (IV, C).

Diabetic retinopathy and/or severe hypertension are absolute contraindications for OR (III, B).

Diabetes without retinopathy is a relative contraindication for OR, but evidence is less clear (IV, C).

Box 13 GO in children

Euthyroidism should be restored promptly and maintained in children as in adults (III, B).

Children with GO should be managed conservatively if vision is not threatened (IV, C).

Simple measures to address specific symptoms can be utilized as for adults (Box 4) (IV, C).

Glucocorticoids should be avoided in children (IV, C).

Orbital radiotherapy is contraindicated in children (IV, C).

Exposure to active and, possibly, passive smoking should be avoided (IV, C).

been used in isolated cases, but RCTs on efficacy and safety are lacking (109).

- Orbital surgery may be necessary in the cases of severe exophthalmos, but for most patients a conservative and expectant approach is appropriate.

Summary of consensus

- All patients with GO should (Fig. 1):
 - Be referred to specialist centers;
 - Be encouraged to quit smoking;
 - Receive prompt treatment in order to restore and maintain euthyroidism.
- Patients with sight-threatening GO should be treated with i.v. GCs as the first-line treatment; if the response is poor after 1–2 weeks, they should be submitted to urgent surgical decompression.
- The treatment of choice for moderate-to-severe GO is i.v. GCs (with or without OR) if the orbitopathy is active; surgery (orbital decompression, squint surgery, and/or eyelid surgery in this order) should be considered if the orbitopathy is inactive.
- In patients with mild GO, local measures and an expectant strategy are sufficient in most cases, but treatment may be justified if QoL is affected significantly.

In memoriam

This document is dedicated to the memory of Mark Prummel (1956–2005), one of the founders of EUGOGO, who greatly contributed to expanding our understanding of clinical and therapeutic aspects of GO.

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