The Consensus Statement of EUGOGO on Multidisciplinary Management of Graves' Orbitopathy

Prof. Luigi Bartalena (University of Insubria, Varese, Italy) on behalf of the European Group On Graves' Orbitopathy

31th Meeting of the Belgian Thyroid Club, Brussels 24th November 2007
EUropean Group On Graves’ Orbitopathy
(www.eugogo.org)

A multidisciplinary consortium of clinicians (endocrinologists and ophthalmologists) with a special clinical interest in Graves’ orbitopathy
<table>
<thead>
<tr>
<th>Country</th>
<th>City</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Brussels</td>
</tr>
<tr>
<td>France</td>
<td>Lyon</td>
</tr>
<tr>
<td>Germany</td>
<td>Essen</td>
</tr>
<tr>
<td>Germany</td>
<td>Mainz</td>
</tr>
<tr>
<td>Greece</td>
<td>Thessaloniki</td>
</tr>
<tr>
<td>Italy</td>
<td>Milano</td>
</tr>
<tr>
<td>Italy</td>
<td>Pisa</td>
</tr>
<tr>
<td>Italy</td>
<td>Varese</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Amsterdam</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Utrecht</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Olten</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Cardiff</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Newcastle-upon-Tyne</td>
</tr>
</tbody>
</table>

Chairman: Professor Wilmar Wiersinga, Amsterdam
Multi-center study on the characteristics and treatment strategies of patients with Graves' orbitopathy: the first European Group on Graves' Orbitopathy experience.

Clinical assessment of patients with Graves' Orbitopathy: The European Group on Graves' Orbitopathy (EUGOGO) recommendations to generalists, specialists and clinical researchers.

A questionnaire survey on the management of Graves' Orbitopathy in Europe.

McKeag D, Lane CM, Lazarus JH, et al.
Clinical features of dysthyroid optic neuropathy: a European Group on Graves' Orbitopathy (EUGOGO) survey.
Prevalence of Graves' orbitopathy in Graves' disease

% of Graves' patients

Absent  Mild to Severe  Sight-threatening

3-5%
Pathogenesis of Graves’ orbitopathy

Wiersinga, TEM 2002
Quality of life is impaired in Graves’ orbitopathy

Terwee, BJO 1998
Prevalence of GO in two different decades

Perros, Clin Endocrinol 1998
# Referral to specialist centres (a questionnaire survey in Europe)

<table>
<thead>
<tr>
<th>Access to joint thyroid-eye clinics</th>
<th>65% (vs 40% in 1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither participating nor referring to a multidisciplinary team</td>
<td>31.5%</td>
</tr>
<tr>
<td>“Reluctant” to refer to an ophthalmologist in the index case with suspected DON</td>
<td>32.7% (non-urgent referral in 27.1%, no referral at all in 5.6%)</td>
</tr>
<tr>
<td>Publication of practice guidelines would be welcome</td>
<td>92%</td>
</tr>
</tbody>
</table>

Perros P and the EUGOGO, Eur J Endocrinol 2006, 155: 207-211
Aims of the EUGOGO Consensus Statement

- To provide practical information for managing patients with GO, for both non-specialists and those with special interest and expertise in this condition
- To be of help also for specialist nurses, orthoptists and those involved in managerial roles
- To provide a focus for audit and research
- To improve the outcomes of patients with GO
Problems addressed by EUGOGO in the Consensus Statement

1. Referral to specialist centres, and initial assessment
2. Management issues of GO that should be addressed by both non-specialists and specialists
3. Management issues of GO that should be addressed in specialist centres
4. Special situations
# Types of Evidence (based on AHCPR, 1992)

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Meta-analysis of randomized controlled studies</td>
</tr>
<tr>
<td>Ib</td>
<td>At least one randomized controlled study</td>
</tr>
<tr>
<td>IIa</td>
<td>At least one well-designed controlled study w/o randomization</td>
</tr>
<tr>
<td>IIb</td>
<td>At least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Well-designed non-experimental descriptive studies, such as comparative, correlation or case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>
# Grading of Recommendations (based on AHRQ, 1994)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence levels</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ia, Ib</td>
<td>At least 1 RCT as part of the body literature of overall good quality and consistency addressing the specific recommendations</td>
</tr>
<tr>
<td>B</td>
<td>IIa, IIb, III</td>
<td>Availability of well-conducted clinical studies but no RCT on the topic of recommendation</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
<td>Evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Absence of directly applicable studies of good quality</td>
</tr>
</tbody>
</table>
Problems addressed by EUGOGO in the Consensus Statement

1. Referral to specialist centres, and initial assessment
2. Management issues of GO that should be addressed by both non-specialists and specialists
3. Management issues of GO that should be addressed in specialist centres
4. Special situations
Criteria for referral recommended by EUGOGO (IV, C)

- Graves’ patients who have neither symptoms nor signs of GO require no further ophthalmological assessments and need not to be referred to a specialist centre
- Physicians without expertise in managing GO should refer patients with GO to specialist centres for further assessment and management
- Patients with unusual presentations (unilateral or euthyroid GO) should be referred however mild their symptoms or signs, in order to make an accurate diagnosis
- Urgent or non-urgent referral should be based on the following criteria (Wiersinga W and the EUGOGO, Eur J Endocrinol 2006, 155: 387-389):
## Urgent Referral

<table>
<thead>
<tr>
<th>Symptoms*</th>
<th>Signs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained deterioration in vision</td>
<td>Obvious corneal opacity</td>
</tr>
<tr>
<td>Changes in intensity or quality of colour vision in one or both eyes</td>
<td>Disc swelling</td>
</tr>
<tr>
<td>History of eye(s) suddenly “popping out” (globe subluxation)</td>
<td>Cornea still visible when the eyelids are closed</td>
</tr>
<tr>
<td></td>
<td>Visual field deterioration</td>
</tr>
</tbody>
</table>

*Particularly if onset is recent*
## Non-urgent Referral

<table>
<thead>
<tr>
<th>Symptoms*</th>
<th>Signs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes abnormally sensitive to light</td>
<td>Troublesome eyelid retraction</td>
</tr>
<tr>
<td>Grittiness not improving after 1 week of topical lubricants</td>
<td>Abnormal swelling or redness of eyelid(s) or conjunctiva</td>
</tr>
<tr>
<td>Pain in or behind the eyes</td>
<td>Restriction of eye movements or manifest strabismus</td>
</tr>
<tr>
<td>Changes in the appearance of the eyes and/or eyelids</td>
<td>Tilting of the head to avoid double vision</td>
</tr>
<tr>
<td>Seeing two separate images</td>
<td></td>
</tr>
</tbody>
</table>

*Troublesome or deteriorating over the past 1-2 months*
Problems addressed by EUGOGO in the Consensus Statement

1. Referral to specialist centres, and initial assessment
2. Management issues of GO that should be addressed by both non-specialists and specialists
3. Management issues of GO that should be addressed in specialist centres
4. Special situations
Association between smoking and GO

Bartalena, JEI 1989
Smokers suffer more severe GO than non-smokers

Prummel, JAMA 1993
Smoking increases the likelihood of progression of GO after RAI therapy.

Smoking worsens the outcomes of treatments for GO

Smoking cessation may be associated with a better outcome of GO.

Pfeilschifter, Clin Endocrinol 1996
EUGOGO recommendations on smoking and GO

- All patients with Graves’ disease should be informed of the risks of smoking for GO (IV, C), emphasising the detrimental effects of smoking on:
  1. development of GO (IIb, B)
  2. deterioration of pre-existing GO (IIb, B)
  3. effectiveness of treatments for GO (IIb, B)
  4. progression of GO after radioiodine (Ib, A)

- If advice alone is ineffective, referral to smoking cessation clinics, or other smoking cessation strategies should be considered (IV, C)
Thyroid dysfunction and GO

Prummel, Acta Endocrinol 1989
Thyroid dysfunction and GO

Karlsson, Lancet 1989
Therapy for hyperthyroidism and course of GO

Marcocci, Clin Endocrinol 1999
Therapy for hyperthyroidism and course of GO

Bartalena, NEJM 1998
# Treatment of hyperthyroidism in the presence of GO (2006 survey)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At presentation (active GO)</th>
<th>After restoration of euthyroidism (still active GO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATDs</td>
<td>91%</td>
<td>0%</td>
</tr>
<tr>
<td>RAI</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>RAI + GC</td>
<td>3%</td>
<td>44%</td>
</tr>
<tr>
<td>Tx</td>
<td>3%</td>
<td>34%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Perros P and the EUGOGO, Eur J Endocrinol 2006, 155: 207-211
The risk of RAI-associated exacerbation of GO is negligible if GO is absent or inactive

- **Study design**: prospective, observational study
- **Patients**: 72 Graves’ patients submitted to RAI therapy, with no steroid cover
- **GO progression after RAI**: no case
- **Baseline GO**: absent or inactive after specific treatments

Perros, JCEM 2005
EUGOGO recommendations on thyroid status and GO (1)

- Euthyroidism should be restored promptly in all patients with GO (III, B)
- The modality of treatment of hyperthyroidism is less important for GO than restoring euthyroidism quickly and effectively and maintaining the euthyroid state (IV, C)
- 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)
EUGOGO recommendations on thyroid status and GO (2)

- Patients with active GO given radioiodine should be offered prophylactic steroid cover (e.g., 0.3–0.5 mg of oral prednisone/kg bw per day 1–3 days after radioiodine and tapering the dose until withdrawal about 2 months later) (Ib, A)

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

Simple measures that may alleviate symptoms:
1. lubricant eye drops during the day and/or lubricant ointments at nighttime are recommended in the presence of symptoms of corneal exposure (III, B)
2. patients with symptomatic diplopia should be given prisms if appropriate (IV, C)
3. botulinum toxin injection into levator palpebrae superioris muscle may be considered for upper lid retraction in centres with expertise in this technique (IV, C)
Problems addressed by EUGOGO in the Consensus Statement

1. Referral to specialist centres, and initial assessment
2. Management issues of GO that should be addressed by both non-specialists and specialists
3. Management issues of GO that should be addressed in specialist centres
4. Special situations
Activity and severity of GO

Wiersinga, TEM 2002
Management issues of GO that should be addressed in specialist centres

※ Grading activity of GO

1. Active GO
2. Inactive GO

※ Grading severity of GO

1. Sight-threatening GO
2. Moderate to severe GO
3. Mild GO
GO activity measures

- 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

Clinical Activity Score = sum of all items present

CAS > 3 = active GO

Derived from Mourits et al, BJO 1989 & Clin Endocrinol 1997
GO severity measures

- Lid aperture
- Swelling of the eyelids
- Redness of the eyelids
- Redness of the conjunctivae
- Conjunctival edema
- Inflammation of the caruncle or plica
- Exophthalmos
- Subjective diplopia score
- Eye muscle involvement
- Corneal involvement
- Optic nerve involvement

\[1\text{www.eugogo.org}\]
## Classification of severity of GO recommended by EUGOGO (IV, C)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sight-threatening GO</strong></td>
<td>Dysthyroid optic neuropathy (DON) and/or corneal breakdown. <strong>Immediate intervention</strong> is required</td>
</tr>
<tr>
<td><strong>Moderate to severe GO</strong></td>
<td>GO is not sight-threatening but has sufficient impact on QoL to justify the risks of immunosuppressive or surgical intervention</td>
</tr>
<tr>
<td><strong>Mild GO</strong></td>
<td>GO has only a minor impact on QoL insufficient to justify the risks of immunosuppressive or surgical intervention</td>
</tr>
</tbody>
</table>
# Features of mild and moderate to severe GO

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lid retraction</th>
<th>Soft tissues</th>
<th>Exophthalmos</th>
<th>Diplopia</th>
<th>Corneal exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>&lt;2 mm</td>
<td>mild involvement</td>
<td>&lt;3 mm</td>
<td>absent or intermittent</td>
<td>absent</td>
</tr>
<tr>
<td><strong>Moderate to severe</strong></td>
<td>&gt;2 mm</td>
<td>moderate or severe involvement</td>
<td>&gt;3 mm</td>
<td>inconstant or constant</td>
<td>mild</td>
</tr>
</tbody>
</table>
Decompression or iv glucocorticoids as first-line treatment for DON?

<table>
<thead>
<tr>
<th>First-line treatment</th>
<th>Inadequate response</th>
<th>Subsequent switch to the other treatment</th>
<th>Subsequent squint surgery</th>
<th>Subsequent eyelid surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital surgery</td>
<td>5/6 (82%)</td>
<td>Yes</td>
<td>3/6</td>
<td>5/6</td>
</tr>
<tr>
<td>Iv GCs</td>
<td>4/9 (45%)</td>
<td>Yes</td>
<td>5/9</td>
<td>4/9</td>
</tr>
</tbody>
</table>

Wakelkamp, Clin Endocrinol 2005, 63: 323–328
Management of sight-threatening GO: 1. DON

- Glucocorticoids (GCs) and orbital decompression are the only treatments proven to be effective in patients with DON (III, B)
- High-dose iv GCs is the preferred first-line treatment for DON (III, B)
- If the response to iv GCs is poor after 1-2 weeks or steroids induce significant side effects, prompt orbital decompression should be carried out (IV, C)
- Both iv GC therapy and orbital decompression should only be undertaken in centres with appropriate expertise (IV, C)
Management of sight-threatening GO: 
2. Corneal breakdown

- Corneal breakdown is an emergency to manage as follows (IV, C):
  1. Topical lubricants, moisture chambers, blepharoraphy, or other temporary measures until the cornea has healed
  2. Systemic GCs or decompression when the above measures are ineffective
  3. In the event of corneal perforation/severe ulceration, appropriate antibiotics, and emergency glueing or grafting need to be considered
  4. Once breakdown is controlled, it is imperative to improve lid closure to prevent further episodes
Comparison between iv and oral glucocorticoids for GO

Marcocci, JCEM 2001
Acute liver damage during iv glucocorticoid therapy for GO

- 7 cases of ALD out of about 800 patients (0.8%)
- Lethal in 3 cases (0.3%)
- Cumulative dose of iv steroids: 4–15 g (>7 g in 6 of 7)
- Oral steroids in the interpulse period: no
- Possible mechanisms: direct hepatotoxicity; preexisting steatosis; viral hepatitis triggered by immunosuppression; autoimmune hepatitis (rebound after immunosuppression)

Marinò, Thyroid 2004
Comparison between iv and oral glucocorticoids for GO

Kahaly, JCEM 2005
Management of moderate to severe GO:
1. Glucocorticoids

- The treatment of choice for moderate to severe and active GO is iv pulses of GCs (Ib, A). This treatment should be undertaken in centres with appropriate expertise (IV, C)
- The total cumulative dose of methylprednisolone should not exceed 8 g (III, B)
- Patients being treated with high-dose iv GCs should be first screened for liver dysfunction, history of peptic ulcer, diabetes, urine infections 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)
Orbital radiotherapy and oral glucocorticoids for GO

Prummel, Lancet 1993
Five recent studies evaluating the effects of orbital radiotherapy on GO
Effects of different radiation doses

Kahaly, JCEM 2000
### Long-term safety data of orbital radiotherapy for GO

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Follow up (years)</th>
<th>Cataract</th>
<th>Cancer</th>
<th>Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcocci</td>
<td>204</td>
<td>11 (5-25)</td>
<td>Not increased</td>
<td>No</td>
<td>DM+AH: 1/7, AH: 1/31, DM: 0/11</td>
</tr>
<tr>
<td>Wakelkamp</td>
<td>157</td>
<td>11 (+3)</td>
<td>Not increased</td>
<td>No</td>
<td>Definite retinopathy: 5 (3 with DM)</td>
</tr>
<tr>
<td>Robertson</td>
<td>42</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>3 (2 with AH + borderline DM)</td>
</tr>
</tbody>
</table>

AH: arterial hypertension; DM: diabetes mellitus
Combination of oral GCs and orbital radiotherapy is more effective than either treatment alone.

Bartalena, JCEM 1983; Marcocci, JEI 1991
Management of moderate to severe GO:
2. Orbital radiotherapy (OR)

- OR should be considered in patients with active GO who have diplopia or restricted motility (Ib, A)
- Lower cumulative doses (10 Gy) may be as effective as and better tolerated than higher doses (20 Gy) (Ib, A). Doses >20 Gy are not recommended (IV, C)
- Caution should be exercised about administering OR to patients younger than 35 yr; OR must be avoided in patients with diabetic retinopathy and/or severe hypertension (III, B)
- Combination of oral GCs and OR is more effective than either treatment alone (Ib, A), but RCTs indicating that combination of iv GCs with OR is better than iv GCs alone are lacking (IV, C)
**Management of moderate to severe GO:**

3. **Other agents**

- Somatostatin analogs, azathioprine, ciamexone, iv immunoglobulins are treatments of marginal or not proven value.
- Two studies have shown the superiority of combined oral GCs and cyclosporine on either treatment alone.
- The potential usefulness of immunomodulatory agents, such as rituximab or etanercept, has insofar been suggested only by open studies.
Management of moderate to severe GO: 4. Surgery

- The timing and order of surgical interventions should be carefully planned (IV, C)
- A fixed sequence of correction (if needed) has to be respected: orbital decompression, squint surgery, lid lengthening with or followed by blepharoplasty/browplasty (III, B)
- Rehabilitative decompression surgery should only be performed in euthyroid patients with GO quiescent for at least 6 months (III, B)
- Rehabilitative surgery should only be undertaken in centres with appropriate expertise (IV, C)
EUGOGO recommendations for mild GO

- GCs 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 GO, quality of life may be so profoundly affected as to justify using treatments as for moderate to severe GO (IV, C)
Special situations:
1. Diabetes and hypertension

- 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)
Special situations:

2. GO in childhood

- 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)
- GCs should be avoided in children (IV, C)
- OR is contraindicated in children (IV, C)
- Exposure to active and, possibly, passive smoking should be avoided (IV, C)
Major points of reached consensus (1)

✦ All patients with GO should:
  1. be referred to specialist centres;
  2. be encouraged to quit smoking;
  3. receive prompt treatment to restore and maintain stable euthyroidism

✦ Iv GCs are the first-line treatment for sight-threatening GO; if response is poor after 1-2 weeks, urgent decompression should be performed
Major points of reached consensus (2)

- Iv GCs (with or w/o OR) are the treatment of choice for moderate to severe and active GO; surgery should be considered if GO is inactive.

- In mild GO local measures and an expectant strategy are sufficient in most cases, but treatments as for moderate to severe GO (including rehabilitative surgery) may be required if QoL is affected significantly.
Something missing: what to do in still active, moderate to severe GO after immunosuppressive treatment?

1. A second course of iv GCs if iv GCs + orbital radiotherapy were used as first-line treatment?
2. Orbital radiotherapy (with or without iv GCs) if iv GCs alone were used as first-line treatment?
3. A second course of iv GCs in any case?
4. Other immunomodulatory agents?
ALL PATIENTS WITH GO

- Restore euthyroidism
- Urge smoking withdrawal
- Refer to specialist centres
- Local measures
- Encourage

MILD
- Local measures
- Wait-and-see
- Stable and inactive
- Rehabilitative surgery (if needed)

MODERATE TO SEVERE
- Active
  - iv GCs (+/- OR)
  - Still active
    - iv GCs (+/- OR)
    - Stable and inactive
      - Rehabilitative surgery

- Inactive
  - Stable and inactive
  - Rehabilitative surgery

SIGHT-THREATENING
- iv GCs
- Poor response (1-2 weeks)
- Prompt decompression
- Still active
- Stable and inactive
- Rehabilitative surgery
Graves’ Orbitopathy
A Multidisciplinary Approach

In recent years, close interdisciplinary cooperation of numerous international experts, both clinicians and basic scientists, within the European Group of Graves’ orbitopathy (EUGOGO) has yielded much valuable progress and new information, which this publication brings together.

Subjects covered include the pathology of Graves’ orbitopathy (GO) and the controversial views on its pathogenesis; assessment of changes using reliable measuring techniques; medical management of GO including established and alternative treatment options; technical explanations and illustrations of various surgical procedures and finally, the molecular, immunologic, and clinical aspects of this complex disorder.

The question-and-answer format facilitates its use as a reference guide for medical practitioners and offers a thorough overview of associated changes in the eyes of patients with GO. Stressing the current management of thyroid eye disease, this publication is an essential resource for ophthalmologists, internists, endocrinologists, pediatricians, immunologists, specialists in nuclear medicine, neuroradiologists and radiotherapists, specialists in laboratory medicine and pathology, otolaryngologists, orbital and neurosurgeons as well as oral and maxillofacial surgeons.